Merenstein & Gardner's Handbook of

NEONATAL INTENSIVE CARE

An Interprofessional Approach

9th edition

Gardner | Carter
Enzman-Hines | Niermeyer

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NEWBORN METRIC CONVERSION TABLES

Temperature

FAHRENHEIT (F) TO CELSIUS (°C)

°F	°C	°F	°C	°F	°C	°F	°C
95.0	35.0	98.0	36.7	101.0	38.3	104.0	40.0
95.2	35.1	98.2	36.8	101.2	38.4	104.2	40.1
95.4	35.2	98.4	36.9	101.4	38.6	104.4	40.2
95.6	35.3	98.6	37.0	101.6	38.7	104.6	40.3
95.8	35.4	98.8	37.1	101.8	38.8	104.8	40.4
96.0	35.6	99.0	37.2	102.0	38.9	105.0	40.6
96.2	35.7	99.2	37.3	102.2	39.0	105.2	40.7
96.4	35.8	99.4	37.4	102.4	39.1	105.4	40.8
96.6	35.9	99.6	37.6	102.6	39.2	105.6	40.9
96.8	36.0	99.8	37.7	102.8	39.3	105.8	41.0
97.0	36.1	100.0	37.8	103.0	39.4	106.0	41.1
97.2	36.2	100.2	37.9	103.2	39.6	106.2	41.2
97.4	36.3	100.4	38.0	103.4	39.7	106.4	41.3
97.6	36.4	100.6	38.1	103.6	39.8	106.6	41.4
97.8	36.6	100.8	38.2	103.8	39.9	106.8	41.6

NOTE: °C = (°F – 32) × ⅝. Celsius temperature equivalents have been rounded to one decimal place by adding 0.1 when the second decimal place is 5 or greater.

See inside back cover for additional tables.

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NEONATAL INTENSIVE CARE: AN INTERPROFESSIONAL APPROACH

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Merenstein & Gardner's Handbook of

NEONATAL INTENSIVE CARE: AN INTERPROFESSIONAL APPROACH

9th edition

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We dedicate this edition to the memory of Gerald B. Merenstein, MD—our friend, colleague, and mentor who was also a wonderful husband, father, and grandfather. As the inspiration for this text, Gerry contributed to the fields of neonatal and pediatric care through his dedication to nurses, nurse practitioners, child health associates, interns, residents, fellows, neonates, and their families. We miss him every day and know that his empathy, knowledge, teaching, and compassion influences all of us, as well as the newborns, children, and families that he and we serve.

SLG BSC MEH SN

In memory of Stephanie Marie Gardner, whose three days of life did have a purpose. To Muffy Roo, Millie Moo, and Mollie Mittens, my sweet rescue dogs, for their eminent patience for the last 3 years!

SLG

To my family: Angel, Sean, Yvonne, Rebecca, and Jacquelyn; my mentors and colleagues; and all of the children and families who have allowed me to share with them both joyous and difficult times in their lives.

BSC

To my family: James, Jennifer, Sean, Finnoula, Steve, and Sarah for their enduring source of love, confidence, and encouragement and to all the families who have informed my practice and knowledge about caring for fragile infants.

MEH

To all of the babies, families, and dedicated caregivers who have been my constant teachers; my mentor Jacinto Hernandez, who opened my horizons to a larger world; and my husband John for his unfailing love and support.

SN

In Memoriam

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PREFACE

The concept of the team approach is important in neonatal intensive care. Each health care professional must not only perform the duties of his or her own role but must also understand the roles of other involved professionals. Nurses, physicians, other health care providers, and parents must work together in a coordinated and efficient manner to achieve optimal results for patients in the neonatal intensive care unit (NICU).

Because this team approach is so important in the field of neonatal intensive care, we believe it is necessary that this book contain input from major fields of health care—nursing and medicine. Both nurses and physicians have edited and co-authored every chapter.

The book is divided into six units, all of which have been reviewed, revised, and updated for the ninth edition. Unit One presents evidence-based practice and the need to scientifically evaluate neonatal therapies, emphasizing randomized controlled trials as the ideal approach. Units Two to Five are the clinical sections, which have been fully updated for this edition. The chapters within these sections include highlighted clinical directions for quick reference, Parent Teaching boxes to aid in discharge instructions, Critical Findings boxes to prioritize assessment data, and medication tables.

The combination of physiology and pathophysiology and separate emphasis on clinical application in this text is designed for neonatal intensive care nurses, nursing students, medical students, and pediatric, surgical, and family practice housestaff. This text is comprehensive enough for nurses and physicians, yet basic enough to be useful to families and all ancillary personnel.

Unit Six presents the psychosocial aspects of neonatal care. The medical, psychological, and social aspects of providing care for the ill neonate and family are discussed in this section. This section in particular will benefit social workers and clergy, who often deal with family members of neonates in the NICU.

In this handbook we present physiologic principles and practical applications and point out areas as yet unresolved. **Material that is clinically applicable is set in bold type so that it can be easily identified.**

INTRODUCTION

In 1974 as the Perinatal Outreach Educator at the Children's Hospital in Denver, Colorado, I took a folder to Gerry Merenstein, MD, at Fitzsimmons Army Medical Center to discuss his lectures for the first outreach education program in La Junta, Colorado. When we finished, he removed from his desk drawer a 1-inch-thick compilation of the neonatal data, graphs, nomograms, and diagrams he had created for the medical housestaff during his fellowship. Giving the document to me, he asked that I review it and let him know what I thought. Several weeks later, I told him it was good *except* there was no nursing care or input, which is essential in every NICU. So Gerry asked, "Want to write a book?"—and the idea for the *Handbook* was born!

With this ninth edition in 2020, we celebrate 35 years of publication of the *Handbook of Neonatal Intensive Care*. Gerry and I co-edited this book for 21 years until his death in December 2007. To fulfill my promise that Gerry's name would always be on the book, the seventh and all subsequent editions are now known as *Merenstein & Gardner's Handbook of Neonatal Intensive Care*. Instead of editing this edition alone or with another physician, I decided to convene an editorial team consisting of myself, a nurse colleague, and two neonatologists. Together we bring 180 years of clinical practice, research, teaching, writing, and consulting in neonatal, pediatric, and family care to this ninth edition.

In the eighth edition, we have the distinction of translation to Korean and Portuguese. We are still working on a Spanish translation because this was an ongoing wish of Gerry Merenstein. In addition, the *Handbook* is available on multiple e-platforms to facilitate use at the bedside. Multiple editions of the *Handbook* (first in 1985; fifth in 2002; seventh in 2011; and eighth in 2016) have won the *American Journal of Nursing* Book of the Year Award. The eighth edition of the *Handbook* placed first in the Critical Care/Emergency Nursing category.

For our new audience and for our continuing loyal readers, this is my opportunity to introduce myself and all members of the editing team.

I am currently the Director of Professional Outreach Consultation (www.professionaloutreach-consultation.org), a national and international consulting firm established in 1980. I plan, develop, teach, and coordinate educational workshops on perinatal/neonatal/pediatric topics. I graduated from a hospital school of nursing in 1967 with a diploma, obtained my BSN at Spalding College in 1973 (magna cum laude), and completed my MS at the University of Colorado School of Nursing in 1975 and my PNP in 1978. I have worked in perinatal/neonatal/pediatric care since 1967 as a clinician (37 years in direct bedside care), practitioner, teacher, author, and consultant. In 1974, I was the first Perinatal Outreach Educator in the United States funded by the March of Dimes. In this role, I taught nurses and physicians in Colorado and the seven surrounding states how to recognize and stabilize at-risk pregnancies and sick neonates. I also consulted with numerous March of Dimes grantees to help them establish perinatal outreach programs. In 1978, I was awarded the Gerald Hencmann Award from the March of Dimes for "outstanding service in the improvement of care to mothers and babies in Colorado." I am a founding member of the Colorado Perinatal Care Council (now the Colorado Perinatal Care Quality Collaborative). I am an active member of the Colorado Nurses Association/American Nurses Association, the Academy of Neonatal Nurses, and the National Association of Neonatal Nurses.

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in Colorado Springs and co-owner and certified Pediatric Nurse Practitioner at Integrative Pediatric Health Care in Englewood, Colorado (www.ip-hcdenver.com). This is the first nurse practitioner owned and operated practice in Colorado. Early in her nursing career, Mary worked in the NICU and PICU as a staff nurse, charge nurse, and nurse manager. After completing her PNP/CNS program and her master's degree at the University of Colorado, Mary became the Neonatal and Pediatric Clinical Nurse Specialist at Denver Health and Hospital, where she created a beginning, intermediate, and advanced orientation for nurses in the NICU and PICU. At the University of Colorado, Mary accepted the practitioner/teacher role in maternal-child services, providing clinical care and mentorship in the NICU and pediatric units where nursing students were placed from the CU nursing program. When University Hospital and The Children's Hospital combined their pediatric services, Mary became the Clinical Nurse Specialist in Research and Education and consulted in the NICU, PICU, and pediatric medical-surgical areas. In this role, she was a founding member of the interdisciplinary Pain Management Team and provided consultation throughout The Children's Hospital for pain management issues. In 1996, Mary became a nursing faculty member at Beth-El College of Nursing and Health Sciences, where she created a student health center at the University of Colorado Colorado Springs and a school-based clinic for schoolchildren in Fountain, Colorado, while maintaining an active pediatric practice at Colorado Springs Health Partners. Currently Mary provides pediatric care at her own practice and continues to teach courses to DNP students at the University of Northern Colorado as an adjunct faculty. Mary is well published in the areas of pediatric, neonatal, and family health care, as well as in legal issues in maternal-child nursing. Mary is also a nurse researcher in the areas of pain, chronic illness, caring/healing praxis, pediatric pain, holistic nursing, and technology in health care.

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of Colorado and received the Avroy Fanaroff Neonatal Education Award from the AAP.

Borrowing from the words of Brian Carter in the introduction to the sixth edition of the *Handbook:*

> *The goals of care should be patient- and family-centered. It is the patient we treat, but it is the family, of whatever construct, with whom the baby will go home. Indeed, it is the family who must live with the long-term consequences of our daily decisions in caring for their baby.*

These goals include the provision of skilled professional care. An effective neonatal intensive care team consists of educated professionals of many disciplines—none of us can do it alone.

It has been my honor and privilege to work with these co-editors, who are all patient- and family-centered, and with the amazing editing team of Laura Klein, Lee Henderson, and Carol O'Connell for this ninth edition.

Sandra L. Gardner, RN, MS,
Retired Clinical Nurse Specialist and Pediatric Nurse Practitioner
Senior Editor

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1 EVIDENCE-BASED CLINICAL PRACTICE

ALFONSO F. PANTOJA AND MARY ENZMAN-HINES

Globally, health care systems are experiencing challenges when evaluating therapies, quality of care, and the risk of adverse events in clinical practice. Over the past several decades, health care disciplines have made major strides to ensure that clinical decisions and actions are based on sound scientific evidence. Expert practice decisions and actions are embedded in a complex web that reflects all forms of knowing and understanding. Each element of knowing has a similar but distinct foundation of reliability and validity. Health care scholars/researchers who provide direct patient care, administrators, and educators have joined in the effort to identify the most reliable and sound scientific evidence available to inform and guide practice.[20]

Often health care systems fail to optimally use evidence. This failure is either from underuse, overuse, or misuse of evidence-based therapies and/or system failures.[92,93] **Evidence-based practice (EBP) requires the integration of the best research evidence with our clinical expertise and each patient's unique values and circumstances.**[92,93] EBP approaches in all fields of health care could prevent therapeutic disasters resulting from the informal "let's-try-it-and-see" methods of testing new therapies that are not recognized as risky. The epidemic of retinopathy attributable to the indiscriminate use of supplemental oxygen; gray baby syndrome attributable to the administration of chloramphenicol; kernicterus attributable to the introduction of sulfonamides[82]; and death due to liver toxicity of 40 premature newborns attributable to the administration of a parenteral form of vitamin E (E-Ferol)[89] are examples of these therapeutic misadventures in the field of neonatal care. Silverman described how painfully slow health care providers were to embrace a culture of skepticism and emphasizes, "We must insist on the highest standards of evidence in studies involving the youngest human beings; and, since there is no short route to this goal, we must prepare to be patient."[82] The use of experimentation and the scientific method has ultimately led to our present views of how to ask and answer clinical questions.[71]

Mistakes have also occurred at the other extreme, resulting in a failure to adopt therapies that are of proven benefit or an assumption that the risks associated with changing practice justify complacency about current treatments. The significant delay in the adoption of antenatal corticosteroids by the obstetric community to promote fetal lung maturation[23,86] is a good example of failure to use the available evidence. **One of the most important benefits of EBP is the constant questioning: "Have our current clinical practices been studied in appropriately selected populations of sufficient size to accurately predict their efficacy, benefit, safety, side effects, and cost?"**

EBP is a systematic way to integrate the best patient-centered, clinically relevant research with our clinical expertise and with the unique preferences, concerns, and expectations that each patient brings to a clinical encounter.[92] Furthermore, EBP presents an opportunity to enhance patient health and illness outcomes, increase staff satisfaction, and reduce health care expenses. **There is great interest in identifying barriers and facilitators that could help in closing the knowledge-to-practice gap that is inherent to the acceptance and adoption of EBP by all providers.**[96]

BLUE type highlights content that is particularly applicable to clinical settings.

FINDING HIGH-QUALITY EVIDENCE

As new therapies are integrated into neonatal care, health care providers must continue to increase existing knowledge of the health and health problems of newborns. **Providers need to formulate well-designed questions about the specific clinical encounter and learn how to evaluate the quality of evidence regarding risks and benefits of new practices.** Most clinical questions arise through daily practice and often involve knowledge gaps in background (general knowledge) and foreground (specific knowledge to inform clinical decisions or actions). The knowledge needs will vary according to the experience of the clinician.[92]

It is not the purpose of this chapter to provide a detailed review of the various research designs that permit reliable scientific inference. Rather, **our purpose is to promote the propositions that (1) challenge clinical observations and wisdom by finding the current best evidence and (2) carefully assess and critique research that supports or challenges the use of new and established clinical practices.**

Clinical observations, although valuable in shaping research questions, are limited by selective perception—a desire to see a strategy work or fail to work. At times, a single case or case study may prompt us to question whether we should consider changing current practice. In some situations, much can be learned from carefully maintained databases. Such knowledge is gained only when we have formed databases with clear intentions and have collected the necessary data.

Sinclair and Bracken[85] described **four levels of clinical research used to evaluate safety and efficacy of therapies,** based on their ability to provide an unbiased answer. **In ascending order, these are (1) single case or case series reports without controls, (2) nonrandomized studies with historical controls, (3) nonrandomized studies with concurrent controls, and (4) randomized controlled trials (RCTs). RCTs test hypotheses by using randomly assigned treatment and control groups of adequate size to examine the efficacy and safety of a new therapy.** In theory, random assignment of the treatment balances unknown or unmeasured factors that might otherwise bias the outcome of the trial. **A *meta-analysis* is a systematic review of the current literature that uses statistical methods to combine the results of individual studies and summarizes the results (**http://neonatal.cochrane.org**).**[22] Tyson[97] has suggested criteria for identifying proven therapies in current literature (Box 1.1). **Ideally, therapeutic recommendations are supported by evidence from systematic reviews of RCTs; however, such evidence is not always available.** It is then important to have a system to grade the strength of the quality of the evidence found. **An international collaboration developed GRADE (Grading of Recommendations Assessment, Development and Evaluation) to provide an explicit strategy for grading evidence and the strength of recommendations.[44] GRADE classifies the evidence into one of four levels: high, moderate, low, and very low (Table 1.1).** The strength of the recommendation is graded as strong or weak. Factors

BOX 1.1 PROVEN THERAPIES

Reported to be beneficial in a well-performed meta-analysis of all trials
or
Beneficial in at least one multicenter trial or two single-center trials

Modified from Tyson JE. Use of unproven therapies in clinical practice and research: how can we better serve our patients and their families? *Semin Perinatol.* 1995;19:98.

TABLE 1.1 LEVELS OF EVIDENCE

LEVEL OF EVIDENCE	THERAPY/PREVENTION/ETIOLOGY/HARM
1a	Systematic reviews of RCTs
1b	Individual RCT with narrow confidence interval
1c	All or none
2a	Systematic review of cohort studies
2b	Individual cohort study (including low-quality RCT [less than 80% follow-up])
3a	Systematic review of case-control study
3b	Individual case-control study
4	Case-control studies
5	Expert opinion without critical appraisal

RCT, Randomized controlled trial.
From Straus SE, Richardson WS, Haynes RB. *Evidence-Based Medicine: How to Practice and Teach It.* 4th ed. London: Harcourt; 2011.

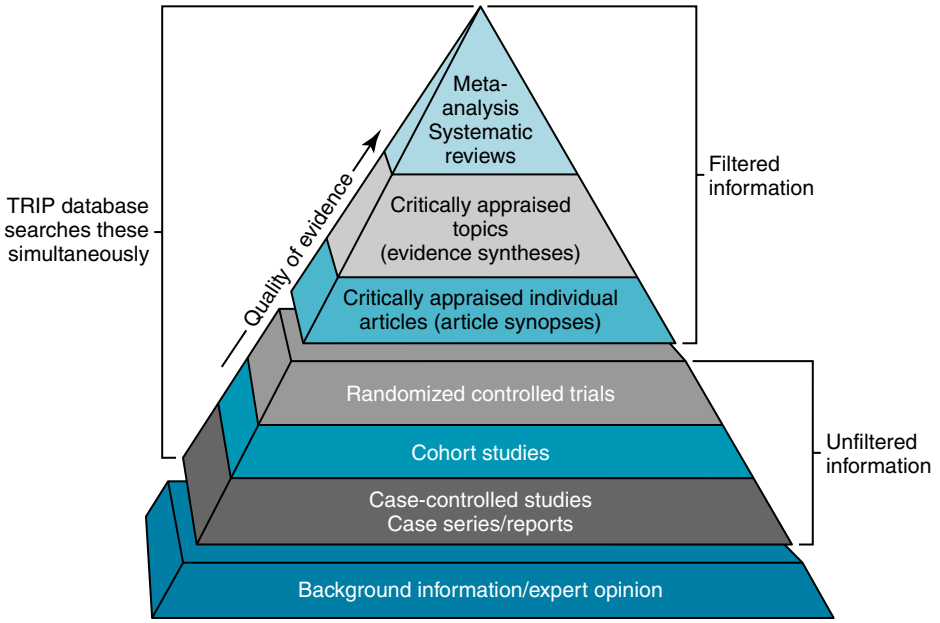

FIGURE 1.1 **Evidence appraisal.** (Modified from DiCenso A, Bayley L, Haynes RB: Accessing pre-appraised evidence: fine-tuning the 5S model into the 6S model. *Evid Based Nurs.* 2009;12(4):99.)

that influence the strength of the recommendation include desirable or undesirable effects, values, preferences, and economic implications (Fig. 1.1).

Although conclusions drawn from quantitative studies (RCTs, meta-analysis of RCTs) are regarded as the strongest level of evidence, evidence from descriptive and qualitative studies should be factored into clinical decisions. **Qualitative research provides guidance in deciding whether the findings of quantitative studies could be replicated in various patient populations. Qualitative research can also facilitate an understanding of the experience and values of patients, parents, and health care providers.** The validity, importance, and applicability of qualitative studies need to be evaluated in a similar way as quantitative studies.

PRESSURES TO INTERVENE

RCTs of appropriate size are cited as providing the best evidence for guiding clinical decisions; however, many take years to complete and publish. Providers find it difficult to delay the introduction of promising therapies. Bryce and Enkin[15] discussed myths about RCTs and rationales for not conducting them. **One myth is that randomization is unethical.** This might be true in rare instances when an intervention is dramatically effective and lifesaving. The more common situation is one in which there is limited evidence for a current or alternative strategy.

Pressure to intervene is, however, often overpowering. Believing that an infant is in trouble, interventions occur through a cascade of interventions, one leading to the next and each carrying risk. One of the most frequently cited examples is the epidemic of blindness associated with the unrestricted use of oxygen in newborns.[81,82] Oxygen, used since the early 1900s for resuscitation and treatment of cyanotic episodes, was noted in the 1940s to "correct" periodic breathing in premature infants. After World War II and the introduction of new gas-tight incubators, an epidemic of blindness occurred, resulting from retrolental fibroplasia (RLF). Silverman[81] pointed out that although many causes were suspected, it was not until 1954 that a multicenter, controlled trial confirmed the association between high oxygen concentrations and RLF. Frequently forgotten, however, is that in subsequent years, mortality was increased in infants cared for with an equally experimental regimen of strict restriction of oxygen administration, and many survivors had spastic diplegia. In the 1960s, the introduction of micro techniques for measuring

arterial oxygen tension permitted better monitoring of oxygen therapy, with a reduction in mortality, spastic diplegia, and RLF, now called *retinopathy of prematurity* (ROP). Severe ROP is currently limited to extremely-low-birth-weight (ELBW) infants.[81] Research continues to explore causes, preventive measures, and treatments (see Chapter 31).

Large multinational, pragmatic RCTs to resolve the uncertainty surrounding the most appropriate levels of oxygen saturation in premature infants have been recently conducted and the results published.[78,94,95] The publication of the results of the SUPPORT trial[94] brought about a significant debate about the ethical aspects of comparative effectiveness research and parental informed consent when one of the elements of the composite outcome was death before discharge.[81] The practice of allowing very-low-birth-weight (VLBW) infants to maintain lower oxygen saturations during the first weeks of life had been widely disseminated throughout the United States and the world due to anecdotal reports of a significant decrease in the severity of ROP and blindness with this approach.[21] A recent report of five multicenter studies (NEOPROM) with similar allocations and outcome measures that were prospectively organized with the aim to answer whether extremely premature infants kept at a low or a high oxygen saturation target had different outcomes. These studies are the SUPPORT trial (Surfactant, Positive Pressure and Pulse Oximetry Randomized Trial), the three BOOST II trials from the United Kingdom, Australia, and New Zealand, and the Canadian Oxygen Trial (COT). Low saturation targets (85% to 89%) until 36 weeks postmenstrual age (PMA) are associated with more deaths and more necrotizing enterocolitis (NEC). Higher saturation targets (91% to 95%) are associated with more ROP.[76] Results from all five trials were systematically reviewed and a final meta-analysis (the NeOProM) performed to determine optimal oxygen saturation targets for preterm infants (mean gestational age of 26 weeks; mean birth weights of 820 to 850 g).[7] At 18 to 24 months corrected age, no significant difference was found between the lower and higher saturation groups in mortality or major disability.[7] Secondary analysis of the data found that the *lower* saturation group had significantly higher death rates prior to 36 weeks PMA, before discharge from the neonatal intensive care unit (NICU), and before reaching 18 to 24 months' corrected age, a significantly higher risk of severe NEC and a significantly higher risk of PDA requiring ligation. Preterm infants randomized to the *higher* saturation group had a significantly higher risk of bronchopulmonary dysplasia (BPD) and ROP requiring treatment but no increase in blindness[7] (see Chapter 23).

The desire to see an intervention "work" encourages practitioners and investigators to seek early signs of benefit. Long-term effects are frequently overlooked. One reason is that they may not be foreseen. Consider the example of diethylstilbestrol (DES). DES administration to pregnant women was introduced in 1947 without clinical trials to prevent miscarriage, fetal death, and preterm delivery.[15,37] It was thought to be effective after uncontrolled studies despite controlled trials summarized in an overview (meta-analysis) by Goldstein et al.[41] (Table 1.2) that showed the opposite. Clearly, DES was not effective, but it continued to be used until the 1970s, when the Food and Drug Administration (FDA) finally disapproved its use. The unforeseen result was that female children born to mothers who were given DES had structural abnormalities of the genital tract, pregnancy complications, decreased fertility, and an increased risk for vaginal adenocarcinoma in young women. Male children had epididymal cysts. This is not the only example of physicians continuing to use therapies that have been shown in RCTs to be of no benefit.[18]

TABLE 1.2 EFFECTS OF DIETHYLSTILBESTROL ON PREGNANCY OUTCOMES

	TYPICAL ODDS RATIO[A]	95% CONFIDENCE LIMITS
Miscarriage	1.20	0.89–1.62
Stillbirth	0.95	0.50–1.83
Neonatal death	1.31	0.74–2.34
All three	1.38	0.99–1.92
Prematurity	1.47	1.08–2.00

[A]An odds ratio is an estimate of the likelihood (or odds) of being affected by an exposure (e.g., a drug or treatment) compared with the odds of having that outcome without having been exposed. Women receiving diethylstilbestrol did not have fewer stillbirths, premature births, or miscarriages than women who were untreated.

Data from Goldstein PA, Sacks HS, Chalmers TC. Hormone administration for the maintenance of pregnancy. In Chalmers I, Enkin M, Keirse M, eds. *Effective Care in Pregnancy and Childbirth.* New York, NY: Oxford University Press; 1989.

The costs of long-term studies and follow-up surveillance are numerous. However, when effects are measured later in life (e.g., psychological problems, ability to function in school), the cost cannot determine study design. Even when randomized trials are conclusive, unanswered questions remain: Will a technology or treatment have the same effect in all settings? Has an "appropriate" target population been selected? Are there long-term unforeseeable consequences?

EVALUATION OF THERAPIES

The major cause of death in premature infants is respiratory failure from respiratory distress syndrome (RDS) (see Chapter 23). Previously called *hyaline membrane disease,* this syndrome of expiratory grunting, nasal flaring, chest wall retractions, and cyanosis unresponsive to high oxygen concentrations was a mystery until the 1950s.[82]

The evaluation of various therapies for RDS contrasts the value of controlled and uncontrolled trials. Sinclair[84] noted that uncontrolled studies were more likely to show benefit than controlled trials. In 19 uncontrolled studies, 17 popular therapies showed "benefit." In 18 controlled studies, only 9 demonstrated benefit. An untrained reviewer of the research might base clinical practice on faulty conclusions of uncontrolled trials.

Surfactant Therapy

In contrast to many proposed treatments, surfactant therapy in premature infants has been well studied in RCTs.[4,5,46,48] Studies have evaluated the use of surfactant in treatment of RDS, including the optimal source and composition of surfactant and prophylactic versus rescue treatment. Morbidity (including pneumothorax, periventricular or intraventricular hemorrhage, BPD, and patent ductus arteriosus) and mortality rates in treatment and control groups have been compared. Systematic reviews of surfactant therapy confirm the effect of surfactant therapy in reducing the risk of morbidity and mortality.[85,90] **Although RCTs involving thousands of newborns have clearly demonstrated the benefits of surfactant therapy, unanswered questions remain.** One of these questions is if prophylactic administration of surfactant to an infant judged to be at risk of developing RDS was better than early selective use of surfactant to infants with established RDS. Early trials demonstrated a decreased risk of air leak and mortality with the prophylactic approach. However, recent RCTs that reflect current practice (i.e., greater utilization of maternal steroids and routine postdelivery stabilization on continuous positive airway pressure [CPAP]) do not support these differences and actually demonstrate less risk of chronic lung disease (CLD) or death when using early stabilization on CPAP with selective surfactant administration to infants requiring intubation[75,94] (Fig. 1.2).

Corticosteroid Therapy

Misuse of corticosteroids in perinatal medicine illustrates the consequences of failure to practice evidence-based care. Many practitioners initially declined to use antenatal steroids to promote maturation of the immature fetal lung and to prevent RDS despite strong supportive evidence, demonstrating a failure to use a proven therapy.

ANTENATAL CORTICOSTEROID THERAPY: SINGLE COURSE

Antenatal administration of corticosteroids to pregnant women who threatened to deliver prematurely was first shown in 1972 to decrease the neonatal mortality rate and the incidence of RDS and intraventricular hemorrhage (IVH) in premature infants.[57] In 1990, Crowley et al.[25] used meta-analysis to evaluate 12 RCTs of maternal corticosteroid administration involving more than 3000 women. The data showed that maternal corticosteroid treatment significantly reduced the risk for neonatal mortality, RDS, and IVH. Sinclair,[86] using a "cumulative meta-analysis" approach of randomized trials, clearly demonstrated that the aggregate evidence that was sufficient to show that this treatment reduces the incidence of RDS and neonatal death was available for almost 20 years before the use of antenatal corticosteroids was widely accepted by the medical community.

This led to the National Institutes of Health (NIH) consensus development conference statement on "Effects of Corticosteroids for Fetal Maturation on Perinatal Outcomes."[63] Antenatal corticosteroid treatment of women at risk for preterm delivery between 24 and 34 weeks of gestation has been shown to be effective and safe in enhancing fetal lung maturity and reducing neonatal mortality. Yet adoption by caretakers was inexplicably slow.[53]

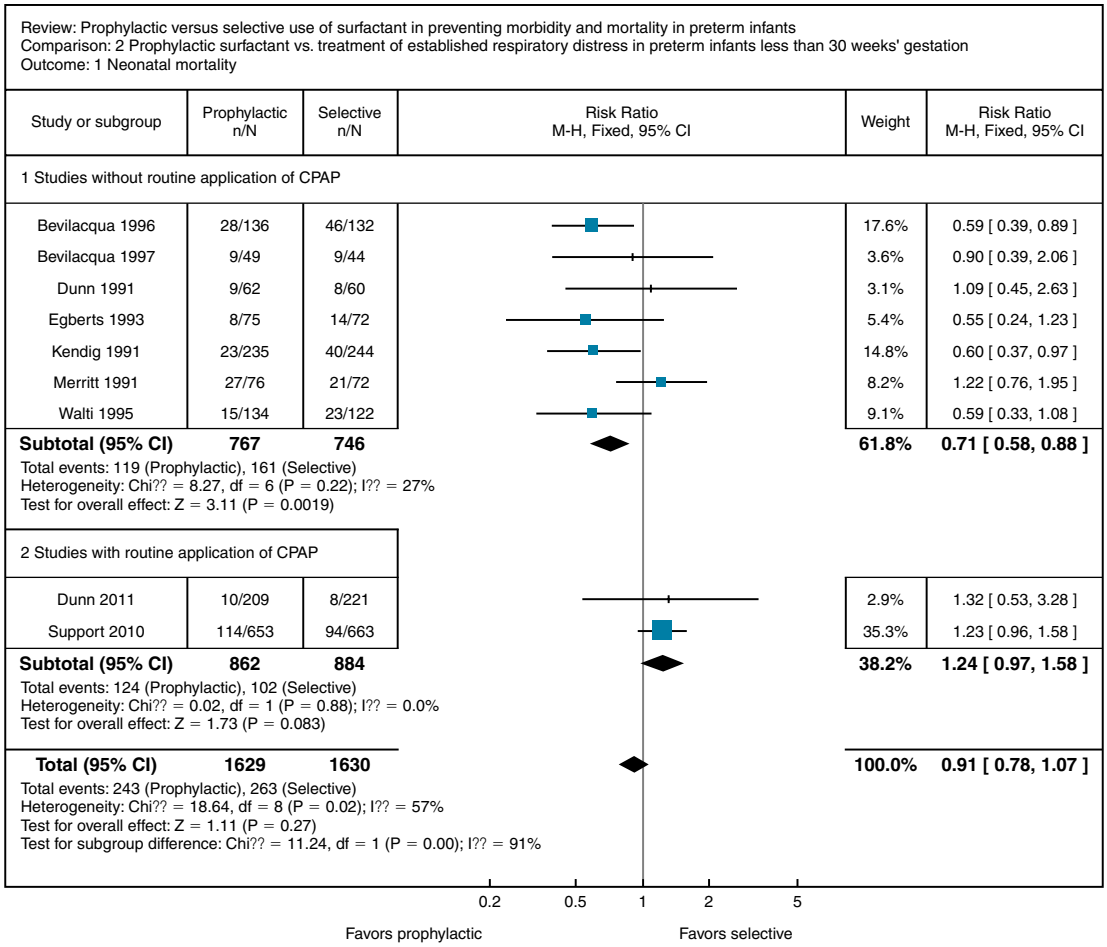

FIGURE 1.2 Table showing effect of prophylactic versus selective surfactant administration on morbidity and mortality rates in preterm infants. (From Rojas-Reyes X, Morley C, Soll R. Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev.* 2012;3:CD000510.)

ANTENATAL CORTICOSTEROID THERAPY: REPEATED COURSES

At the same time, **other practitioners administered repeated doses despite lack of evidence of additional benefit and questions about safety, representing unproven use of a proven therapy.** Repeated courses of antenatal corticosteroids have been shown in humans and animals to improve lung function and the quantity of pulmonary surfactant.[26,43] They may also have adverse effects on lung structure, fetal somatic growth, and neonatal adrenocortical function, as well as poorly understood effects on blood pressure, carbohydrate homeostasis, and psychomotor development.[25,61] A 2000 NIH Consensus Development Conference found limited high-quality studies on the use of repeated courses of antenatal steroids.[64] **The consensus statement discouraged routine use of repeated courses of antenatal corticosteroids.** Published preliminary reports of infants exposed to multiple doses of antenatal steroids reaching school age are emerging.[9] A recent meta-analysis of infants who were exposed to more than one course of antenatal corticosteroids concluded that "although the short-term neonatal benefits of repeated courses of antenatal corticosteroids support their use, long-term benefits have not been demonstrated, and long-term adverse effects have not been ruled

out. The adverse effect of repeated doses of antenatal corticosteroids on birth weight and weight at early childhood follow-up is a concern. Caution should therefore be exercised to ensure that only those women who are at particularly high risk of very early preterm birth are offered treatment with repeated courses of antenatal corticosteroids."[27] **The American College of Obstetricians and Gynecologists (ACOG) recommends a repeat course of antenatal steroids if the fetus is less than 34 weeks of gestation and the previous course of antenatal steroids was administered more than 14 days earlier.[6]**

POSTNATAL STEROID THERAPY

Postnatal glucocorticoids, administered to the infant after birth, have been widely used despite weak evidence of long-term benefit and suggestions of possible harm, illustrating use of an uncertain therapy.[53] Despite early calls for caution in the use of postnatal corticosteroids to decrease the risk for CLD and limit ventilator time, they were used liberally in the 1990s.[88,91] **A number of years passed before RCTs of postnatal corticosteroid administration included long-term follow-up.** Taken together, these studies showed positive short-term effects on the lungs. Studies also showed increased blood pressure and blood glucose concentrations in the short term; increased incidence of septicemia and gastrointestinal perforation in the intermediate term; and with dexamethasone administered soon after birth, abnormal neurodevelopmental outcome, including cerebral palsy, in the long term.[3,31,46,54,91] An increased risk for septicemia should have been anticipated, because it was first identified in an RCT by Reese et al.[74] over 50 years earlier.

In 2002, the American Academy of Pediatrics (Committee on Fetus and Newborn) and the Canadian Paediatric Society (Fetus and Newborn Committee) advised against the use of systemic dexamethasone and suggested that "outside the context of a RCT that include assessment of long-term development, the use of corticosteroids should be limited to exceptional clinical circumstances (e.g., an infant on maximal ventilator support and oxygen requirement)."[2] A 2005 reanalysis of many of the same data by Doyle et al.[31] suggests that relative risks and benefits of postnatal corticosteroids vary with level of risk for BPD. When the risk for BPD or death is high, the risk for developmental impairment from postnatal corticosteroids might be outweighed by benefit.[33, 36] Watterberg et al.[100] suggested that hydrocortisone might have the benefits of dexamethasone on the lungs without adverse neurologic effects. Following these statements, the exposure of at-risk premature infants decreased dramatically.[99,100] After reviewing the short-term and long-term effects of systemic and inhaled corticosteroid use for the prevention and treatment of CLD/BPD in the VLBW infant, both the AAP and the Canadian Pediatric Society issued and reaffirmed position statements regarding the use of postnatal steroids.[14,15,52]

QUALITATIVE RESEARCH EVALUATING EXPERIENCES IN THE NEONATAL INTENSIVE CARE UNIT

The contribution of qualitative research to EBP is evident when "best evidence from RCTs" may or may not work within the context of specific NICU environments. The context can be quite variable and influenced by practitioners, staff, the unit leadership, and family influence within the unit. **The implementation of family-centered care in the NICU has shown promising outcomes, including minimizing parental stress related to the technology and complex care of a tiny, fragile preterm infant.[59] An environment of family-centered care has also contributed in a positive way to the success of the implementation of clinical practice guidelines and evaluating outcomes.[32]** An additional area garnering focus in recent qualitative research is discharge planning for VLBW infants and how teams have implemented EBP projects to address the issues identified as key to parental success once the infant is discharged to home.[62,66,73,77] Findings suggest that discharge planning must include early integration of parents into the care team, CPR readiness of parents, how to deal with emergencies facing parents at home, and supportive infant care of the fragile infant for successful transition to home.

Qualitative studies are useful when limited information exists about a phenomenon or a deficiency is evident in the quality, depth, or detail of research in a specific area of clinical practice. **Qualitative research contributes to EBP in several**

areas: (1) describing patient needs and experiences; (2) providing the groundwork for instrument development and evaluation; and (3) elaborating on concepts relative to theory development.[60]

Systematic reviews and meta-analyses are emerging in qualitative literature researching parental experiences in the NICU.[40,65] In neonatology, qualitative studies provide in-depth views of parental and provider experiences within the NICU setting to humanize the health care of fragile infants. **Parents of infants who require NICU care begin an experience of parenthood in an unfamiliar and intimidating environment that results in delayed attachment**[47,79,80]**; high levels of stress, including anxiety, depression, trauma symptoms, and isolation (both physical and emotional) from their infant**[16,38]**; lack of disclosure of their infant's condition; and a lack of control.**[19] Mothers often experience feelings of ambivalence, shame, guilt, and failure because the infant is in the NICU.[79] Parents also experience the tension between exclusion and participation in their infant's care.[101,102,103] In contrast, **parents describe factors that contribute to parental satisfaction in the NICU, including assurance, caring communication, provision of consistent information, education,**[24] **environmental follow-up care, appropriate pain management,**[38] **parental participation in care, and emotional, physical, and spiritual support.**[24] Conversely, health care professionals' experiences of parental presence and participation in the NICU revealed similar findings to those described by parents: the need to develop a caring environment for parents to be present and take care of their child by guiding parents and giving parents permission to care for their child and the need for personnel training in the art of dealing with parents in crisis, identifying a balance between closeness and distance, and dealing with parental worry.[102,103]

Quality care is a major issue currently evaluating the delivery of health care services, yet little research has been conducted on what parents of premature infants perceive as quality nursing care. Price[72] used **a qualitative approach to reveal the meaning of quality nursing care from parents' perspectives and identified concepts inherent in the process of receiving quality nursing care. Four stages were identified: (1) maneuvering, (2) a process of knowing, (3) building relationships, and (4) quality care. For parents, nontechnical aspects of care, such as comforting infants after painful procedures, were as important as the technical aspects of care.** Another qualitative study revealed seven categories that influence changes in practice: (1) staffing issues, (2) consistency in practice, (3) the approval process for change, (4) a multidisciplinary approach to care, (5) frequency and consistency of communication, (6) rationale for change, and (7) the feedback process. Three categories further delineate quality care: human resources, organizational structure, and communications.[103] Conversely, nurse descriptions of quality care included five core measure sets for evidence-based developmental care: (1) protected sleep, (2) pain and stress assessment and management, (3) developmental activities of daily living, (4) family-centered care, and (5) providing a healing environment.[28] Nurses also revealed their experiences in developmental care as "walking the line between the possible and ideal" illuminated through the five aspects of care: (1) being attentive to the infant-mother dyad, (2) developing parent and provider relationships (the body tells it all), (3) timing is everything, (4) working in the quiet and caring, crowded and distressing space, (5) teamwork—demanding, smooth and helpful.[45] Introducing developmental care in the NICU requires an understanding of expectations, timing, and relationships.

Another aspect currently investigated is the integration of parents as members of the care team in the NICU (Family Integrated Care [FIC]). A recent multicenter, multinational, cluster randomized controlled trial that included 26 tertiary NICUs from Canada, Australia, and New Zealand demonstrated that infants assigned to FIC had improved infant weight gain, decreased parent stress and anxiety, and increased high frequency of exclusive breastmilk feeding at discharge[66] (see Chapter 29).

SYSTEMATIC REVIEW IN PERINATAL CARE AND EVIDENCE-BASED PRACTICE

Evidence-based practice is the integration of the best possible research evidence with clinical expertise and patient needs.[71,92] Examples from the literature, such as those cited in the preceding sections, illustrate how the application of the principles of EBP offer a strong argument countering those who

assert that EBP is nothing more than "typical practice using good clinical judgment." **Proponents of EBP argue that the principal four steps of evidence-based practice—formulating a clinical question, retrieving relevant information, critically appraising the relevant information, and applying the evidence to patient care—provide a foundation for practice that leads to improved newborn outcomes and avoidance of repeating medical disasters.**

Believing that the results of perinatal controlled trials had to be summarized in a manner useful to practitioners, Chalmers[17] and other perinatal professionals from various countries developed a registry of RCTs. They reviewed a vast amount of literature from published trials, sought out unpublished trials, and encouraged those who had begun, but not completed, studies to make them known to the registry. Once gathered, the studies' findings were summarized in "overviews."

A *meta-analysis* is a systematic review of the current literature that uses statistical methods to combine the results of individual studies (preferably well-conducted RCTs with similar characteristics of the participants and the treatments) and summarizes the results.[92] These results produce unbiased estimates of the effect of an intervention on clinical outcomes and are distinguished from nonsystematic reviews in which author opinions often are reported along with the evidence. Table 1.1 and Fig. 1.2 were developed after pooling the results of different studies.

From these systematic reviews, practitioners can learn the strengths or weakness of clinical trials and evaluate the claims of benefit for implementing a strategy. The result of the efforts of Chalmers et al. was the 1989 publication of a remarkably useful book, *Effective Care in Pregnancy and Childbirth*.[18] and an updated edition in 1993.[35] At the end of the book, the authors reported their own views of the reviewed treatments based on conclusions formed in the preceding articles. They found that although some strategies and forms of care were useful, others were questionable. Some interventions believed to be useful were not useful, of little benefit, or, in fact, harmful. In 1992 a companion publication, *Effective Care of the Newborn Infant,*[85] compiled and reviewed neonatal RCTs.

Multiple networks have been developed to perform multicenter RCTs. This is particularly useful, providing an opportunity to see whether treatments have similar effects in different practice settings. It is also useful in that practitioners in individual settings may not always see enough cases to reach robust conclusions. **Rare conditions and rare outcomes are better understood when trials are replicated or findings are pooled.** Systematic reviews provide the opportunity to understand these findings in the context of clinical practice.

About the same time the Chalmers et al. book was published, the **Cochrane Collaboration was established, again largely through the efforts of Ian Chalmers (**www.cochrane.org/index.htm**). The Cochrane Collaboration is a worldwide group with more than 50 Collaborative Review Groups whose members prepare, maintain, and disseminate systematic reviews based primarily on the results of RCTs.** These reviews are published electronically in the Cochrane Library, which contains the Cochrane Database of Systematic Reviews (CDSR: www.cochranelibrary.com/cdsr/about-cdsr), along with editorial comments on these reviews. **Comments come from an international group of individuals and institutions dedicated to summarizing RCTs relevant to health care.** In addition to the Collaborative Review Groups, there are now 14 Cochrane Centers in the world. These centers provide support for the review groups. The Neonatal Group is based at the University of Vermont.[64] **Cochrane Neonatal Reviews are available at www.neonatal.cochrane.org.[63]**

Additional sources of high-grade integrative literature are available to the practicing clinician. Critical appraisal of published research takes considerable time, and several groups assemble high-grade literature using a uniform methodology that is typically described to readers as a supplementary article.[12,13] Reading this article once can inform the practitioner if the method used to assemble a review or guideline is sufficiently rigorous. Also, a number of sites do not produce integrative literature but collect it from a number of sources. Some of these sites discuss the quality of the information presented. If we cannot appraise the method used to collect this information, we should always proceed with caution. Additional reliable sites include the following:

- The Database of Abstracts of Reviews of Effectiveness (DARE) (www.crd.york.ac.uk/CRDWeb), a collection of international reviews including those from the Cochrane Collaboration. Reviewers at the National Health Service Centre for Reviews and

Dissemination at the University of York, England, provide quality oversight, including detailed structured abstracts that describe the methodology, results, and conclusions of the reviews. The quality of the reviews is discussed along with implications for health care.

- The National Guidelines Clearinghouse (www.guideline.gov), maintained by the U.S. Department of Health and Human Services, Agency for Healthcare Research and Quality (AHRQ), that was originally created in partnership with the American Medical Association (AMA) and the American Association of Health Plans (AAHP). This site provides a wide range of clinical practice guidelines from institutions and organizations. Structured abstracts facilitate critical appraisal, and abstracts on the same topic can be compared on a side-by-side table, allowing comparisons of relevance, generalizability, and rigor of research findings. Links also are provided to the full text of each guideline, when available.

Conducting systematic reviews is time-consuming; thus not many are available. Often, the power of RCTs, especially in neonatology, is low. The evidence in published studies does not always apply to our specific patient. In addition, locating relevant evidence is time-consuming and may require access to online resources and a higher level of information-seeking skills than are available. Finally, although recognizing that medical expertise and scientific knowledge are crucial components of neonatal care, these rigorous, objective, scientific evaluations create the potential to overlook valuable experiential knowledge of the NICU provided by practitioners and parents.

Reasons to use an evidence-based approach have been well documented. According to Asztalos,[8] there are basically **two reasons to try to keep up with the literature: (1) to maintain clinical competence, and (2) to solve specific clinical problems.** Phillips and Glasziou[71] suggest that clinicians seek information "just in time" (as a clinician seeing patients) and "just in case" (an almost impossible task to keep up with information pertinent to a particular clinical specialty). The former can be achieved by actively searching for information in filtered, summarized clinical point-of-care resources. FirstConsult (www.firstconsultet.com), DynaMed (https://dynamed.ebscohost.com), and UpToDate (www.uptodate.com/home) fall into this category. The latter, "just in case" learning, also called *surveillance of the literature,* is best achieved by using technology tools to survey the current original literature. These tools include Evidence-Updates from the BMJ (http://group.bmj.com/products/evidence-centre/evidence-updates), auto-alerts, and RSS feeds in PubMed or online databases and journals. Learning about these ever-changing resources is a challenge. **Many hospitals and clinics are beginning to include a clinical librarian or informationist as part of the health care team.**[10,11,12,58,87,98]

Newer and practical resources to support evidence-based health care decisions are rapidly evolving. Large multicenter RCTs answer important clinical questions and provide more robust evidence synthesis and synopsis services that are currently integrated into electronic medical records. DiCenso et al.[30] propose a hierarchic organization of pre-appraised evidence linking evidence-based recommendations with individual patients. This 6S model describes the levels of evidence building from *original single studies* at the foundation, and building up from *syntheses* (systematic reviews, such as Cochrane reviews); *synopses* (succinct descriptions of selected individual studies or systematic reviews, such as those found in the evidence-based journals); *summaries,* which integrate the best available evidence from the lower layers to develop practice guidelines based on a full range of evidence (e.g., Clinical Evidence, National Guidelines Clearinghouse); to the peak of the model, *systematic reviews,* where the individual patient's characteristics are automatically linked to the current best evidence that matches specific circumstances. **Practitioners should start by looking at the highest-level resources available for the problem that prompts research.** These resources have gone through a filtering process to generate evidence that is rigorous and exhibited over multiple studies. **Evidence-based clinical information systems integrate and concisely summarize all relevant and important research evidence about a clinical problem, are updated as new research evidence becomes available, and automatically link (through an electronic medical record) specific patient circumstances to the relevant information.** Fig. 1.1 depicts elements of the 6S model.

At the end of this chapter is a list of additional evidence-based practice resources. To use these resources effectively, individuals must

become familiar with the principles and value of evidence-based patient care.

TRANSLATING EVIDENCE INTO PRACTICE

Literature demonstrates that EBP interventions can produce changes in clinicians' knowledge and skills. Even when it is difficult to demonstrate, EBP may induce changes in health care provider behaviors and attitudes.[92] Changes in clinical outcomes are more difficult to demonstrate. In neonatology, the extent to which Cochrane reviews are used and are in agreement with clinical practice guidelines have been found to be disappointingly low.[14] A quality chasm of evidence exists in NICUs.[34] Enormous variations in the use of established therapies exist, so it is not surprising that multiple neonatal networks throughout the world have demonstrated an unexplained center-to-center variability in outcomes.[39,49,50] There are reports of how EBP can be practiced successfully at the single NICU level.[67] However, the **implementations of "bundles" of EBPs by multiple NICUs using collaborative quality improvement efforts have reported meaningful results.[68,69,70]** Nosocomial infection rates seem to be the outcome most amenable to reduction using quality improvement methods.[29] However, other outcomes, such as chronic lung disease and necrotizing enterocolitis, decrease with similar approaches.[56,69]

In a recent multinational study in NICUs located in 19 European regions (Effective Perinatal Intensive Care in Europe), units were encouraged to implement four high-level evidence practices for infants between 24 and 28 weeks of gestation: delivery in a maternity unit with appropriate neonatal care services, any administration of antenatal corticosteroids before delivery, effective prevention of hypothermia, and surfactant use within 2 hours after birth or early nasal continuous positive airway pressure. While only 58.3% of very preterm infants received all of the four evidence-based practices for which they were eligible, those infants who received all four evidence-based practices had higher risk-adjusted survival without severe morbidity.[104]

Recently the formation of State Collaboratives to implement bundles of EBPs[42] using the Plan-Do-Study-Act (PDSA) model for improvement[55] has resulted in significant advancement in important outcomes of neonatal care such as decreasing nosocomial infections, increasing use of human milk for premature infants, antibiotic stewardship, and better obstetric care (antenatal use of progesterone for prevention of premature deliveries,[51] antenatal use of steroids, and decreasing the rate of primary cesarean sections).

CLINICAL PRACTICE GUIDELINES

Clinical practice guidelines are systematically defined statements that assist providers and patients with decisions about appropriate health care for specific clinical circumstances.[92] Valid clinical guidelines create components from evidence derived from systematic reviews and all relevant literature. **Essential components that should be considered when implementing the use of selected guidelines are: validity, meaning to be based in the highest level of evidence available; early participation and engagement of the different disciplines that will be affected by the guideline;[1] and detailed instructions for its application.** In addition, "killer *B*s" affect the instructions for application (Box 1.2). Detailed guides for assessing the validity of clinical guidelines have been developed. **The AGREE Collaboration has developed an instrument for assessing the**

BOX 1.2 THE KILLER Bs

Burden: Is the burden of illness (frequency in our community, or our patient's pretest probability or expected event rate [PEER]) too low to warrant implementation?

Beliefs: Are the beliefs of individual patients or communities about the value of the interventions or their consequences incompatible with the guideline?

Bargain: Would the opportunity cost of implementing this guideline constitute a bad bargain in the use of our energy or our community's resources?

Barriers: Are the barriers (geographic, organizational, traditional, authoritarian, legal, or behavioral) so high that it is not worth trying to overcome them?

From Straus SE, Richardson WS, Haynes RB. *Evidence-Based Medicine: How to Practice and Teach It.* 4th ed. London: Harcourt; 2011.

validity of the clinical guidelines, including items focusing on six domains: (1) scope and purpose, (2) stakeholder involvement, (3) rigor of development, (4) clarity of presentation, (5) applicability, and (6) editorial independence (www.agreetrust.org). As stated by Silverman[83]

> *Since ours is the only species on the planet that has achieved rates of newborn survival which exceed 90 percent, it seems to me we must demand the highest order of evidence possible before undertaking widespread actions that may affect the full lifetimes of individuals in the present, as well as in future generations. Here a strong case can be made for a slow and measured pace of medical innovation.*

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EVIDENCE-BASED PRACTICE RESOURCES

DATABASES OF EVIDENCE AND SEARCH ENGINES

ACP Journal Club (http://annals.org/journalclub.aspx): Evidence-based evaluative summaries of articles taken from 100 clinical journals, written by MDs and others, with comments from MDs.

Campbell Collaboration (www.campbellcollaboration.org): An independent, international, nonprofit organization that aims to help people make well-informed decisions about the effects of interventions in the social, behavioral, and educational arenas. The vision of the Campbell Collaboration is to bring about positive social change and to improve the quality of public and private services across the world by preparing, maintaining, and disseminating systematic reviews of existing social science evidence. The Campbell Collaboration's substantive priorities include, but are not confined to, education, social welfare, and crime and justice.

Cochrane Library (www.thecochranelibrary.com): Premier evidence-based medicine resource composed of the following:

- Database of Systematic Reviews containing systematic reviews and meta-analyses conducted by Cochrane Study Groups.
- Database of Reviews of Effects including systematic reviews and meta-analyses from non-Cochrane sources, many with structured abstracts with comments on the reviews.
- Center Register of Controlled Trials: Indexes many trials not included in MEDLINE.

ClinicalTrials.gov (http://clinicaltrials.gov/ct/gui): Provides regularly updated information about federally and privately supported clinical research in human volunteers. Gives information about a trial's purpose, who may participate, locations, and phone numbers for more details.

Current Controlled Trials (www.controlled-trials.com): Allows users to search, register, and share information about randomized controlled trials.

Health Services/Technology Assessment Texts (HSTAT) (http://nlm.nih.gov): A free, Web-based resource of full-text documents that provide health information and support health care decision making. HSTAT's audience includes health care providers, health service researchers, policy makers, payers, consumers, and the information professionals who serve these groups.

Health Technology Assessment (HTA) and National Health Service (NHS) Economic Evaluation Database (EED) (www.crd.york.ac.uk/CRDWeb/SearchPage.asp): This is the HTA Web-based site that features the NHS EED focused on the economic evaluation of health care interventions and technical literature in the United Kingdom.

National National Health Service Centre for Reviews and Dissemination (www.york.ac.uk/inst/crd): Resource for systematic reviews of health economics and technology assessment. Also maintains the DARE, Health Technology Assessment, and NHS Economic Evaluation Databases included in Cochrane.

Turning Research into Practice (TRIP) database (www.tripdatabase.com): Locates high-quality, evidence-based medical literature using this metasearch engine. Some resources in the results list may require subscription.

World Health Organization Clinical Trial Search Portal (www.who.int/trialsearch): Enables researchers, health practitioners, consumers, journal editors, and reporters to search more easily and quickly for information on clinical trials.

DATABASES OF GUIDELINES

Agency for Healthcare Research and Quality. Canadian Medical Association (CMA) Infobase, Membrane Resources tab and then Clinical Practice Guidelines (www.cma.ca): Click on Clinical Resources tab; requires membership. Excellent access to guidelines and other point-of-care resources.

Guidelines International Network (G-I-N) (www.g-i-n.net): Guidelines organized by health topic. Links to worldwide sources of guidelines.

National Guideline Clearinghouse (www.guideline.gov): Use "Detailed Search" link on left for more specific searches. A U.S. resource for evidence-based clinical practice guidelines. A display tool allows side-by-side comparison of guidelines.

National Health Service National Institute for Clinical Excellence (NICE) (www.nice.org.uk): Evidence-based guidance on technology use, clinical care, and interventional procedures.

U.S. Preventive Services Task Force (USPSTF) (www.ahrq.gov-/clinic/uspstfix.htm): A collection of materials related to the work of an independent panel of experts in primary care and prevention that systematically reviews the evidence of effectiveness and develops recommendations for clinical preventive services.

EVIDENCE-BASED PRACTICE RESOURCES

Centre for Evidence-Based Medicine (Oxford, United Kingdom) (www.cebm.net): Major website for learning about, practicing, and teaching EBM. The Toolbox provides valuable resources for learning and practice.

Centre for Evidence-Based Medicine (Toronto, Canada) (www.cebm.utoronto.ca): In addition to learning resources, this site provides links only.

Centre for Health Evidence (www.cche.net): Based in Alberta, Canada, this center provides resources and support for evidence-based practice.

Cochrane Collaboration (www.cochrane.org): This international nonprofit and independent organization is dedicated to making up-to-date, accurate information about the effects of health care readily available worldwide through systematic reviews of medical research.

Evidence Based Medicine Toolkit (www.ebm.med.ualberta.ca): A collection of tools for identifying, assessing, and applying relevant evidence for better health care decision making.

JAMAevidence (www.JAMAevidence.com): Excellent self-paced learning modules based on the JAMA Users' Guides series, featuring interactive activities designed to reinforce learning.

Pediatric Critical Care Evidence-Based Medicine Resources (http://www.pedsccm.org/clinical-resources.php): An online collection of resources and training tools for the pediatric professional.

Understanding Evidence-Based Healthcare: A Foundation for Action (https://training.cochrane.org/resource/understanding-evidence-based-healthcare-foundation-action): A Web course created by the U.S. Cochrane Center that is designed to help the user understand the fundamentals of evidence-based health care concepts and skills.

Perinatal Quality Care Collaboratives (www.cdc.gov/reproductive-health/maternalinfanthealth/pqc-states.html): State quality improvement collaboratives whose websites contain free information about their initiatives, toolkits, resources, and projects.

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2 PRENATAL ENVIRONMENT: EFFECT ON NEONATAL OUTCOME

JENNIFER WOO, SUZANNE M. CARRINGTON, AND ANNE AMBIA

The human fetus develops within a complex maternal environment. Structurally defined by the intrauterine/intraamniotic compartment, the character of the prenatal environment is determined largely by maternal variables. The fetus totally depends on the maternal host for respiratory and nutritive support and is significantly influenced by maternal metabolic, cardiovascular, and environmental factors. In addition, the fetus is limited in its ability to adapt to stress or modify its surroundings. **This creates a situation in which the prenatal environment exerts a tremendous influence on fetal development and well-being.** This influence lasts well beyond the period of gestation, often affecting the newborn in ways that have profound significance for both immediate and long-term outcome.

There is great utility in identifying maternal factors that adversely affect the condition of the fetus. Providers of obstetric care have long used this information to identify the "at-risk" population and design interventions that prevent or reduce the occurrence of fetal and neonatal complications. **It is equally important that neonatal care providers obtain a clear picture of the prenatal environment and use this information before birth to anticipate the newborn's immediate needs and make appropriate preparations for resuscitation and initial nursery care.** After birth, an awareness of the likely sequelae of environmental compromise helps focus ongoing assessment and aids in clinical decision making.

The purpose of this chapter is to help neonatal care providers evaluate maternal influences on the prenatal environment, identify significant environmental risk factors, and anticipate the associated neonatal problems. **Maternal factors and environmental influences are important determinants in neonatal outcome.**

PHYSIOLOGY

Two variables have a critical influence on fetal well-being throughout gestation: uteroplacental functioning and inherent maternal resources. The interplay of these factors is a major determinant of fetal oxygenation, metabolism, and growth. Alterations in the development and function of the placenta also influence fetal growth and development. The fetus may be affected to the point that survival is threatened. Likewise, extrauterine well-being may be compromised.

The placenta has a dual role in providing nutrients and metabolic fuels to the fetus. First, placental secretion of endocrine hormones, chiefly human chorionic somatomammotropin, increases throughout pregnancy, causing progressive changes in maternal metabolism. The net effect of these changes is an increase in maternal glucose and amino acids available to the fetus, especially in the second half of pregnancy.[46,121] Second, the placenta is instrumental in the transfer of these (and other) essential nutrients from the maternal to the fetal circulation and, conversely, of metabolic wastes from the fetal to the maternal system. Adequate maternal and fetal blood flow through the placenta is essential throughout the entire pregnancy.

BLUE type highlights content that is particularly applicable to clinical settings.

Fetal respiration also depends on adequate placental function. Respiratory gases (oxygen and carbon dioxide) readily cross the placental membrane by simple diffusion, with the rate of diffusion determined by the P_{O_2} (or P_{CO_2}) differential between maternal and fetal blood.[51]

Although the placenta mediates the transport of respiratory gases, carbohydrates, lipids, vitamins, minerals, and amino acids, the maternal reservoir is their source. Maternal-fetal transfer depends on the characteristics and absolute content of substances within the maternal circulation, the relative efficiency of the maternal cardiovascular system in perfusing the placenta, and the function of the placenta itself. The fetal environment can be disrupted by inappropriate types or amounts of substances (e.g., ethanol) in the maternal circulation, decreases or interruptions in placental blood flow (e.g., placental abruption), or abnormalities in placental function (e.g., small placenta). Maternal nutrition, exercise, and disease can impair placental uptake and transfer of substances across the placenta to the fetus.

COMPROMISED FETAL ENVIRONMENT

Maternal Disease

DIABETES

The prevalence of diabetes mellitus and gestational diabetes mellitus (GDM) is increasing worldwide. **Diabetes is the most common endocrine disorder affecting pregnancy,** having doubled in the past decade with approximately 4% to 10% of pregnant women in the United States diagnosed with GDM annually with a prevalence of 9.2% annually.[56] This increase is likely fueled by the obesity epidemic and the older age of pregnant women[46] Despite major reductions in mortality rates over the past several decades, the infant of a diabetic mother (IDM) continues to have a considerable perinatal disadvantage. The physiologic changes in maternal glucose use that accompany pregnancy, coupled with either a preexisting hyperglycemia (as found in types 1 and 2 diabetes) or an inability to mount an appropriate insulin response (as seen in patients with GDM), result in a significantly abnormal fetal environment. This is because of the increased level of maternal glucose, often in concert with episodic hypoglycemia, as well as high levels of triglycerides and free fatty acids. Early in pregnancy, this environment may have a teratogenic effect on the embryo, accounting for the dramatic increase in spontaneous abortions and congenital malformations in the offspring of diabetic women with poor metabolic control.[18,51] During the second and third trimesters, the mechanics of placental transport dictate that fetal glucose levels depend on, but are slightly less than, maternal levels.[25] Assuming adequate placental function and perfusion, elevations in maternal glucose lead to fetal hyperglycemia and increased fetal insulin production. Repeated or continued elevations in blood glucose result in fetal hyperinsulinism, alterations in the use of glucose and other nutrients, and altered patterns of growth and development.[18,25,32]

There is increasing evidence that maternal hyperglycemia with impaired glucose tolerance, in the absence of diabetes, increases the risk of neonatal morbidity.[70] Compared with women with normal glucose tolerance, those **with elevated blood sugar have an increased risk of having infants with a birth weight greater than the 90th percentile, increased cord blood C-peptide levels, and increased neonatal hypoglycemia.[76]**

Fetal macrosomia (greater than the 90th percentile for weight) occurs in 25% to 42% of diabetic pregnancies because of hyperinsulinemia. These macrosomic infants suffer increased morbidity and mortality rates from unexplained death in utero, birth trauma, hypertrophic cardiomyopathy, vascular thrombosis, neonatal hypoglycemia, hyperbilirubinemia, erythrocytosis, and respiratory distress.[98,126] Although intrauterine fetal death (IUFD) is an increased risk for pregnant women with preexisting or overt diabetes, the most contemporary literature does not support an increased risk for IUFD for those with true GDM.[98,126] However, there is a **fourfold increased incidence of fetal anomalies in those with fasting hyperglycemia with GDM.**[51,76] Macrosomic infants have an increased risk for shoulder dystocia during vaginal birth, as well as brachial plexus injury, facial nerve palsy, dysfunctional labor patterns, and operative vaginal birth.[51]

In addition to the basic metabolic disturbances, diabetes predisposes the pregnant woman to several other complications, including gestational hypertension, preeclampsia, renal disease, and vascular disease. As a consequence, the fetus may be compromised further by chronic hypoxia and other insults, which can lead to intrauterine demise, prematurity, growth restriction, cardiovascular problems, respiratory

distress syndrome (RDS), and long-term neurologic problems.[18] In terms of predicting perinatal morbidity and mortality, the **prognostically bad signs of pregnancy include diabetic ketoacidosis, hypertension, and maternal noncompliance, though risk of adverse neonatal outcome occurs on a continuum with no clear threshold.[18,51]**

For the woman with GDM, the standard therapy remains subcutaneous insulin, because multiple studies have documented its safety. For women using an oral agent, several medications have been studied for use during pregnancy. Metformin does not cause any short-term adverse effects, but long-term effects on the fetus are unknown because of lack of long-term neonatal follow-up.[11] If metformin is used, it is discontinued after the first trimester because metformin crosses the placenta. Oral glyburide has been studied for women who cannot or will not use subcutaneous insulin. When glyburide was compared to insulin for prevention of perinatal complications (i.e., macrosomia, neonatal hypoglycemia, neonatal hyperbilirubinemia), there was no clear evidence that the use of glyburide resulted in significantly fewer perinatal complications.[144] Therefore, these researchers concluded that the use of glyburide as a first-line treatment is not justified.

In preparing for the delivery of an IDM, the neonatal team should consider the classification of maternal diabetes (type 1 or 2, or gestational). In addition, the quality of metabolic control throughout the pregnancy and labor, maternal complications, and the duration of the pregnancy should be considered, along with indicators of fetal growth and well-being.[70] In cases in which oral hypoglycemic agents have been used, there should be careful assessment of the neonate because sulfonylurea (i.e., glyburide) may cause neonatal jaundice. Glyburide crosses the placenta, as does metformin, with the potential to affect neonatal physiology.[26] Both of these medications are thought to be safe for the neonate during lactation (see Chapter 18**).**

THYROID DISEASE

Thyroid disorders during pregnancy are relatively common. The thyroid hormones *triiodothyronine (T_3)* and *thyroxine (T_4)* cross the placenta in small amounts, though the significance of the transfer has not been well elucidated. The fetus depends on maternal T_4 in the first trimester of pregnancy. Maternal T_4 is transferred to the fetus throughout pregnancy.[13] At 8 to 10 weeks of gestation, the fetal thyroid begins to concentrate iodine and produce T_4. At approximately 24 weeks, thyroid-stimulating immunoglobulins (TSIs) or thyroid-stimulating hormone receptor antibodies (TRAbs), which are classes of immunoglobulin G (IgG), cross the placenta and stimulate fetal thyroid. Iodine is readily transferred from the mother to the fetus. **The fetal thyroid gland concentrates iodine and synthesizes its own hormones as early as 10 to 12 weeks of gestation; this is independent of maternal thyroid function.** Maternal T_4 contribution continues to remain important throughout gestation.[113] Maternal thyroid hormones are believed to be important for fetal neurologic development in the first trimester, and untreated hypothyroidism has been associated with a decrease in the intelligence quotient (IQ) of offspring.[2,51,92]

In analyzing thyroid function tests during pregnancy, reference ranges for normal function are different. Thyroid-stimulating hormone (TSH) is the best test of thyroid function in pregnancy. However, both the lower and upper limits of normal for pregnant women are lower than for nonpregnant women.[2]

Subclinical hypothyroidism is defined as an elevated TSH with a normal free T_4 level. In patients with subclinical hypothyroidism, thyroid peroxidase antibody (TPO-Ab) levels should be measured. If the pregnant woman has subclinical hypothyroidism and is TPO-Ab positive, treatment with levothyroxine is indicated because of the increased risk of pregnancy loss, preterm delivery, and neonatal hospitalization.[2,113] Pregnant woman who are TPO-Ab negative do not need treatment. Pregnant women with overt hypothyroidism, defined as an elevated TSH with low free T_4 levels, should be treated with levothyroxine[53] Lack of treatment during pregnancy is associated with increased neurodevelopmental delay in offspring, pregnancy loss, prematurity, preeclampsia, low birth weight, and placental abruption.[2] Treatment with replacement hormone during pregnancy is well tolerated by the fetus and reduces these risks.[53] However, a recent study showed that children of women treated for subclinical hypothyroidism did not have significantly better cognitive outcomes through 5 years of age than children whose mothers were not treated.[39]

Maternal hyperthyroidism presents a different situation. Thyroid-stimulating antibodies, commonly found in patients with Graves' disease, as well as many of the drugs used to treat hyperthyroidism, cross the placenta and can have a significant effect

on the fetus. Antibodies, including long-acting thyroid stimulant and TSIs, can increase fetal thyroid hormone production. High levels are associated with fetal and neonatal hyperthyroidism. Untreated Graves disease with maternal thyrotoxicosis has been linked to preterm delivery, intrauterine growth restriction (IUGR), low birth weight, and stillbirth.[128] **In rare cases, the offspring of women with Graves' disease may themselves have this condition. In fetuses and newborns, this is evidenced by elevations in heart rate, growth restriction, prematurity, goiter, and congestive heart failure.[53]** Administration of antithyroid medication to the mother can decrease thyroid hormone production in both the mother and the fetus but may result in fetal hypothyroidism and goiter.[53] In the first trimester, propylthiouracil (PTU) is the safest therapy, since methimazole has been associated with increased rate of congenital malformations.[53] In the second and third trimester, either propylthiouracil or methimazole are equally safe.[2]

Another maternal antibody, TSH-binding inhibitor immunoglobulin, also crosses the placenta and can prevent the expected fetal thyroid response to TSH. The result is a transient fetal and neonatal hypothyroidism. Iodine deficiency in the mother is another cause of fetal and neonatal hypothyroidism and, in its severe form, leads to cretinism because of the fetus's dependence on maternal iodine reserves.[53]

PHENYLKETONURIA

Phenylketonuria (PKU) is an inherited disorder in which an enzymatic defect precludes conversion of the essential amino acid *phenylalanine* to *tyrosine.* **This metabolic derangement is evidenced by an accumulation of excessive amounts of phenylalanine and alternative pathway byproducts in the blood, and these are toxic to the central nervous system (CNS).** Historically, PKU resulted in virtually certain mental retardation; affected individuals often were institutionalized and rarely reproduced. With the advent of universal neonatal screening in the United States since the 1960s and effective dietary treatment to prevent hyperphenylalaninemia during infancy and early childhood, genetically affected persons may avoid the devastating effects of this disease, have relatively normal development, and become pregnant. For women who do conceive, PKU poses a significant environmental risk for their developing fetus. The care of these women and their infants presents a unique perinatal challenge.

An estimated 3000 healthy young women of childbearing age with successfully treated PKU are in the United States.[105] However, most discontinued their special diet in childhood because, at the time, most doctors believed it was safe to do so. Unfortunately, their blood phenylalanine levels are very high when they become pregnant if they are eating a normal diet. In up to 90% of such cases, the offspring will be microcephalic, and/or have severe developmental delay. These babies also have an increased incidence of low birth weight, congenital heart defects, and characteristic facial features regardless of whether they are themselves affected with PKU, as well as preterm birth and intrauterine fetal death.[129,161] They cannot be helped by the PKU diet, or they suffer from brain damage caused entirely by their mothers' high phenylalanine levels during pregnancy. To prevent such damage, these women should resume their PKU diets, consuming specific types of protein low or free of phenylalanine, during preconception and pregnancy.[8,148,161] Studies have identified improved long-term outcomes when desirable phenylalanine levels (2 to 8 mg/dL) are achieved at least 3 months before pregnancy and maintained throughout gestation.[83] **Phenylalanine levels drop quickly once dietary restrictions are instituted, and there is a strong correlation between maternal blood levels and neonatal outcome.[103,129,148,161,162]**

PKU is an inborn error of metabolism, and approximately 1 baby in 14,000 inherits PKU when both parents have the *PKU* gene and both pass it on to their baby. **Neonatal blood screening will identify these PKU babies. If this screening is performed within the first 24 hours of life, the American Academy of Pediatrics recommends rescreening at 1 to 2 weeks of age to avoid missed cases of PKU.** Once identified, infants with PKU are fed a combination of special formula and breastfeeding with close monitoring of blood and urine levels of phenylalanine (see Chapter 18). When mothers of PKU babies are invested in breastfeeding, they need support to be successful.[23] When treatment is discontinued too soon, risks include blindness, learning disabilities, behavioral disturbances, and a decrease in IQ. When no treatment is instituted at all, phenylalanine accumulates in the bloodstream and causes brain damage and severe developmental delay.[25,29]

RENAL DISEASE

Maternal adaptation to pregnancy involves major changes in renal function and structure. Renal hemodynamic changes begin early in pregnancy and before significant expansion of plasma volume. Renal blood flow increases in the first trimester by 35% to 60% and then decreases from the second trimester to term. Additional changes include an increase in the glomerular filtration rate and effective renal plasma flow, a decrease in renal vascular resistance, an activation of the renin-angiotensin-aldosterone system, and increased retention of sodium and water.[51] These changes place unique demands on the renal system. Women with preexisting renal disease may have a successful pregnancy outcome with proper prenatal care; however, some women experience fetal loss and deterioration in renal function. Furthermore, moderate or severe renal dysfunction complicates pregnancy and increases maternal and fetal risks and adverse outcomes.[73]

Renal disease in pregnancy may occur as a result of urinary tract infections, nephrolithiasis, glomerular disease, or severe hypertension or as a complication of systemic diseases, including diabetes and systemic lupus erythematosus. Regardless of the underlying etiologic factors, pregnancy outcome relates most closely to these factors: the presence of hypertension and the degree of renal insufficiency before and during pregnancy.[73] Many women with renal disorders are hypertensive before pregnancy, and they often develop a superimposed pregnancy-induced hypertension leading to preeclampsia.[152] Even those with previously normal blood pressures run an increased risk for developing hypertension during pregnancy. **The presence of hypertension in these pregnancies represents a significant risk to the fetus and is strongly associated with IUGR, preterm delivery, and perinatal loss.**

Drug therapy to control chronic hypertension has been shown to have a beneficial effect on fetal outcome and generally is continued throughout pregnancy. Renal insufficiency, as measured by creatinine clearance or serum creatinine level, also has implications for fetal outcome. Mild to moderate renal insufficiency (serum creatinine <1.5 mg/dL) is associated with a generally favorable outcome, whereas severe insufficiency (serum creatinine >1.6 mg/dL) often carries an increased risk for perinatal death. Persistent proteinuria also may increase fetal loss, and a urinary protein excretion rate higher than 0.5 g per 24 hours may be an independent predictor of fetal outcome. As a rule, the number of preterm deliveries and growth-restricted infants increases with increasing blood pressure and decreasing renal function.[73]

Bacteriuria occurs in 2% to 7% of pregnancies. If untreated, asymptomatic bacteriuria may lead to pyelonephritis or acute cystitis. **Risks for the fetus are preterm birth and IUGR.** Fetal death is an additional risk with pyelonephritis. Prophylactic antibiotics (suppressive therapy) should be given to women with persistent or frequent recurrence of bacteriuria or a history of pyelonephritis in pregnancy.[170]

Two special circumstances in chronic renal disease are dialysis during pregnancy and pregnancy after renal transplant. Previously, it was felt that women with end-stage renal disease undergoing dialysis rarely become pregnant, and if pregnancy did occur, it was associated with significant perinatal morbidity and mortality risks, with spontaneous abortions reaching 50%. However, more recently, studies show that intensive hemodialysis improves fertility, although the rate of pregnancy is still lower, and can improve pregnancy outcomes.[124] Pregnancy after transplantation is more common and has a more favorable prognosis than pregnancy managed by dialysis.[165] Where maternal serum creatinine remains less than 1.5 mg/dL and the woman is on a stable immunosuppressive regimen, outcomes can be expected to be positive.[73,165] Neonatal outcomes are typically favorable unless there is maternal hypertension with impaired kidney functioning, in which case rates of preterm birth, small-for-gestational-age (SGA) infants, and neonatal mortality increase.[73,165]

NEUROLOGIC DISORDERS

The risks that accompany pregnancies complicated by maternal neurologic disorders vary according to the individual disease entity and pertain to both the course of the mother's disease and the pregnancy outcome. The physiologic and hormonal changes of pregnancy can influence the course of chronic neuromuscular disorders, such as epilepsy, multiple sclerosis, and myasthenia gravis. The medications used to control these disorders can be particularly problematic for the fetus.

The prevalence of *maternal seizure disorders* is about 4 in 1000 pregnancies, and most are treated with antiepileptic drugs (AEDs). The

disorders and/or the AEDs have been associated with increased fetal and neonatal risks, including spontaneous abortion, prematurity, low birth weight, SGA infants, congenital defects, intrauterine demise, neonatal depression, and hemorrhage.[160] In women with preexisting seizure disorders, prepregnancy planning is essential to minimize the risk of congenital malformations. Women anticipating pregnancy should begin daily folic acid supplementation. Maternal folic acid supplementation improves pregnancy outcomes for women taking AEDs and decreases the risk of spontaneous abortion, lower verbal IQ, and birth defects.[77] Women who are anticipating pregnancy should have the dose of their AED changed to the lowest effective dose, and valproic acid should be discontinued.[68] European recommendations include avoiding the use of valproate in women of childbearing age unless there are situations in which pregnancy is highly unlikely.[156]

Significant numbers of epileptic women experience an increase in seizure activity during pregnancy. This may be caused by decreased compliance with medication regimens, physiologic changes associated with pregnancy, and gestational changes in plasma levels of anticonvulsant drugs.[66,94] There is evidence that maternal seizures may compromise fetal oxygenation, possibly because of diminished placental blood flow or maternal hypoxemia resulting from postseizure apnea. For these reasons, control of maternal seizure activity with anticonvulsants is one of the primary goals of prenatal care.

Placental transport of anticonvulsants does occur, resulting in fetal levels that approximate or, in some cases, exceed maternal levels.[77] Although the majority of infants born to women with epilepsy are normal, these infants are at increased risk for poor outcomes.[156] **There is an increased risk of congenital malformations and adverse cognitive outcomes in offspring of epileptic women treated with some types of anticonvulsants.[77,156]** The risks of congenital malformations are highest with the use of valproic acid, and there is some increased risk with topiramate.[68] There is also a higher risk with polypharmacy than for those women on a single agent.[159] The AEDs with the greatest safety profile for use during pregnancy are levetiracetam and lamotrigine, and these medications are recommended if an AED is necessary.[114] Phenytoin, phenobarbital, and carbamazepine are intermediate-risk medications, being much safer than valproic acid and topiramate, but with a lower safety profile than levetiracetam and lamotrigine. **The most common major congenital malformations associated with AEDs are neural tube defects (e.g., spina bifida), orofacial defects (e.g., cleft lip, cleft palate), heart malformations (e.g., ventricular septal defect), urogenital defects (e.g., hypospadias), and skeletal abnormalities (e.g., radial ray defects, phalangeal hypoplasias).[66]** The influence of the seizure disorder itself, as well as genetic makeup, cannot be ignored. **Infants born to mothers treated with anticonvulsants, especially barbiturates, may exhibit signs of generalized depression, including decreased respiratory effort, poor muscle tone, and feeding difficulties. They also may have symptoms indicative of drug withdrawal (see Chapter 11). These symptoms are usually present in the first week of life and include tremors, restlessness, hypertonia, and hyperventilation.[35]** **In addition, abnormal clotting and hemorrhage in the offspring of women treated with phenytoin, phenobarbital, and primidone have been reported. This appears to be caused by a decrease in vitamin K–dependent clotting factors. Hemorrhage usually starts within the first 24 hours, is often severe, and may result in death. Infants born to these mothers should have cord blood clotting studies done, vitamin K prophylaxis soon after birth, and close observation. Breastfeeding should be encouraged, though adverse effects may occur if the mother is taking phenobarbital[77] (see Chapter 18).**

Multiple sclerosis (MS) frequently strikes women during their reproductive years. The onset of MS usually is insidious; the course is marked by a seemingly capricious cycle of exacerbation and remission. A wide range of sensory, motor, and functional changes is associated with this disease; the type and severity of symptoms vary dramatically from one individual to another and in any one patient over time. The disease is a T-cell–mediated autoimmune disease of the CNS triggered by unknown exogenous agents in individuals with specific genetics.[50] Pregnancy usually is well tolerated and may be associated with MS stability or improvement. The reported effects of the disease on pregnancy outcomes, including risk for malformations, cesarean section rates, newborn birth weight, and rate of preterm delivery, are inconsistent. Some groups report no increase in adverse pregnancy outcomes,

whereas others report a higher cesarean and infection rate and a greater number of preterm births in mothers with MS.[102] Alterations in neural function, fatigue, and general weakness may play a role in pregnancy outcomes. However, in women with MS, the disease process itself is not a threat to fetal or neonatal well-being.[50] **The priority for neonatal care providers is to determine the extent of the mother's disability, including her level of fatigue and her ability to care for her infant. The availability of appropriate support systems, both personal and professional, should be assessed, and the required follow-up and referrals should be made.**

Even though the prognosis for these infants is excellent, some factors associated with MS are potentially problematic. Bladder dysfunction, common in women with MS, often results in urinary tract infections during pregnancy. Associated fetal and neonatal problems include preterm delivery and sepsis. Early identification and prompt treatment with appropriate antibiotics should minimize these risks. Despite the fact that many women do have improvement or remission during pregnancy, 17% of women do experience a relapse of their MS, which is more likely in the late second and third trimesters.[5]

An additional area of concern is the variety of drugs administered to MS patients. Immunosuppressants are frequently used during severe exacerbations. The placental transport and fetal risk vary with the individual agent used. It is generally recommended that pregnant women with MS discontinue their disease-modifying drugs (DMDs) prior to conception. If they have to continue their medication because of the risk for relapse, then it is recommended to avoid mitoxantrone, fingelimod, and terflunomide.[82] Conversely, glatiramer acetate, interferon B, and steroids are considered safe.[50,82] A final consideration is the long-term one: The incidence of MS in offspring of a parent with the disease is about 2.5%, compared with 0.13% in the general population; the risk is even greater when a sibling has MS.[50]

Myasthenia gravis (MG) is a chronic autoimmune disease that causes neuromuscular dysfunction and is encountered rarely in pregnancy; only 1 in 20,000 pregnancies is complicated by MG.[90] Cells of the immune system make proteins called *antibodies* that block nerve impulses to the muscles. Antibodies to acetylcholine receptor (AchR) have been found in most affected persons. Distinguishing features include generalized weakness and muscle fatigue with activity. Pregnant women with MG also may experience respiratory compromise resulting from muscle weakness compounded by pressure of the fetus against the diaphragm,[109] as well as difficulty swallowing.[90] The course of MG during pregnancy is unpredictable and may vary in different pregnancies in the same woman.[64] Unmasking or exacerbations of MG occur in approximately 40% of pregnancies and remission in 30%, with the remaining 30% experiencing no change. During the first trimester and the first month postpartum, exacerbations are more likely.[90] Corticosteroids can be used to maintain the remissions of MG and should be continued on the lowest possible doses throughout the pregnancy and postpartum period. Certain immunosuppressive agents, such as methotrexate, cyclophosphamide, mycophenolate mofetil, and rituximab are contraindicated in pregnancy. If a patient is already on azathioprine or cyclosporine A, it may be continued, but these drugs should not be started in pregnancy.[74] Plasmapheresis and intravenous immunoglobulins are the safest modalities to use for an exacerbation and can be effective in the treatment of myasthenic crises during pregnancy.[67] Though uterine smooth muscle is not compromised during labor because it is not affected by AchR, patients with MG may become exhausted during the second stage of labor necessitating instrumental delivery.[90,109]

Infants born to myasthenic mothers may be affected by the drug therapy and the underlying immunologic dysfunction. Increased rates of premature rupture of membranes (PROM), preterm delivery, and cesarean birth have been reported, although a nationwide study found no increased risk in prematurity, LBW, SGA infants, or cesarean delivery.[59,64,167] **An additional risk stems from transplacentally acquired anti–acetylcholine receptor antibodies, which cause approximately 12% to 13% of these newborns to experience a transient, self-limited course of neonatal myasthenia gravis.[59]** It is difficult to predict which pregnancies will result in an affected infant, although infants born to women with very high AchR antibody titers may be at highest risk.[90] **Affected infants usually present within the first 48 hours of life with transient neonatal MG, demonstrating generalized weakness, a feeble cry, diminished**

suck and swallow, and a decreased respiratory effort that may require mechanical support.[64] Therefore, plans should be made in advance for delivery of the mother with MG, and intensive care facilities for the newborn should be available immediately. Neonatal MG generally subsides within 3 to 4 weeks after birth and does not recur.[64]

MG is not a contraindication to pregnancy and can usually be managed well with relatively safe and effective therapies, including maternal rest. Standard therapies for some obstetric complications, such as preeclampsia and preterm labor, may need to be altered in women with MG.[51] Vaginal delivery is recommended if possible.[51] Breastfeeding is not contraindicated but depends on maternal medications and on infant and maternal health postpartum (see Chapter 18).

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is an autoimmune disease that presents primarily in women of childbearing age. The pathogenesis involves the production of autoantibodies and immune complexes. The clinical effects of lupus range from mild or subclinical disease to serious illness affecting multiple organ systems. The leading causes of death are infections and renal failure. In pregnancy, SLE is associated with an increased incidence of preeclampsia, thromboembolic events, spontaneous abortion, preterm delivery, IUGR, congenital defects, and the need for neonatal intensive care.[36,123] Outcome is most favorable when infections, renal disease, and hypertension do not complicate pregnancy and when pregnancy occurs with prolonged disease remission.[57,106,139] One study suggests that 4 months of disease quiescence before pregnancy is enough to ensure a safe pregnancy.[122] The presence of lupus nephritis is the highest risk factor for perinatal complications.[91,122] Lupus nephritis is associated with an increased rate of hypertension, preeclampsia, and preterm delivery.[91] Additionally, it can cause a disease flare, with worsening of renal function.[91] Overall reported frequency of SLE flares in pregnancy is 15% to 60%.[1] When necessary, treatments used with pregnancies complicated by SLE include antiinflammatory, antimalarial, immunosuppressive, and biologic drugs and/or anticoagulants.[57,106]

The neonatal manifestations of SLE are rare and are attributed to the placental transfer of maternal antibodies to the fetus. Usual findings of neonatal lupus include a transient lupuslike rash (erythematous lesions of the face, scalp, and upper thorax), thrombocytopenia, and hemolysis.[1] These findings generally are transient and clear within a few months. A strong association has been established between maternal antibodies to the anti–Ro/SS-A and anti–La/SS-B antigens and congenital heart block, a rare manifestation of neonatal lupus syndrome.[1,122] The fetal heart block may be detected with antenatal testing; some authors believe that antenatal fetal surveillance with nonstress tests (NSTs) should begin at 28 weeks of gestation. Infants are treated with cardiac pacemakers (64% of neonates) after delivery; however, about one-third of affected infants die within 3 years.[106,122]

HEART DISEASE

Significant changes in cardiovascular function accompany normal pregnancy. Plasma and red blood cell volumes rise, heart rate and cardiac output increase, and peripheral vascular resistance falls. These changes facilitate increased uterine blood flow, placental perfusion, and fetal oxygenation and growth. They also increase maternal oxygen consumption and cardiovascular workload and can further compromise the cardiovascular status of women with preexisting serious heart disease. Approximately 2% to 4% of childbearing-age women have concomitant heart disease, which may be congenital (the most common type in the United States) or acquired (which includes valvular disease, cardiomyopathy, and pulmonary hypertension).[101,140,164] In the United States from 2003 to 2012, the incidence of pregnant women with heart disease increased by 24.7%.[101] Pregnancy creates a risk for maternal cardiovascular complications, but especially for those with underlying heart disease, and includes an increased incidence of arrhythmias, heart failure, thromboembolism, and sudden death.[69,115,164] In the United States, cardiac disease during pregnancy is the leading cause of maternal morbidity and mortality.[107] In some cases, such as Eisenmenger's syndrome and primary pulmonary hypertension, the risk to maternal survival is so great that pregnancy is contraindicated.[164] Pulmonary hypertension is associated with an increased risk for major adverse cardiac events during the hospitalization for delivery, especially when there is concomitant cardiomyopathy.[101,154] In general, how well the woman with heart disease

tolerates pregnancy depends on the specific disease process and the degree to which her cardiac status is compromised.

Maternal heart disease also affects the fetus. Fetal risks are the result of genetic factors, alterations in placental perfusion and exchange, and the effect of maternally administered drugs. **The genetic risk is demonstrated by the increased incidence of congenital heart defects that occur in the offspring of parents who have such a defect.** The exact risk depends on the specific parental lesion, mode of inheritance, and exposure to environmental triggers.[115,140]

Alterations in placental perfusion and gas exchange occur when the mother's condition involves chronic hypoxemia or a significant decrease in cardiac output. These factors increase the threat to the fetus, with fetal risk increasing as maternal cardiac status declines. Chronic maternal hypoxemia results in a decrease in oxygen available to the fetus and is associated with fetal loss, prematurity, and IUGR. Significant reductions in maternal cardiac output create decreased uterine blood flow and diminished placental perfusion with a resulting impairment in the exchange of nutrients, oxygen, and metabolic wastes. **Possible fetal and neonatal consequences include spontaneous abortion; IUGR; neonatal asphyxia; CNS damage; need for preterm delivery; and intrauterine, intrapartum, or neonatal death.**[115,140,164]

A wide variety of drugs are used in the management of maternal cardiovascular disease. Although sometimes it is difficult to differentiate drug effects from the effects of the underlying disease, some associations between drug administration and fetal outcomes can be made. Anticoagulants are used to decrease the risk for thromboembolism, especially in women with artificial valves, a history of thrombophlebitis, or rheumatic heart disease. **Oral anticoagulants, specifically warfarin sodium (Coumadin), have been associated with fetal malformations, including nasal hypoplasia and epiphyseal stippling, when administered during the first trimester. They also have been associated with eye and CNS abnormalities when administered later in pregnancy. The incidence of warfarin embryopathy is estimated to be 15% to 25%.** Warfarin also is associated with maternal and fetal hemorrhage. Because of these risks, warfarin is contraindicated in pregnancy except in special circumstances, such as pregnancy in women with prosthetic heart valves. Heparin is considered the preferred agent for anticoagulation therapy during pregnancy. **Heparin does not cross the placenta; therefore it does not result in fetal anticoagulation or neonatal hemorrhage (although maternal hemorrhage still may occur), nor has it been associated with congenital defects. Low-molecular-weight heparin is another alternative for anticoagulation during pregnancy.**[115,140] In general, patients being treated with low-molecular-weight heparin during pregnancy are converted to unfractionated heparin during the final weeks of pregnancy because of the ease of rapid reversal of anticoagulation for labor and delivery. Some studies, however, did not demonstrate any difference in bleeding complications for gravidas continued on low-molecular-weight heparin versus those who were converted to unfractionated heparin.[115]

Antiarrhythmic medications and cardiac glycosides used during pregnancy cross the placenta to varying degrees. They have not been implicated in fetal malformations and, although several have been associated with minor complications, generally are considered safe for use in pregnancy.[115] Reported complications include uterine contractions (quinidine, disopyramide), decreased birth weight (digoxin, disopyramide), and maternal hypotension with a sudden decrease in placental perfusion (verapamil).

Antihypertensives and diuretics also have been used in the treatment of cardiovascular disease during pregnancy. Labetalol and methyldopa are commonly used in pregnant women with chronic hypertension. These medications have been studied in prospective trials that revealed no adverse fetal or maternal outcomes, though methyldopa is not recommended postpartum because it is associated with increased incidence of depression.[115] Their use in the first trimester has also demonstrated safety. Atenolol has been associated with fetal IUGR and abnormal placental growth.[115,140] Calcium channel blockers, such as nifedipine, are also safely used during pregnancy without an increase in major birth defects or adverse neonatal outcomes.[115,140] Diuretic use in pregnancy remains an area of some controversy. **Fetal and neonatal compromise can result from diuretic-induced electrolyte and glucose imbalance and decreased placental perfusion caused by maternal hypovolemia. The use of thiazide diuretics has been linked to neonatal liver damage and thrombocytopenia.** In general,

diuretic use is restricted to women with pulmonary edema or acute cardiac or renal failure.[115]

Although a great number of complications are possible, remember that, with few exceptions, most of the drugs used in the treatment of maternal heart disease can be used in pregnancy if the maternal condition warrants it. **Angiotensin-converting enzyme inhibitors are contraindicated in pregnancy because of an association with fetal injury (renal dysfunction, fetal oliguria, oligohydramnios, fetal skull hypoplasia) and fetal death.**

RESPIRATORY DISEASE

Respiratory function is altered even in normal pregnancy. Changes include a decrease in lung volume and increases in oxygen consumption, tidal volume, and minute ventilation.[79] Significant decreases in maternal respiratory function and oxygenation can result in fetal growth restriction and fetal hypoxia with negative outcomes, but careful management of respiratory disease during pregnancy generally results in a favorable outcome.

Asthma is the most common respiratory disease in pregnancy, occurring in 4% to 12% of women, and the prevalence among pregnant women is rising.[4] For about two-thirds of pregnant women, the course of asthma worsens.[4] **Infants born to women whose asthma is well controlled usually do well;** unstable or worsening disease, especially status asthmaticus, increases fetal risk. Commonly used asthma medications (e.g., long-acting beta agonists, inhaled corticosteroids, oral corticosteroids, other bronchodilators, and cromones) are generally considered safe for use in pregnancy.[111] Although children of women with asthma are 10% more likely to have malformations than those of nonasthmatic mothers, large controlled studies have concluded that most asthma medications had no impact on the overall risk for malformations.[108] The exception is cromone exposure, which slightly increases the risk of fetal musculoskeletal malformation.[108] Additional research is needed to determine whether a real risk exists and to guide asthma treatment during pregnancy. Presently, clinical evidence supports pharmacologic asthma control because the fetus is at greater risk from inadequate control of asthma than from asthma medications.[108]

Fetal risks related to maternal asthma depend on the severity of the condition. Controlled asthma carries few risks for the fetus. However, severe or uncontrolled asthma increases the risk for infant death and the incidence of low birth weight, IUGR, preterm birth (possibly influenced by steroid use), and the need for cesarean delivery.[108] Risks are higher in poorly controlled asthma patients.[20] Noncompliance with treatment, respiratory tract infections, allergens and irritants, smoking, gastroesophageal reflux, and exercise can lead to asthma exacerbations.[111]

Cystic fibrosis (CF) was once considered a lethal childhood disease, but the life expectancy of a person with CF has increased, and one study reports that those who had CF in 2000 will have a life expectancy of over 40 years.[62] With careful planning and appropriate medical care, women with CF of childbearing age may conceive and have successful pregnancies with favorable neonatal outcomes, especially if their nutritional state and lung function remain good.[61,132,155] Women with severe disease may be cautioned to avoid conception because there is a risk for significant deterioration during gestation. Women who are positive for *Burkholderia cepacia* in sputum also have a poorer prognosis.[155] Pregnancy in women with CF is likely to be associated with increased health care utilization and more antibiotic use compared with that of nonpregnant women with CF; a high rate of GDM (14%) compared with non-CF pregnancies; and aggressive interventions to ensure weight gain, including the use of total parenteral nutrition for some.[155] Although pregnancy with CF does not increase maternal mortality risk, women with CF have a shorter life span, and therefore their days as a parent may be limited. Twenty percent of mothers with CF will not live to see their child's tenth birthday and for those with severe CF, 40% will have died.

Fetal risks related to CF include prematurity, IUGR, and perinatal death, caused primarily by maternal hypoxemia and infection. Because all infants born to mothers with CF will be heterozygous carriers for CF (at least), genetic counseling and carrier testing of the father are important components of preconceptual care and early prenatal care.[7,155]

Maternal Behavior

Maternal health behavior is an important component of neonatal and childhood health and may even be the single most important factor for the overall health of a child.[117, 136] Health

behaviors evaluated here are smoking, substance abuse, and nutrition, but other maternal behaviors also influence pregnancy outcomes, such as sleep patterns and exercise. Appropriate preconceptual and prenatal counseling regarding maternal health behaviors can help optimize neonatal health.[117,135]

SMOKING

According to the latest Pregnancy Risk Assessment and Monitoring System (PRAMS) data, 10% of women in the United States smoked during the last 3 months of pregnancy.[22,39,98] Of women who smoked 3 months before pregnancy, 55% quit during pregnancy, and 40% of those who quit during pregnancy resumed smoking within 6 months after delivery.[39] Smoking during pregnancy is an even bigger problem globally.[99] **Maternal smoking during pregnancy is a risk factor for stillbirth, IUGR, placental abruption, placenta previa, PROM, and preterm labor.[22,43]** Mothers with pregestational diabetes who also smoke have an increased risk of congenital anomalies and preterm birth.[32] **Long-term effects include childhood obstructive airway disease, sudden infant death syndrome (SIDS), neurodevelopmental abnormalities (i.e., movement, eating, developmental disorders, and attention-deficit/hyperactivity disorder), early puberty in both boys and girls, and childhood cancer,[22,33,43,72] and concerns about exposure to secondhand smoke continue to escalate.** The exact mechanism by which fetal growth is restricted or fetal health is compromised is not entirely clear; reduced uterine artery blood flow, reduced placental blood flow resulting from vasoconstriction of smaller fetal capillaries in the placental capillary bed, elevated nicotine and carbon monoxide levels, and chronic fetal hypoxia all may play a role. Fetal risk increases with the number of cigarettes smoked, maternal anemia, and poor nutrition.[120] Complications of fetal growth are the most common issues of infants born to smoking mothers. These neonates are at increased risk for low-birthweight birth (<2500 g) and preterm birth, which is both dose-dependent and time-specific.[22] **The babies of smokers may undergo withdrawal-like symptoms manifested by jittery movements, and may be more difficult to soothe.[120]**

Eliminating or reducing smoking, especially by the end of the first trimester, can improve fetal growth and health. Smoking cessation programs consistently implemented during prenatal visits have been shown to significantly improve smoking cessation rates.[34] Smoking cessation during pregnancy must be a major priority in counseling women preconceptually and prenatally because these are times when women may be most receptive to quitting because of a strong desire for a healthy pregnancy and baby.[34] A recent systematic review of digital interventions for smoking cessation during pregnancy found that text messaging and computer-based interventions were the most effective platforms.[71] Nicotine replacement therapy (NRT) may increase smoking cessation rates, but a systematic review cites evidence that when potentially-biased and non-placebo randomized controlled trials (RCTs) are excluded, NRT is no more effective than placebo.[46] Only one trial followed infants after birth and found that NRT promotes healthy developmental outcomes.[47]

SUBSTANCE ABUSE

Prenatal substance abuse rates vary greatly; however, it is estimated that about 11% of childbearing women have used illegal substances.[120] There is a strong association between maternal smoking during pregnancy and use of other substances including cannabis, opioids, cocaine, amphetamines, tricyclic antidepressants, and benzodiazepines.[118] **Use of drugs and alcohol by the mother places the fetus and newborn at risk for a plethora of structural, functional, and developmental problems.** Perinatal morbidity is related to the direct effects of the abused substance on the developing fetus, its sudden withdrawal, the interactions of multiple abused substances, the nutritional effects of addiction on the mother, and the social and health care implications of substance abuse.[80,120]

Alcohol is one of the most commonly abused substances during pregnancy. Although known to be a teratogen since the 1970s, about 40% of women in the United States drink some alcohol during pregnancy, and about 1% to 5% drink heavily throughout pregnancy.[88] Alcohol in the maternal circulation crosses the placenta, resulting in direct fetal exposure to alcohol and its metabolites.[88] **There may be a wide range of effects on the exposed fetus; these include developmental and behavioral abnormalities, spontaneous abortion, stillbirth, craniofacial malformations, growth restriction, preterm birth, CNS dysfunction, and organ or joint abnormalities.[83,89]** The mechanism of fetal injury is not entirely clear but is likely related to

three main factors: a teratogenic effect, hypoxia as a result of increased oxygen consumption, and a diminished ability to use amino acids in protein synthesis.[37] The expression of fetal alcohol effects ranges from subtle to extreme and depends on the timing of exposure, the dose, and the genetic response of the mother and fetus to the effects of alcohol. Secondary factors, such as maternal age, nutritional status, general health, and the effects of other abused substances also may influence outcome.[75,117]

When the more severe effects are exhibited, the condition is known as ***fetal alcohol syndrome (FAS).*** **FAS is characterized by growth restriction; physical dysmorphic features, including facial anomalies (small palpebral fissures, low nasal bridge, indistinct philtrum, thin upper lip, shortened lower jaw); and neurologic dysfunction, including mental retardation and neurodevelopmental deficits.[83] Other physical abnormalities involve the heart, skeletal system, and ears. *Fetal alcohol spectrum disorders (FASD)* is an umbrella term for FAS and other less physically noticeable yet long-term effects of alcohol exposure on the fetus.[37] Infants with FASD also may exhibit problems with suck, tremors, irritability, and hypertonus related to alcohol withdrawal.** Continued abnormalities in motor, behavioral, and intellectual development often persist into childhood. Safe levels of alcohol intake have not been established; therefore women should be advised to avoid alcohol intake during pregnancy.

Chemical dependency in pregnancy is a complex problem and creates a high-risk patient. The mother's reporting of drug use often is unreliable; frequently, more than one substance is involved, and there may be a cycle of drug use and periodic abstinence during pregnancy. In addition, a host of medical and social problems are associated with maternal drug abuse. Substance abusers generally have poor health; infectious diseases, such as pneumonia, sexually transmitted diseases (including human immunodeficiency virus [HIV] infection and acquired immunodeficiency syndrome [AIDS]), urinary tract infections, and hepatitis are common.[24,80,120] Nutrition and prenatal care often are inadequate; anemia frequently is seen. These factors contribute to a poor pregnancy outcome and make it difficult to isolate the effects of any one drug on the fetus. However, several generalizations can be made. The majority of drugs used by the mother, including opiates (e.g., methadone, heroin), barbiturates, and sedative-hypnotic drugs, cross the placenta and affect the fetus. **Fetal risks include growth restriction, malformations, intrauterine demise, prematurity, asphyxia, CNS dysfunction, and neurobehavioral abnormalities. Fetal drug dependence does occur and is associated with neonatal abstinence syndrome (NAS), which is manifested by CNS irritability and vasomotor, metabolic, respiratory, and gastrointestinal dysfunction[120] (see Chapter 11).**

Marijuana (cannabis) is the most commonly used illicit drug during pregnancy.[34] With legalization of marijuana in many states in the United States, about 1 in 20 pregnant women report using marijuana.[151] Perinatal effects of marijuana use on the fetus/newborn include low birth weight and preterm delivery, which is attributable to concomitant tobacco and other substance use,[41,48] altered neurobehavior/sleep, and minimal alteration on motor development.[163] Long-term effects include altered attention/executive function, academic achievement, and behavior.[163] Recommendations are to cease marijuana use during pregnancy and lactation.[17,131]

Cocaine use by the mother merits special attention. Cocaine is a CNS stimulant that produces vasoconstriction, tachycardia, and hypertension in both the mother and the fetus. **Its use during pregnancy has been linked to IUGR, smaller head circumference, genitourinary tract anomalies, placental abruption, stillbirth, RDS, congenital infection, NAS, and cerebral infarcts, as well as impaired performance as measured with the Brazelton behavioral assessment tool.[38]**

All prenatal care providers should thoroughly assess pregnant women for alcohol and substance abuse at each prenatal visit, and treatment interventions should be initiated when abuse is identified. Toxicology screening of maternal blood or urine can verify suspicions of abuse; however, universal screening is not currently recommended. **Neonatal urine or meconium screening can provide an accurate indication of exposure when there are clinical indications of drug effect.** Laws in some states consider prenatal drug exposure to be a form of child abuse; thus the practitioner may be required to report positive drug tests in pregnant women or their newborns (see Chapter 11 for a complete discussion of complications in drug-exposed neonates).

MATERNAL NUTRITION, MALNUTRITION, AND OBESITY

Maternal nutritional status and placental function during pregnancy can significantly influence the growth, development, and health of the fetus and newborn. Nutritional problems that interfere with fetal cell division (increases in cell number) can have permanent consequences. If the fetus is at a stage in which cells are only enlarging (increases in cell size), nutritional deficits may be reversed if a healthy maternal dietary intake is resumed soon enough in the pregnancy. All women presenting for prenatal care should be questioned about their usual dietary intake and should have their weight and height assessed so that body mass index (BMI) can be determined and appropriate nutrition counseling initiated.[138] BMI can be calculated by dividing a woman's prepregnancy weight in kilograms by her height in meters squared; it is the most frequently used single tool in determining obesity. If a woman's prepregnancy weight is unknown, the value obtained at the first prenatal visit should be used. Although the BMI values for classification vary, the Institute of Medicine (IOM) employs the relative weight classification and prepregnancy BMI values as follows[86]:

- Underweight: less than 18.5
- Healthy weight: 18.5 to 24.9
- Overweight: 25 to 29.9
- Obese: greater than or equal to 30

Optimal ranges for weight gain in singleton pregnancies are also based on the IOM recommendations. As a general rule, weight gain should be as follows: underweight women should gain 28 to 40 lb; normal-weight women, 25 to 35 lb; overweight women, 15 to 25 lb; obese women, 11 to 20 lb. The optimal weight gain for women carrying twins is 35 to 45 lb.[86] The IOM guidelines are continually being evaluated, but at least one study confirms that following these guidelines can improve pregnancy outcomes. However, fewer than one-half of women gain the recommended weight during pregnancy, with 43.3% of women gaining above the IOM guidelines.[147] Excessive weight gain in obese women is highly associated with an increased risk of emergency cesarean delivery.[96] A recent study found that the strongest predictor of pregnancy outcome was the amount of gestational weight gain rather than the presence of GDM.[27] Excessive gestational weight gain is an independent factor for fetal macrosomia and birth at less than 37 weeks.

Prenatal nutrition involves more than appropriate weight gain; a variety of healthy foods should be consumed, providing essential nutrients.[169] The dietary reference intakes increase for most nutrients during pregnancy. Protein, iron, vitamin A, and iodine requirements nearly double, yet some nutrient requirements do not change much.[157] Other maternal factors that should be considered when counseling women on nutrition include age, parity, preconceptual nutritional status, preexisting medical conditions, current medical conditions complicating the pregnancy, food likes and dislikes, and cultural influences. Each woman's counseling should be individualized, and referral to a nutrition specialist and other medical specialists may be indicated.

Malnourished and underweight mothers have more perinatal losses and preterm births, and their newborns have lower Apgar scores and more frequently are of low birth weight (<2500 g). This is especially true of significantly underweight women (low BMI) and women with eating disorders, such as anorexia and bulimia, who fail to gain adequate weight during pregnancy.[119,166] SGA newborns, defined as below the 10th percentile birth weight for gestational age, have higher mortality rates in the perinatal period and are at risk for later problems, such as insulin resistance and poor school performance.[166] However, it may be difficult to draw direct correlations between inadequate maternal diet and fetal growth unless the nutritional disturbances are severe. Many fetuses grow well despite suboptimal maternal nutrition, in part because of the complexities of placental transport and the ability of the fetus to be preferentially supplied with some nutrients.

Although reduced birth weight is associated with inadequate carbohydrate, protein, and total caloric intake, inappropriate amounts of other nutrients may also affect the fetus. Vitamin and mineral deficiencies have been linked to miscarriage and stillbirth, congestive heart failure (thiamine), megaloblastic anemia (folic acid, vitamin B_{12}), congenital anomalies, including neural tube defects (folic acid, zinc, copper), and skeletal abnormalities (vitamin D, calcium).[49,65,158]

Recently, a plethora of evidence has been published about the impact of maternal vitamin D deficiency and an association with poor pregnancy outcomes such as preterm birth, preeclampsia, GDM, perinatal depression, SGA infants, and asthma symptoms in

offspring.[138] However, RCTs of vitamin D supplementation to improve perinatal outcomes has resulted in conflicting evidence because of a lack of consistency with dosing regimens and differing gestational ages when supplementation was initiated. One important result of the multiple meta-analyses that have been published about vitamin D supplementation in pregnancy is that there were no incidences of vitamin D toxicity despite using doses as high as 200,000 units intramuscular injection.[138]

Women who become pregnant after surgery are at increased risk for nutritional deficiencies and require close monitoring.[97,149] The current guidelines from the American College of Obstetricians and Gynecologists (ACOG),[9] the American Society of Metabolic and Bariatric Surgery, the Obesity Society, and the American Association of Clinical Endocrinology[110] recommend delaying pregnancy for at a minimum of 12 to 18 months after bariatric surgery.[97] Recent meta-analysis shows a decreased risk of GDM, large-for-gestational-age (LGA) infants, gestational hypertension, all hypertensive disorders, postpartum hemorrhage, and cesarean delivery rates in pregnant women after bariatric surgery.[97] However, there is an increased risk of SGA infants, IUGR, and preterm birth after bariatric surgery.

Obesity is not only an epidemic in the United States and other developed countries, but is a major problem globally.[21,171] Public health officials now cite obesity as the leading health problem confronting women today. Obesity is a complex problem resulting from a combination of genetic, cultural, behavioral, socioeconomic, and environmental influences. Obesity affects all organ systems and contributes to a multitude of physiologic complications, such as cardiovascular disease, GDM, infections, preeclampsia, and other adverse perinatal outcomes.[116,171]

Approximately 30% of pregnant women are obese (BMI ≥30) and at risk for perinatal complications.[116] Overweight, obese, and morbidly obese women (BMI >40) are at risk for chorioamnionitis, preeclampsia, stillbirth, cesarean delivery, instrumental delivery, postpartum hemorrhage, perineal lacerations, and prolonged hospital stay.[21,171] **Their offspring may suffer macrosomia, shoulder dystocia, meconium aspiration, fetal distress, preterm birth, early neonatal death, abnormal labor, complications from cesarean birth, birth defects, and higher risk of admission to the NICU.**[116,171] A 1% decrease in the number of obese pregnant women in the United States would result in 16,000 fewer cesarean births per year.[44]

In addition, obese women may be struggling with associated psychosocial problems, such as poor self-esteem, guilt about weight, depression, and ridicule from family and others. Some may not seek prenatal care until pregnancy is well into the second or third trimester. Thus obese women should be considered at high risk for childbearing complications, and these women and their fetus/newborn should be monitored closely throughout gestation and the perinatal period. Preconception or early pregnancy dietary counseling, taking into account the increased risk of GDM for women with obesity, and promoting routine exercise and sleep hygiene can improve maternal health and pregnancy outcomes. Women with obesity are less likely to stay within the gestational weight gain recommendations, yet staying within weight gain guidelines promotes normal birth weight (appropriate for gestational age) and improves perinatal outcomes.[116]

In conclusion, maternal health behavior, including smoking, problems with nutrition, and drug use, before and during pregnancy is associated with adverse outcomes for the newborn and also long-term health risks of the newborn well into adulthood. Supportive, informed prenatal care for pregnant women at risk is essential to improved newborn health.

Obstetric Complications

ANTEPARTUM BLEEDING

Maternal cardiovascular support is crucial to fetal well-being. Chronic blood loss can lead to maternal anemia and a related decrease in oxygen-carrying capacity. Uncompensated acute bleeding results in diminished blood volume, decreased systolic pressure, decreased cardiac output, and ultimately decreased placental perfusion. The net effect on the fetus is decreased oxygenation and impaired nutrient delivery.

Gestational bleeding in the first or second trimester of pregnancy has been linked to increased risk of preterm labor, preterm birth, PROM, and low birth weight.[42] The most common causes of hemorrhage late in pregnancy include placental abruption and placenta previa. The incidence of placental abruption is approximately 1%,[19] and it is more common in older pregnant

women.[46] In an abruption, a normally implanted placenta separates from the uterine wall before the time of delivery, resulting in maternal bleeding and a functional decrease in uteroplacental size. A relationship between hypertensive disorders, cocaine use, and cigarette smoking and an increased incidence of abruptions has been reported.[51] In those with preterm rupture of membranes, the incidence of placental abruption is 2% to 5%.[14] In the presence of an intrauterine infection, the relative risk increases ninefold. The separation may be partial or complete, involving peripheral and/or central portions of the placenta. **Fetal compromise relates to the extent of the separation and to the frequent need for preterm delivery.** When the abruption is small and bleeding is minimal, the pregnancy may continue without significant fetal compromise; however, remember that the decrease in uteroplacental surface area is irreversible and reduces the absolute placental capability. As the fetus grows or experiences additional stressors, its ability to tolerate the abruption may change. Extensive abruptions are poorly tolerated by both the fetus and mother; the resulting maternal hemorrhage and decreased placental function lead to fetal asphyxia and, without immediate intervention, to intrauterine demise.

A ***placenta previa*** exists when the placenta lies abnormally low in the uterus and to some extent covers or encroaches on the internal cervical os. In the latter part of pregnancy, the normal elongation of the lower uterine segment and changes in the cervix disrupt the attachment of the overlying placenta. This generally presents as episodic, painless maternal bleeding, often accompanied by preterm labor. To avoid active labor with resulting maternal hemorrhage, fetal lung maturity is assessed at 36 to 37 weeks.[28] If the lungs are sufficiently mature, a cesarean delivery is scheduled before the onset of labor. Multiparity, maternal age, prior intrauterine operations (≥3), and cigarette smoking are risk factors for placental previa.[46,63,133] **Fetal compromise relates to the extent of the previa, severity of maternal hemorrhage, degree of the resulting fetal hypoxia, degree of impaired fetal growth, and gestational age at delivery.[51,130]**

Other placental abnormalities leading to antepartum bleeding include velamentous insertion and vasa previa. A ***vasa previa*** occurs when naked fetal vessels traverse the cervical os below the level of the fetal presenting part; it is associated with a high perinatal mortality rate. A ***velamentous insertion*** is defined as the insertion of the umbilical cord into the chorioamnionic membranes rather than the mass of the placenta. These unprotected cord vessels have a higher rate of rupture. Rupture requires emergency cesarean delivery to prevent fetal demise and maternal hemorrhage. Antenatal diagnosis of vasa previa and velamentous insertion with ultrasonography enables hospitalization in the third trimester with planned delivery before the onset of labor.[31]

HYPERTENSIVE DISORDERS OF PREGNANCY

Chronic hypertension in pregnancy, defined as hypertension diagnosed before pregnancy or before 20 weeks of gestation, complicates 1% to 6% of births in the United States each year. **Chronic hypertension is associated with IUGR, preterm birth, placental abruption, and stillbirth.[51]** The degree of fetal compromise is related to the duration, degree, and control of maternal hypertension.[51] Women with chronic hypertension have a 25% risk for developing superimposed preeclampsia.[51,135]

Gestational hypertension was defined by the Working Group on Research on Hypertension in Pregnancy as hypertension arising after 20 weeks in the absence of proteinuria.[135]

Preeclampsia, a type of pregnancy-induced hypertension, is a condition in which hypertension, accompanied by proteinuria and edema, develops during the second half of pregnancy in women with or without preexisting hypertensive disease. It is most common in primigravidae, obese women, and women with multiple gestations and molar pregnancies, family history of preeclampsia, and history of pregestational diabetes mellitus.[51] As a perinatal complication, preeclampsia is significant because of its high toll in terms of both maternal and fetal well-being.

Pregnancy is normally associated with vasodilation and decreased peripheral vascular resistance. The net effect is that, even though there is a significant increase in blood volume, maternal blood pressure does not increase during pregnancy. In contrast, pregnancy-induced hypertension is associated with vasoconstriction and an increase in peripheral vascular resistance and arterial pressure. The result is a reduction in blood flow to the vital organs, including the kidney, liver, brain, and uterus; reduced maternal blood volume; and a host of maternal hepatic, CNS, and coagulation

abnormalities. **Associated fetal and neonatal risks include IUGR, prematurity with all of its attendant problems, perinatal asphyxia, and perinatal death.** The risk to the infant increases with earlier onset and increasingly severe maternal disease, such as chronic hypertension with superimposed preeclampsia. **Maternal seizures (eclampsia) further compromise the fetus by promoting hypoxemia and acidosis, which can result in intrauterine demise.**

HELLP syndrome, a severe form of pregnancy-induced hypertension manifested by hemolysis, elevated liver enzymes, low platelets, and renal function abnormalities, carries a high risk for fetal and maternal death. In many cases of HELLP syndrome, immediate delivery is indicated regardless of the gestational age of the fetus.[51] The use of steroids in HELLP syndrome has been shown to improve maternal oliguria, mean arterial pressure, mean increase in platelet count, mean increase in urinary output, and liver enzyme elevations. However, no evidence suggests an improvement in maternal and perinatal mortality or morbidity rates with the use of maternal corticosteroids except with regard to improvement in fetal lung maturity.[51]

Drugs commonly used to treat pregnancy-induced hypertension include magnesium sulfate, hydralazine, labetalol, nifedipine, and other antihypertensive agents. Magnesium sulfate is the most commonly used agent in the United States for the prevention of maternal seizures and has been shown to be more effective than other regimens.[51]

Hypotonia and CNS depression have been reported as neonatal side effects, but magnesium therapy appears to be safe for the fetus.[150] Hypotonia and CNS depression are more likely the result of coexisting complications, such as prematurity and asphyxia. Hydralazine and other antihypertensives are used in the treatment of severe maternal hypertension; actions include relaxation of the arterial bed, decreased vascular resistance, and decreased blood pressure. Maternal response to antihypertensives must be monitored carefully, because precipitous decreases in blood pressure reduce placental perfusion and further compromise the fetus.

INFECTION

Group B streptococcus (GBS) is a major cause of sepsis, meningitis, and death among newborn infants. It is estimated that 10% to 30% of all pregnant women are colonized with GBS in the vagina or rectum. The ACOG Committee on Obstetric Practice now recommends "vaginal or rectal group B streptococci screening cultures at 35 to 37 weeks of gestation for all pregnant women." Treatment for women with a positive culture, GBS bacteriuria in the current pregnancy, or a previously GBS-infected infant is usually penicillin.[6]

PRETERM LABOR

Preterm birth, **defined as any birth before 37 weeks of gestation, poses an unparalleled threat to neonatal survival and well-being. In the United States, 12% of all births are preterm, and prematurity accounts for 70% of all neonatal deaths.[15]** Its cost, both human and economic, is staggering, and its prevention is a primary focus of modern obstetric care. Prevention is best accomplished through an aggressive effort to identify women at risk and close follow-up to achieve early recognition and appropriate intervention should preterm labor occur. Unfortunately, many women continue to receive inadequate prenatal care or no care at all. Even women who obtain early and ongoing care often fail to recognize the signs of preterm labor and delay reporting symptoms until intervention becomes difficult if not impossible.[51]

Risk assessment markers in clinical use today include an extensive review of obstetric, social, and medical history.[51] Measurements of cervical length remain controversial. There are proponents of universal cervical length screening in those women with no history of prior preterm birth. Applying universal screening of cervical length presents the difficulties of patient access and the potential for unnecessary intervention. While the choice of universal screening in a low-risk population is left up to the discretion of the prenatal provider, if an incidentally short cervix is noted at the time of the second-trimester ultrasound examination, subsequent evaluation is necessary.[12]

Fetal fibronectin is a glycoprotein secreted by fetal membranes. Its presence in cervical-vaginal secretions between 22 and 35 weeks of gestation has been associated with an increased risk for preterm labor and delivery. Its absence (high negative predictive value) can be used to identify patients who are at low risk for preterm delivery. ***Cervical length*** is assessed by three consecutive measurements using transvaginal ultrasonography. The average length of the cervix varies with gestational change but

is approximately 4 cm in length from 26 weeks. Length of cervix has been inversely correlated with risk for preterm birth. Thus a combination of fetal fibronectin and cervical length may be used to assess the risk for preterm delivery for a given patient.[52]

Depending on onset of short cervix in pregnancy, cervical cerclage, intramuscular progesterone (17-hydroxyprogesterone caproate), and vaginal progesterone have been used to prevent preterm labor with encouraging success.[29,142] A recent systematic review and meta-analysis of RCTs of vaginal versus intramuscular progesterone found that daily vaginal progesterone, begun at 16 weeks of gestation, is a reasonable, if not better alternative for the prevention of recurrent spontaneous preterm, singleton birth.[142] However, the quality of the research data was evaluated as low or very low *grade,* indicating that the true effect may be different from the estimate of effect in the three RCTs included in the meta-analysis.[142] More recent studies found differing outcomes based on the types of progesterone used[95,145] and that vaginal progesterone was not associated with an increase in GDM risk.[172] The Ohio Perinatal Quality Collaborative launched a statewide initiative to reduce premature births by 10% by promoting progesterone prophylaxis and achieved a 13% reduction in births before 32 weeks in women with prior preterm birth.[85]

Even though there has been some conflicting evidence showing efficacy of intramuscular progesterone, it is still recommended for use in women with risk factors for preterm birth.[95] Evidence supports the use of vaginal progesterone for women with short cervix and no prior history of preterm delivery and early cerclage with short cervix and history of preterm delivery.

Although in many specific instances a definitive cause cannot be identified, it is possible to identify several factors that generally are associated with preterm labor and delivery.[12] **When preterm labor cannot be halted, it culminates in the delivery of a physiologically immature infant. The result is a host of neonatal problems that relate largely to the degree of immaturity** and also to compounding problems, such as infant anomalies or maternal disease, and to the events that led to the preterm delivery (e.g., asphyxia resulting from a bleeding placenta previa). **Problems commonly encountered in preterm infants include respiratory distress, asphyxia, hyperbilirubinemia, metabolic disturbances, fluid and electrolyte imbalances, neurologic and behavioral problems, infection, nutritional deficits and feeding problems, ineffective thermoregulation, cardiovascular disturbances, chronic respiratory disease, and hematologic disturbances.**

Beta-sympathomimetic agents are sometimes used to prolong pregnancy in women having uterine contractions but no sign of infection. Mothers may experience tachycardia and dysrhythmias, hyperglycemia, hypokalemia, anxiety, nausea, and vomiting. Myocardial ischemia and pulmonary edema are rare but serious maternal side effects. The fetus also may develop tachycardia and hyperglycemia. **Neonates born after beta-sympathomimetic therapy may develop a rebound hypoglycemia in response to in utero hyperglycemia and overproduction of insulin. Beta-sympathomimetic tocolytic agents increase fetal aortic blood flow and fetal cardiac output that might increase fetal systolic pressure and cerebral blood flow, which can lead to an increased incidence of intracranial bleeding in immature fetal brains.** More recent studies show lower risk of side effects and improved prolongation of pregnancy from nifedipine compared with beta-sympathomimetic tocolytics (see paragraph on calcium channel blockers later).[87]

Magnesium sulfate has also been employed as a tocolytic. Magnesium sulfate decreases muscle contractility, thereby inhibiting uterine activity and effectively interrupting preterm labor. **Neonatal consequences of maternal magnesium administration include decreased muscle tone and drowsiness, as well as decreases in serum calcium level.[92]** Serious maternal complications can occur with concomitant usage of beta-adrenergic receptor agonists or calcium channel blockers.[12] Antenatal administration of magnesium sulfate for neuroprotection of the preterm fetus, especially related to gross motor function, is well established.[55,58,146]

Prostaglandins play an important role in the onset of labor. *Prostaglandin synthetase inhibitors,* such as indomethacin, are a class of pharmacologic agents that interfere with the body's synthesis of prostaglandin, thereby inhibiting prostaglandin-mediated uterine contractions. These drugs have been used to treat preterm labor. They can cause in utero constriction, or closure, of the ductus arteriosus with resulting development of fetal pulmonary hypertension and congestive heart

failure. They also may lead to **oligohydramnios and must be used with caution, especially late in the third trimester. Other neonatal risks include decreased platelet activity and gastrointestinal irritation.**[92] Use of cyclooxygenase (COX-2) inhibitors in preterm labor treatment is being investigated.[100]

Calcium channel blockers, such as nifedipine, also have a demonstrated ability to interfere with the labor process. Uterine contractility is directly related to the presence of free calcium. Increased calcium concentration enhances muscle contractility, whereas decreased calcium levels inhibit contractility. Calcium antagonists block the entry of calcium into cells and inhibit uterine muscle contraction. In animal studies, these drugs have been associated with fetal acidosis. **However, lower umbilical artery pH values or lower Apgar scores have not been associated with nifedipine.**[92]

Corticosteroid treatment of pregnant women who are at sufficient risk to deliver prematurely was first introduced in 1972 to enhance fetal lung maturity. Human studies suggested possible benefits in reduction of the incidence and severity of RDS and the incidence of patent ductus arteriosus. **Little or no evidence supported a reduction in mortality rate or in the incidence of intraventricular hemorrhage, chronic lung disease, sepsis, necrotizing enterocolitis, or retinopathy of prematurity with repeated antenatal corticosteroid therapy. Some of the suggested fetal risks of repeated antenatal corticosteroid therapy include decreased somatic and brain growth, adrenal suppression, neonatal sepsis, chronic lung disease, and death.** All pregnant women between 24 and 34 weeks of gestation who are at risk for preterm delivery within 7 days should be considered candidates for antenatal treatment with a single course, such as 2 × 12 mg of betamethasone administered intramuscularly, within 24 hours. Recent data have also shown that administration of betamethasone in the late preterm period between 34 and 38 weeks of gestation is associated with decreased neonatal respiratory complications.[12] **The evidence to date is clearly against the routine administration of multiple antenatal steroid courses.**[16,134] **The latest ACOG** practice **bulletin recommends a single repeat course of antenatal corticosteroids for women: (1) who are less than** $^{36}/_{7}$ **weeks of gestation, (2) who are at risk of preterm delivery within 7 days, and (3) whose prior course of antenatal steroids was more than 14 days previously.**[16]

ENVIRONMENTAL EFFECTS OF LABOR ON THE FETUS

Effects of Contractions

During labor, the dynamics of uterine contractions alter the intrauterine environment and influence the fetus. **A "healthy" fetus is equipped to withstand the challenge of labor, but when the fetus is compromised or the labor is dysfunctional, the fetus can be taxed beyond its capacity, placing it at risk for further compromise, asphyxia, or intrauterine death.**

Strong uterine contractions are characterized by decreased blood flow through the intervillous spaces in the placenta. As blood flow decreases, a corresponding decline in placental gas exchange occurs and the fetus must depend on its existing reserves to maintain oxygenation until placental blood flow is reestablished. The net effect is that fetal Pao_2 decreases as the consequence of uterine contraction. In the fetus with adequate reserves, the fall in Pao_2 is not drastic; the fetus remains adequately oxygenated and so can tolerate the stress of labor.

Fetal Reserve

The factors that influence fetal reserves fall into two general categories: those that diminish reserves and those that exhaust reserves. When fetal oxygen reserves are diminished, the fetus has less-than-optimal oxygenation at the onset of a contraction. This may occur as a consequence of any condition that decreases placental exchange, including reduced placental surface area caused by abruption, placenta previa, an abnormally small placenta, decreased placental perfusion caused by maternal hypotension or hypertension, or maternal hypoxemia. Oxygen reserves can be diminished also as a result of a reduction in fetal oxygen-carrying capacity, as in severe anemia or acute fetal hemorrhage.[88]

A fetal reserve that is adequate at the onset of labor can be exhausted by factors that place unusual demands on the fetus. Exhaustion of

reserves occurs with contractions that last for a prolonged period, are of extremely high intensity, or occur with increased frequency and without an adequate recovery period between individual contractions.[88] This is often a consequence of the use of oxytocic agents to induce or augment labor.

Determination of cord gases at delivery provides objective evidence of the fetal metabolic state at the time of birth.[51] A base excess of less than or equal to 12 mmol/L generally is defined as the threshold that may be associated with hypoxic injury.[124,137] Fetal pulse oximetry may also be used. Decreased fetal pulse oximetry values, especially prolonged and recurrent recordings less than 30%, are correlated with abnormal fetal heart rate patterns, indicating an association with fetal compromise and metabolic acidosis.[153] However, a systematic review found that the addition of fetal pulse oximetry does not reduce and may increase the caesarean delivery rate and that a better method to assess fetal well-being in labor is needed.[60]

Fetal Response to Contraction-Induced Hypoxia

When the fetal oxygen reserve is diminished or exhausted, uterine contractions can precipitate a significant fall in Pa_{O_2}. The fetus is quite limited in its ability to compensate for this hypoxemia. The adult mechanism, which involves increasing total cardiac output by increasing heart rate, does not play a major role in the fetal response. **Instead, the fetus responds with a redistribution of cardiac output as a means of maintaining critical function; blood flow to the brain and heart increases, whereas perfusion of less critical organs is reduced.[10]** This mechanism enables the fetus to survive brief episodes of hypoxia, but severe and prolonged hypoxic episodes are poorly tolerated.

Acute hypoxemia leads to the development of acidosis and also produces a reflex bradycardia as a result of vagal stimulation, both of which further compromise fetal oxygenation. In addition, myocardial hypoxia has a direct bradycardic effect.[10] These mechanisms give rise to one of the classic signs of fetal distress, the late deceleration, in which the peak of uterine pressure, which also represents the nadir of intervillous blood flow and the onset of fetal hypoxemia, is followed by a decline in fetal heart rate. Late decelerations are significant in that they help identify the fetus who cannot tolerate labor because of inadequate oxygen reserves and they allow for the implementation of measures to enhance fetal reserve, improve placental perfusion, or interrupt labor.[168]

***Late decelerations* are particularly ominous when accompanied by loss of fetal heart rate variability and/or fetal baseline tachycardia, because these findings are indicative of fetal acidosis.** In the preterm infant, the findings of decreased variability and tachycardia, with or without late decelerations, correlate highly with acidosis, depression, and low Apgar scores.[168]

Other Factors That Evoke a Fetal Response During Labor

HEAD COMPRESSION

Pressure on the fetal head during labor, especially with pushing efforts in the second stage, also produces a vagal response and a reflex slowing of the fetal heart rate. In general, this does not indicate hypoxia or fetal compromise and often is seen in a healthy fetus. The deceleration that accompanies head compression, also called an *early deceleration,* is differentiated from the late deceleration of fetal asphyxia by its timing in relation to a contraction. **In early deceleration, the heart rate begins to fall as a contraction builds, reaching its lowest point as the contraction peaks. As the contraction subsides, the heart rate returns to baseline. The result is a uniformly shaped dip that mirrors the shape of the contraction.** In comparison, **a late deceleration also has a uniform shape but lags behind the contraction, with the fall in heart rate beginning at or slightly after the contraction peak and continuing to fall as the contraction subsides. With a late deceleration, the heart rate does not return to baseline until well after the contraction has ended.**

CORD COMPRESSION

Compression of the umbilical cord occurs when the cord is looped around fetal body parts, when it is knotted or prolapses, or when amniotic fluid is low (oligohydramnios). During labor, cord

compression may be exacerbated by contractions and descent of the fetus, resulting in varying degrees of occlusion of the umbilical vessels and diminution of blood flow. Partial venous occlusion may be manifested by fetal heart rate acceleration, whereas significant occlusion precipitates a rapid fall in heart rate, caused at least in part by vagal reflex. ***Variable decelerations* can be spontaneous, occurring at any time, or periodic, occurring with contractions. They typically have an abrupt descent in heart rate and may be *V*-, *U*-, or *W*-shaped—hence the term *variable deceleration*.** Periodic variable decelerations are identified by a decline in heart rate that generally begins before the contraction peaks but, unlike early decelerations, falls rapidly and does not mirror the shape of the contraction. **Typically, recovery of the heart rate also is rapid. However, when the occlusion is severe or of long duration or if the fetus has diminished oxygen reserves, recovery may be slow, indicating fetal hypoxia and, in essence, incorporating a component of late deceleration within the variable deceleration.**[168]

When variable decelerations are persistent and worsening during labor in the presence of oligohydramnios, intrapartum amnioinfusions have significantly decreased fetal heart rate abnormalities, acidemia at birth, and rates of cesarean delivery.[81] An *amnioinfusion* involves infusion of fluid into the uterine cavity via an intrauterine pressure catheter. This fluid provides cushioning of the umbilical cord, which may reduce the frequency and severity of the cord compression. However, amnioinfusion is no longer standard practice when moderate or thick meconium is present.[18,81]

MATERNAL PAIN MEDICATION

Maternal anesthesia and/or analgesia has the potential to affect the infant, either during labor and delivery or in the newborn period. The risk is increased if the fetus is preterm or is otherwise compromised. This is not to say that there is no place for these drugs in obstetric care—only that they must be used judiciously and with a clear understanding of the risks and benefits involved. Table 2.1 **summarizes the effects of commonly used analgesic and anesthetic agents on the fetus and newborn.**[18,127]

TABLE 2.1 FETAL AND NEONATAL EFFECTS OF MATERNAL ANALGESIA AND ANESTHESIA DURING LABOR

DRUG	POSSIBLE FETAL AND NEONATAL SIDE EFFECTS
Narcotics	Fetal and neonatal effects are related to the dose, route, and timing of maternal administration and may be reversed by the administration of a narcotic antagonist (naloxone): • CNS depression • Fetal bradycardia • Depressed respiratory effort • Decreased muscle tone and reflexes • Decreased responsiveness
Paracervical block	Fetal bradycardia and asphyxia related to decreased uterine blood flow and direct fetal myocardial depression
Epidural and spinal block	Fetal bradycardia and asphyxia related to maternal hypotension Fetal/neonatal toxicity Neonatal respiratory depression after epidural containing fentanyl
General (inhalation) anesthesia	Fetal and newborn effects related to the duration and depth of maternal anesthesia include the following: • CNS depression • Respiratory depression • Decreased responsiveness

CNS, Central nervous system.

ASSESSMENT OF FETAL WELL-BEING

Over the past 30 years, the capability to assess fetal well-being has advanced from simple auscultation of the fetal heart to direct physiologic and biochemical measurement of fetal status. With these advances, an appreciation of the similarities between the fetus and newborn, as well as a more complete understanding of the unique features of fetal life, has been gained. This knowledge reinforces the importance of viewing fetal physiology as a precursor of neonatal function and especially as a significant influence on the success with which the fetus will complete the adaptations required by the birth process.

The goal of antepartum fetal surveillance is to answer the following questions: What is the safest

environment for a fetus at the gestational age at which the testing is taking place? Is the fetus more likely to survive in utero for the week after testing, or does the fetus have a significant risk for in utero death based on the degree of environmental or intrinsic intolerance demonstrated through testing? In the case of preterm infants, this may mean delivery at a gestational age at which there is a high likelihood for respiratory, neurologic, cardiac, gastrointestinal, and immunologic immaturity that will require neonatal intensive care.

The obstetric practitioner has several tools available to help answer the preceding questions. First and foremost is the identification of maternal conditions that may predispose the fetus to in utero compromise. Examples of such conditions include type 1 diabetes mellitus, chronic hypertension, collagen vascular disease, antiphospholipid antibody disease, maternal cardiac or pulmonary disease, preeclampsia, blood group isoimmunization, in utero infection, PROM, and maternal substance abuse. This list is not all-inclusive but demonstrates several commonly encountered conditions for which antepartum fetal surveillance is warranted.

Once the decision is made to assess fetal well-being, four modalities are available in general practice to help the practitioner and patient answer questions about the optimal environment for the fetus at any given time—fetal movement counts, the contraction stress test (CST), the NST, and the fetal biophysical profile. Two additional tools often used by maternal-fetal medicine specialists in certain clinical situations are Doppler flow studies and percutaneous umbilical cord blood sampling (PUBS). None of these tools is used as the sole determinant for delivery; rather, each is used in conjunction with the entire clinical picture. The choice of testing method also is clinically driven; each method is useful in certain clinical settings, but no one method is the correct choice in all situations.

Although most of the procedures used to monitor fetal well-being are decidedly high-tech, the simple "kick count," or *fetal movement survey,* is a low-tech, low-cost screening tool. Many women with an intrauterine fetal demise have no identifiable risk factors that would place them in a fetal testing protocol. **Fetal motor activity reflects the fetal condition in utero, and a decrease in or absence of fetal movements often presages fetal death.** This is one reason that many institutions ask their patients to begin a fetal movement counting protocol at 26 to 32 weeks of gestation. Although there are continuing study results, some centers have demonstrated a significant decrease in the incidence of fetal mortality rates after the institution of a fetal movement counting protocol.

There are several different approaches to fetal movement counting. None has been shown to be superior.[10] One approach is to have the patient choose a certain time every day to rest in the lateral position and count fetal movements. The perception of 10 distinct fetal movements within 2 hours constitutes a reassuring session. The most important aspect of this type of testing is to emphasize to the patient the importance of notifying her practitioner immediately if the fetal movement counting has not met the established criteria. A system must be in place in which patients have immediate access to health care personnel 24 hours per day.

The CST is used in an attempt to evaluate fetal response to uterine contractions.[84] The principle behind the CST is that uterine contractions cause a transient interruption in uteroplacental perfusion. With normal fetal reserve, this intermittent interruption is well tolerated. With inadequate or exhausted reserve, late fetal heart rate decelerations appear. Because late decelerations during labor had been associated with fetal hypoxia and acidosis, it was reasoned that similar interpretations could be applied to contractions induced in the antepartum patient. **Thus the CST is considered a test of uteroplacental reserve.**

During a CST, uterine contraction activity is evoked with either the use of maternal nipple stimulation or an intravenous infusion of oxytocin. The fetal heart rate is charted using graph paper attached to a monitor that uses a continuous wave ultrasound transducer placed on the maternal abdomen over the uterus. The minimum number of spontaneous or evoked contractions necessary for adequate testing is three contractions of 40 seconds' duration in a 10-minute period. The results are interpreted as follows:

- A negative CST result is one in which no late fetal heart rate decelerations occur during the examination.
- In a positive CST result, late decelerations occur after 50% or more of the contractions, even if contraction frequency is fewer than three in 10 minutes.

- A suspicious or equivocal finding is one in which intermittent late or significant variable decelerations occur.
- A CST result is considered unsatisfactory if fewer than three contractions occur per 10 minutes or a poor-quality tracing is obtained.

In many clinical situations, a positive CST warrants delivery of the fetus because of suspected in utero hypoxemia during periods of uterine contraction. However, there are numerous exceptions to this rule. For example, if a positive CST is noted in the presence of maternal diabetic ketoacidosis, a correction of the underlying metabolic process may reverse the fetal acidosis and a negative CST may be obtained subsequently. Thus the delivery of a neonate who has metabolic acidosis and is preterm can be avoided.

The NST is a tool used to indirectly assess the integrity of the fetal autonomic nervous system. The fetal heart is under the dual influences of the sympathetic and parasympathetic nervous systems. By approximately 28 weeks of gestation, 85% of fetuses demonstrate fetal heart rate accelerations in response to fetal movement. Lack of these intermittent fetal heart rate accelerations usually indicates a fetal sleep cycle. However, many other intrinsic and extrinsic factors, including fetal acidosis, may lead to an absence of these intermittent accelerations in heart rate. Examples include but are not limited to medication exposure, maternal smoking, uteroplacental insufficiency, and fetal structural or chromosomal anomalies. Factors leading to maternal acidosis (severe anemia, congenital heart disease, and sepsis) also can result in fetal acidosis and nonreactive NST.

The NST is performed with the patient in a semi-Fowler's or lateral tilt position. As in the CST, the fetal heart rate is monitored with an external transducer. NSTs are interpreted as either reactive or nonreactive. An accepted definition of a reactive NST is an increase in fetal heart rate of 15 beats/min for 15 seconds above the baseline heart rate occurring twice in a 20-minute period.[10] A nonreactive NST is defined as lacking the necessary fetal heart rate accelerations during a 40-minute period. The following may be candidates for nonstress testing:

- Women who have diabetes that must be controlled with medication
- Women who have pregnancy-induced hypertension, preeclampsia, or intrinsic renal disease
- Women in whom fetal IUGR, oligohydramnios, or postdate pregnancy has been determined
- Women who have reported decreased fetal movement

The NST has certain advantages over the CST. It does not entail the production of uterine contractions, and so there are fewer potential problems or contraindications to the NST. Because the NST is quicker and easier to conduct, it is often the first-line screening test of fetal well-being. Its disadvantages are that it does not evaluate uteroplacental reserve and that it has a higher false-positive rate than the CST.

When the NST is nonreactive, an option that is often used in lieu of the CST or delivery of the fetus is the *biophysical profile* (BPP) (Table 2.2). This test combines the NST with real-time ultrasound

TABLE 2.2 BIOPHYSICAL PROFILE SCORING

BIOPHYSICAL VARIABLE	NORMAL (2)	ABNORMAL (0)
Fetal breathing—At least one episode of at least 30 seconds during a 30-minute observation	Present	Absent
Gross body movement—At least three body or limb movements during a 30-minute observation	≥3	≤2
Fetal tone—One episode of extension or flexion of limbs or trunk during a 30-minute observation	Present	Absent
Reactive nonstress test—At least two episodes of 15 beats/min fetal heart rate accelerations during 30-minute observation	Yes	No
Amniotic fluid volume—A pocket of fluid that measures at least 2 cm in two planes perpendicular to each other (2 × 2–cm pocket)	Present	Absent
Normal Score: 8–10		

evaluation of the fetus. Although there are several different BPP scoring systems, the one most generally accepted assigns a numerical score of 0 or 2 for the absence or presence, respectively, of five different parameters: fetal movement, tone, "breathing" movements, amniotic fluid volume, and the NST. One advantage to evaluation of several different fetal biophysical variables is enhanced specificity of testing with a diminished incidence of delivery for false-positive results. The presence or absence of acute markers (movement, tone, breathing, and NST) helps reflect fetal status at the time of testing. However, the absence of a given marker may be difficult to interpret, because it may simply reflect normal periodicity.

The biophysical activities that mature first in fetal development disappear last as acidosis worsens. Fetal tone (flexion and extension) is present at 7½ to 8½ weeks after the last menstrual period. This activity, as well as gross body movement, is mediated in the cortex and nuclei of the CNS. Fetal movement is present by 9 weeks. Fetal breathing movements (i.e., rhythmic breathing movements of 35 seconds or more) can be seen by 20 weeks of gestation. The CNS center responsible for control of this activity is the ventral surface of the fourth ventricle. The final acute marker to mature is fetal heart rate acceleration in response to movement (reactive NST) seen in the later second trimester. The posterior hypothalamus and medulla control this activity. Given that the first marker to appear in development is the last to disappear with worsening fetal acidosis, the absence of fetal tone has been found to be associated with high perinatal morbidity and mortality rates. Chronic sustained fetal hypoxia or acidosis may produce a protective redistribution of cardiac output away from less vital fetal organs (e.g., kidney, lung) toward the essential organs (e.g., brain, heart, adrenal glands). Redistribution of fetal blood flow may be so profound that renal perfusion decreases to the point that oligohydramnios is established. When the largest vertical amniotic fluid pocket within the uterus is less than 1 cm, the perinatal mortality rate is as high as 110 per 1000.[42,78]

A BPP score of 8 or 10 is normal; a score of 6 is equivocal, and the profile should be repeated in 12 to 24 hours. A score of 4 or less is abnormal. Management in the presence of an abnormal BPP depends on the gestational age and the maternal and/or fetal factors contributing to the altered state.

The BPP employs the advantages of real-time ultrasonography to observe fetal behavior.[51] One of its major advantages is as an intermediate step in the evaluation of a fetus with a nonreactive NST before a time-consuming CST is performed. It is also a useful tool for patients with contraindications to the CST, such as premature labor, PROM, placenta previa, malpresentation, unexplained vaginal bleeding, or multiple gestation. The modified BPP, which combines an acute marker (NST) with the chronic marker of fetal well-being (amniotic fluid index [AFI]), has been shown by some centers to be as predictive of fetal well-being as the full BPP. Because evaluation of the AFI is less time-consuming and requires less technical skill, this may be an acceptable alternative for many centers. Finally, it should be noted that though widely used, there is insufficient evidence from RCTs to support the use of BPP as a test of fetal well-being in high-risk pregnancies.[10,51]

No matter which of these testing modalities is used, the patient should be counseled as to the predictive value of a "normal" test. The incidence of stillbirth within 1 week of a reactive NST is 1.9 per 1000; for a negative CST, it is 0.3 per 1000; and for a normal BPP, it is 0.8 per 1000.[10] Although some investigators have reported a decreased incidence of fetal mortality after initiation of a fetal movement counting program for "low-risk" patients,[141] more recent studies have found no difference in perinatal outcomes with fetal movement counting.[54] More controlled studies are needed.[54,104]

The role of *Doppler flow assessment* of the fetal arterial and venous systems in the prediction of in utero well-being is also accepted. Measurement of umbilical artery velocity is used as a method of fetal surveillance for growth-restricted fetuses. Specifically, decreased or absent end-diastolic flow may appear days before conventional antenatal tests become abnormal. In cases such as these, at a minimum, intensive fetal surveillance is advised.[51] **Reversal of diastolic flow is highly predictive of in utero fetal demise within 24 hours and warrants immediate intense investigation or delivery.[51]**

The dramatic improvement in ultrasound image quality over the past 15 years also has made it possible to directly sample fetal blood and tissue. The technique of *percutaneous umbilical blood sampling (PUBS)* has given the obstetrician access to

the fetal circulation with relative safety for both the fetus and mother. In this procedure, real-time ultrasonography is used to guide the insertion of a needle into the umbilical vein or artery. Samples of fetal blood can be obtained, or, as in the case of red cell isoimmunization, transfusions can be carried out. The fetal loss rate is generally quoted as 1% to 2%.[143]

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3 PERINATAL TRANSPORT AND LEVELS OF CARE

MARIO AUGUSTO ROJAS, AMANDA FLAHERTY, HEATHER FURLONG BROWN, AND TAMARA RUSH

Perinatal transport is the timely and appropriate transfer of high-risk pregnant mothers to health care facilities in which expertise and resources for optimal care are available to improve mortality and morbidity of both the mother and her fetus. If transfer of the mother is not possible because of risk outweighing potential benefit, the objective then shifts to optimizing delivery, and birth of the high-risk infant. In the latter situation, it is **necessary to have adequately trained professionals to resuscitate and stabilize the infant before his or her transfer to a medical center that has the appropriate expertise and resources.**

For perinatal transport to effectively support high-risk mothers and their fetuses, as well as sick newborn infants, each country, state, or region must identify its perinatal resources with respect to physical and human capabilities. This review should include classification of levels of care and expertise, as well as mapping of resources as they exist within specific geographic areas. **Classification of perinatal resources according to the different levels of care as recommended by the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (ACOG) in their *Guidelines for Perinatal Care*[4] will direct organization, identification of resources, and roles of patient referral and retrieval centers, as well as reveal the natural elevation of care within the geographic area of question** (Table 3.1). Historically, regionalization has been recommended as the most effective and cost-efficient use of perinatal resources.* The implementation of this important strategy is subject to qualitative variance depending on the characteristics of the health care system and resources where it is applied. In countries in which universal health care is the norm, regionalization is more easily implemented, whereas in market-driven health care systems in which de-regionalization is predominant, these provisions for care become more challenging.† Whatever the circumstances, perinatal providers must use innovative strategies to maintain regionalization of services and high-quality perinatal transport systems.[25,31]

Because all hospitals cannot provide all levels of perinatal care, interhospital transport of pregnant women and neonates is an essential component of any regional perinatal effort. Women who are at risk for complications and pose significant risk for adverse outcomes or whose neonates are likely to require intensive care support should be considered candidates for referral during the antepartum period.[32] Similarly, it is accepted medical practice to transfer a neonate to a hospital that can provide the services needed or anticipated to be needed if the birth hospital cannot provide that level of sevice.‡

Once resources are identified and classified, a model for integration of perinatal services may be constructed. Strategic planning at this level will direct the design of the organizational structure of the perinatal transport system, including identification of leadership functions, the different member nurseries/units and their roles, and the definition and process for perinatal elevation of care. This integration will then allow for the creation of a system for continuous data collection and analysis, facilitating a systems approach to problem solving and the implementation of quality improvement strategies within the system.[78]

*References 9, 11, 17, 19, 52, 67, 86.

†References 11, 21, 25, 28, 42, 48, 70.

‡References 9, 13, 14, 21, 28, 35, 36, 42, 48, 53, 70, 84, 86.

BLUE type highlights content that is particularly applicable to clinical settings.

TABLE 3.1 LEVELS OF PERINATAL AND NEONATAL CARE AND THEIR EXPECTED CAPABILITIES*

	PERINATAL CARE	PERSONNEL
	All institutions providing perinatal care should be capable of neonatal resuscitation and stabilization	
Birth Center: Peripartum care of low-risk women with uncomplicated singleton pregnancies with a vertex presentation who are expected to have an uncomplicated birth. Example: Term, singleton, vertex presentation	• Capability and equipment to provide low-risk maternal care and a readiness at all times to initiate emergency procedures to meet unexpected needs of the woman and newborn within the center, and to facilitate transport to an acute setting when necessary • An established agreement with a receiving hospital with policies and procedures for timely transport • Data collection, storage and retrieval • Ability to initiate quality improvement programs that include efforts to maximize patient safety • Medical consultation available at all times	• Every birth attended by at least two professionals: Primary maternal care providers CNMs, CMs, CPMs, and licensed midwives who are legally recognized to practice within the jurisdiction of the birth center; MDs (FPs: Ob-Gyns) • Availability of adequate numbers of qualified professionals with competence in level I criteria and ability to stabilize and transfer high-risk women and newborns
Level 1: Basic Care Care of uncomplicated pregnancies with the ability to detect, stabilize, and initiate management of unanticipated maternal-fetal or neonatal problems that occur during the antepartum, intrapartum, or postpartum period until patient can be transferred to a facility at which specialty maternal care is available. Examples: Any patient appropriate for a birth center plus capable of managing higher-risk conditions such as: • Term twin gestation • Trial of labor after cesarean delivery • Uncomplicated cesarean delivery • Preeclampsia without severe features at term	Ability to begin emergency cesarean delivery within a time interval that best incorporates maternal and fetal risks and benefits with the provision of emergency care • Available support services, including access to obstetric US, laboratory testing, and blood bank support supplies at all times • Protocols and capabilities for massive transfusion, emergency release of blood products, and management of multiple component therapy • Ability to establish formal transfer plans in partnership with a higher-level receiving facility • Ability to initiate education and quality improvement programs to maximize patient safety, and/or collaborate with higher-level facilities to do so	Birth center providers plus • Continuous availability of adequate number of RNs with competence in level I care criteria and ability to stabilize and transfer high-risk women and newborns • Nursing leadership has expertise in perinatal nursing care • Obstetric care provider with privileges to perform emergency cesarean available to attend all deliveries • Anesthesia services available to provide labor analgesia and surgical anesthesia
Level II: Specialty Care Level I facility plus care of appropriate high-risk antepartum, intrapartum, and postpartum conditions, both directly and admitted and transferred from another facility. Examples: Any patient appropriate for level I care, plus higher-risk conditions such as: • Severe preeclampsia	Level I facility capabilities plus • CT scan and ideally MRI with interpretation available	Level I facility providers plus • Continuous availability of adequate numbers of RNs with competence in level II care criteria and ability to stabilize and transfer high-risk women and newborns who exceed level II criteria

TABLE 3.1 LEVELS OF PERINATAL AND NEONATAL CARE AND THEIR EXPECTED CAPABILITIES* — cont'd

	PERINATAL CARE	PERSONNEL
• Placenta previa with no prior uterine surgery	• Basic US services for maternal and fetal assessment • Special equipment needed to accommodate the care and services needed for obese women	• Nursing leadership and staff have formal training and experience in the provision of perinatal nursing care and should coordinate with respective neonatal care services • Ob-Gyn available at all times • Director of obstetric services is a board-certified Ob-Gyn with special interest and experience in obstetric care • MFM available for consultation on-site, by telephone, or by telemedicine, as needed • Anesthesia services available at all times to provide labor analgesia and surgical anesthesia • Board-certified anesthesiologist with special training or experience in obstetric anesthesia available for consultation • Medical and surgical consultants available to stabilize obstetric patients who have been admitted to the facility or transferred from other facilities
Level III: Subspecialty care Level II facility plus care of more complex maternal conditions, obstetric complications, and fetal conditions. Examples: Any patient appropriate for level II care, plus higher-risk conditions such as: • Suspected placenta accreta or placenta previa with prior uterine surgery • Suspected placenta percreta • ARDS • Expectant management of early severe preeclampsia at less than 34 weeks of gestation	Level II capabilities plus • Advanced imaging services available at all times • Ability to assist level I and II centers with quality improvement and safety programs • Provide perinatal system leadership if acting as a regional center in areas where level IV facilities are not available • Medical and surgical ICUs accept pregnant women and have critical care providers onsite to actively collaborate with MFMs at all times. • Appropriate equipment and personnel available onsite to ventilate and monitor women in labor and delivery until they can be safely transferred to the ICU.	• Level II care providers plus • Continuous availability of adequate numbers of nursing leaders and RNs with competence in level III criteria and ability to transfer and stabilize high-risk women and newborns who exceed level III care criteria, and with special training and experience in the management of women with complex maternal illnesses and obstetric complications • Ob-Gyn available on-site at all times • MFM with inpatient privileges available at all times, either on-site, by telephone, or by telemedicine • Director of MFM services is a board-certified MFM • Director of obstetric service is a board-certified Ob-Gyn with special interest and experience in obstetric care • Anesthesia services available at all times on-site • Board-certified anesthesiologist with special training and experience in obstetric anesthesia in charge of obstetric anesthesia services • Full complement of subspecialists available for inpatient consultations

Continued

TABLE 3.1 LEVELS OF PERINATAL AND NEONATAL CARE AND THEIR EXPECTED CAPABILITIES* — cont'd

	PERINATAL CARE	PERSONNEL
Level IV: Regional Perinatal Health Care Centers Level III facility plus on-site medical and surgical care of the most complex maternal conditions and critically ill pregnant women and fetuses throughout antepartum, intrapartum, and postpartum care. Examples: Any patient appropriate for level III care plus higher-risk conditions such as • Severe maternal cardiac conditions • Severe pulmonary hypertension or liver failure • Pregnant women requiring neurosurgery or cardiac surgery • Pregnant women in unstable condition and in need of an organ transplant	Level III facility capabilities plus • On-site ICU care for obstetric patients • On-site medical and surgical care of complex maternal conditions with the availability of critical care unit or ICU beds • Perinatal system leadership, including facilitation of maternal referral and transport, outreach education for facilities and health care providers in the region, and analysis and evaluation of regional data, including perinatal complications and outcomes and quality improvement	Level III health care providers plus • MFM care team with expertise to assume responsibility for pregnant women and women in the postpartum period who are in critical condition or have complex medical conditions. This includes co-management of ICU-admitted obstetric patients. An MFM team member with full privileges is available at all times for on-site consultation and management. The team is led by a board-certified MFM with expertise in critical care obstetrics. • MD and nursing leaders with expertise in maternal critical care obstetrics • Continuous availability of adequate numbers of RNs who have experience in the care of women with complex medical illnesses and obstetric complications; this includes competence in level IV care criteria. • Director of obstetric service is board-certified MFM, or board-certified Ob-Gyn with expertise in critical care obstetrics • Anesthesia services are available at all times on-site • Board-certified anesthesiologist with special training or experience in obstetric anesthesia in charge of obstetric anesthesia services. • Adult medical and surgical specialty and subspecialty consultants available on-site at all times to collaborate with MFM care team
	NEONATAL CARE	**PERSONNEL**
Level I: Well Newborn Care	• Provide neonatal resuscitation at every delivery • Evaluate and provide neonatal care to stable term newborn infants • Stabilize and provide care for infants born at 35–37 weeks of gestation who remain physiologically stable • Stabilize newborn infants who are ill and those born before 35 weeks of gestation until transfer to a higher level of care	• MDs: (FPs, pediatricians) • Advanced practice nurses (NNPs, PNPs, FNPs)

TABLE 3.1 LEVELS OF PERINATAL AND NEONATAL CARE AND THEIR EXPECTED CAPABILITIES* — cont'd

	PERINATAL CARE	PERSONNEL
Level II: Special care nursery	• Level I capabilities plus • Provide care for infants born at 32 weeks of gestation or later and weigh 1500 g or more who have physiologic immaturity or who are moderately ill with problems that are expected to resolve rapidly and are not anticipated to need subspecialty services on an urgent basis • Provide care for infants convalescing after intensive care • Provide mechanical ventilation for brief duration (less than 24 hours) or continuous positive pressure airway pressure, or both • Stabilize infants born before 32 weeks of gestation and weigh less than 1500 g until transfer to an NICU facility	Level I health care providers plus • Neonatologists • Pediatric hospitalists • Neonatal nurse practitioners
Level III: NICU	• Level II capabilities plus • Provide sustained life support • Provide comprehensive care for infants born before 32 weeks of gestation and weigh less than 1500 grams and infants born at all gestational ages and birth weights with critical illness • Provide prompt and readily available access to a full range of pediatric medical and surgical subspecialists, pediatric anesthesiologists, and ophthalmologists • Provide a full range of respiratory support that may include CMV and/or HFV, and iNO. • Provides advanced imaging, with interpretation on an urgent basis, including CT, MRI, and echocardiography	Level II health care providers plus • Pediatric medical subspecialists† • Pediatric anesthesiologists† • Pediatric surgeons† • Pediatric ophthalmologists†
Level IV: Regional NICU	Level III capabilities plus • Located within an institution with the capability to provide surgical repair of complex congenital or acquired conditions • Maintain a full range of pediatric medical and surgical subspecialists, and pediatric anesthesiologists on-site • Facilitate transport and provide outreach education	Level III health care providers plus • Pediatric surgical subspecialists

*Includes all health care providers with relevant experience, training, and demonstrated competence

†At the site or at a closely related institution by prearranged consultative agreement.

ARDS, Adult respiratory distress syndrome; *CM,* certified midwife; *CNM,* certified nurse midwife; *CPM,* certified professional midwife; *CT,* computed tomography; *FNP,* family nurse practitioner; *FP,* family practice; *ICU,* intensive care unit; *MD,* medical doctor; *MFM,* maternal-fetal medicine; *MRI,* magnetic resonance imaging; *NICU,* neonatal intensive care unit; *NNP,* neonatal nurse practitioner; *NRP,* Neonatal Resuscitation Program; *Ob-Gyn,* obstetrician-gynecologist; *PNP,* pediatric nurse practitioner; *RN,* registered nurse; *S.T.A.B.L.E.,* S.T.A.B.L.E. Program; *US,* ultrasonography.

Modified from American Academy of Pediatrics, American College of Obstetricians and Gynecologists: Organization of perinatal health care. In *Guidelines for Perinatal Care.* 8th ed. Elk Grove Village, IL: The Academy; 2017.

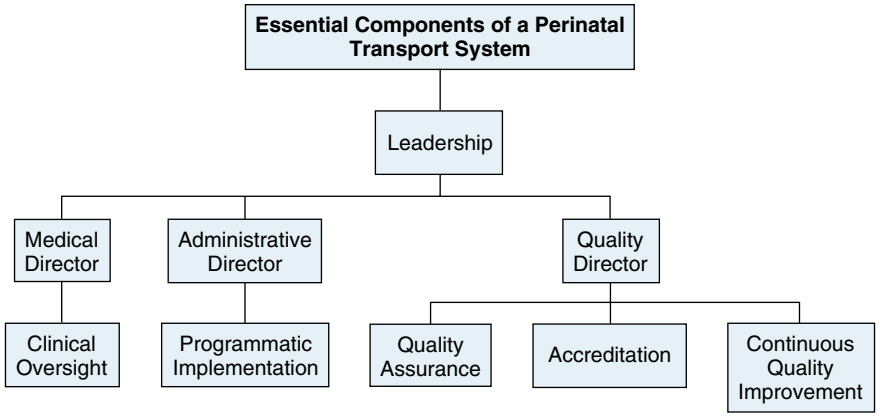

FIGURE 3.1 Organizational structure of neonatal/perinatal transport system.

REGIONAL PERINATAL REFERRAL AND TRANSPORT SYSTEM

Independent of the health care system with which one identifies (universal versus market driven), **the referral system must identify a subspecialty care regional perinatal center, for which the responsibility of coordinating interfacility perinatal transfer lies.** Although many different models provide clinical care in transport, the transport system should include the minimal components of (1) leadership (both medical and administrative), (2) communication, and (3) quality assurance (Fig. 3.1).

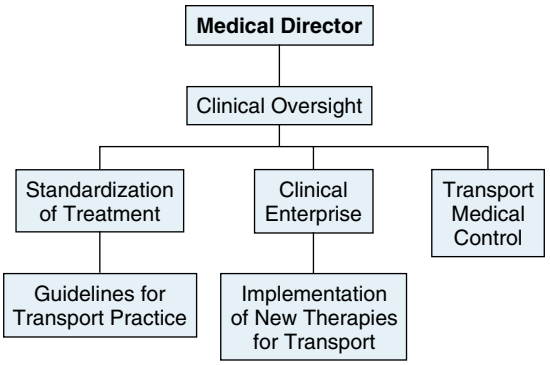

FIGURE 3.2 Role of medical director of transport services.

Leadership

One proposed model is the implementation of a leadership team that comprises a medical director, administrative director, and quality director. This team approach enables collaborative and timely oversight of the transport system with potential for growth and quality improvement. The medical director should be a physician with expertise in transport medicine and evidence-based care. The medical director's role includes overseeing the following[54] (Fig. 3.2):

- Development, implementation, and monitoring of patient care and transport standards
- Scope of practice of team members
- Team selection
- Training and continuing education
- Support of perinatal partnerships and advocacy

The administrative director working in conjunction with the medical director oversees the budget and day-to-day management of the transport process, including maintenance of equipment. The administrative director should possess clinical transport knowledge paired with strong administrative qualities, because this role includes oversight of finance, human resources, and communication operations (Fig. 3.3).[54] The quality director should be a health care provider with a professional background in continuous quality improvement, process analysis, and management. In association with the medical director and administrator, the quality director is responsible for the development and maintenance of a transport database for operational management, quality assurance, and analysis. This administrator should also be able to apply the basic concepts of quality improvement and lean management to implement novel interventions aimed at improving the perinatal transport system (Fig. 3.4).[78]

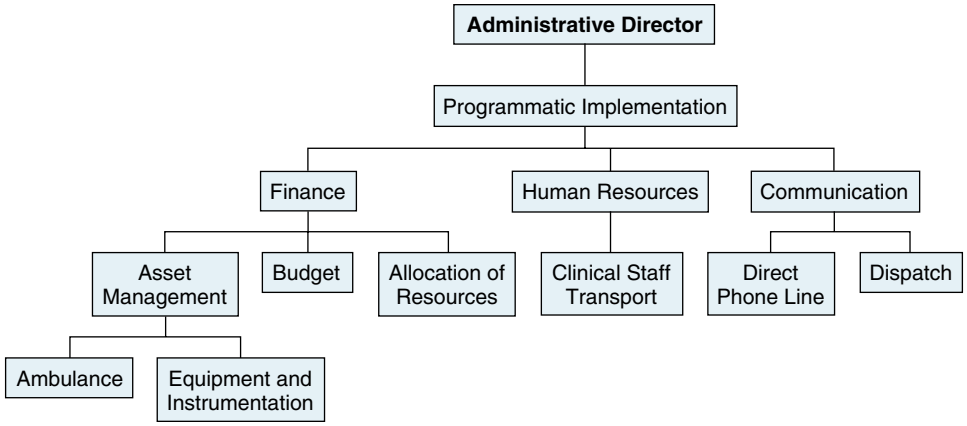

FIGURE 3.3 Role of administrative director of transport services.

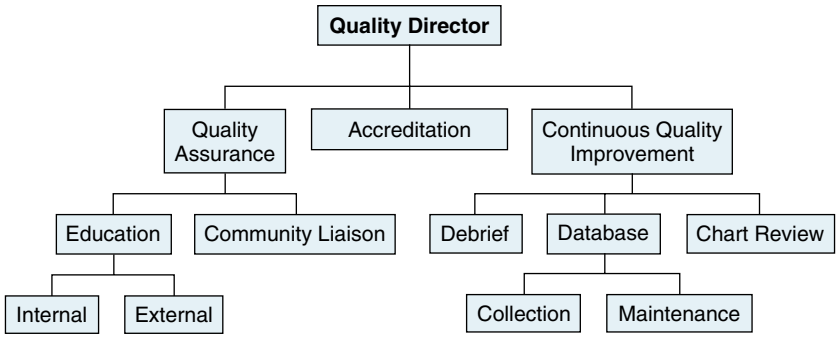

FIGURE 3.4 Role of quality director of transport services.

Communication

As indicated in Table 3.1, a regional subspecialty perinatal care center should be responsible for coordination of perinatal transport. **Integral to the regional transport system is the creation of a centralized communication center with a perinatal regional hotline.**[27] The communication center is responsible for coordinating maternal and neonatal transports within the different levels of care. Roles within this center include referring physician, dispatcher, bed locator, and transport medical control officer (obstetrician and neonatologist). The inclusion of specialized personnel in the initial communication process may support rendering institutions appropriate treatment strategies while decreasing diagnostic discordance.[68]

For purposes of basic communication, a central dedicated telephone line is recommended to provide direct, easy, and immediate access to the regional system. This access should be staffed 24 hours per day, 7 days per week and should be unencumbered. This model also includes the transfer of the referral call to the transport medical control officer, thereby greatly simplifying the process for the referral-consultation. The ability to support communication among the referring physician, the dispatcher, and the medical control officer simultaneously can speed up decision making and the initiation of transport. Once the transport is initiated, communication among the transport team, the referring physician, and the medical control officer becomes integral to the care provided (Fig. 3.5). Changes in weather, patient status, equipment needs, and bed status need to be communicated in a timely manner. This information may demand a review of the transport plan and is best facilitated through a central communication center.[27,54] **The**

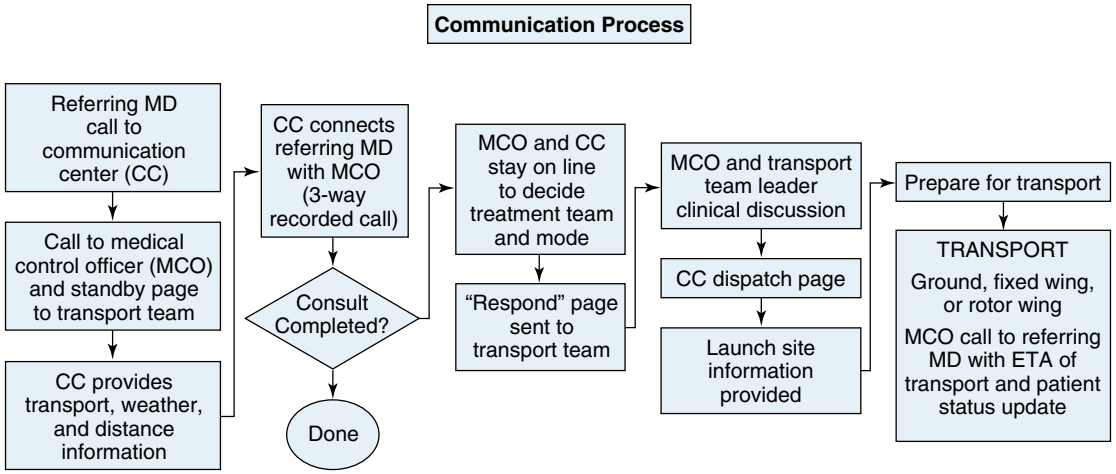

FIGURE 3.5 Working model of Vanderbilt Transport Communication Tool (unpublished), version September 2008. (Contributed by S. Brodtrick, D. Quinn, and M. Cortez.)

organization of a perinatal regional hotline has been shown to significantly increase both in utero and neonatal transports, allowing for safe, 24-hour, on-call management of perinatal transports and the collection of epidemiologic indicators relative to perinatal transfers.[27]

The rapidly advancing field of telecommunications offers a wide variety of opportunities for transmitting medical information, subject to proper consideration of privacy and confidentiality requirements. This medium permits the use of satellite technology and video-conferencing equipment to conduct a real-time consultation between medical specialists in two geographically different areas. Store-and-forward telemedicine involves acquiring medical data (e.g., medical images, bio-signals) and then transmitting these data to a medical specialist for assessment offline. It does not require the presence of both parties at the same time. These technologies may facilitate appropriate referral of patients according to complexity and may decrease incidence of inappropriate transfer or diagnostic discordance, allowing for optimal use of resources.[67,85] Furthermore, these innovative strategies have the potential to overcome de-regionalization of services by creating virtual regional networks for perinatal transport.

Telemedicine consults by neonatologists have been found to improve the quality of high-risk newborn resuscitations.[28] Fang et al. conducted a retrospective cohort study comparing newborns who received a telemedicine consult during resuscitation at a community hospital to those who did not receive a consult.[28] They found that for those who received a consult, not only was the care of the newborn enhanced, but that the remote neonatologist had a positive impact on team behaviors in the form of additional leadership and management. **The newborns in the telemedicine consult group were more likely to have had their temperature, glucose, and blood gas monitored.**[28] Fang et al. concluded that telemedicine programs had the potential to reduce disparities in access to care and increase the quality of care.[28]

Quality

The regional subspecialty perinatal care center, as noted in Table 3.1, is responsible for regional outreach support, education, and continuous quality oversight. Traditionally, quality improvement was assigned to the medical director. However, in light of current health care complexities and regulatory specifications surrounding the quality and safety of patient care, it is recommended that this role be assigned to an individual with the expertise to effectively evaluate programmatic performance at all levels of the organizational structure. This continuous evaluation of the process will facilitate modification of the transport system when potential problems are identified.[78]

The leadership team should oversee overall transport performance. The systematic collection and analysis of carefully selected performance indicators such as patient demographics, management and outcome data, safety standards, logistics, equipment malfunction, and cost will drive quality initiatives. **A quality review of individual transports, incidence reports, and occurrence debriefs will enhance this process.**[54,89] Using a validated transport physiologic score (e.g., the transport risk index of physiologic stability [TRIPS]) to evaluate patient status before, during, and after transport can assist team and transport performance.[48,51,54]

The Academy of Pediatrics Section on Transport Medicine has developed a database for neonatal/pediatric critical care transport quality metrics. The GAMUT database (Ground and Air Medical qUality Transport database) borrows its name from the expression "run the gamut." **Quality metrics include those listed in** Box 3.1. GAMUT welcomes all types of transport programs big or small, academic or corporate, adult or pediatric—all programs that wish to collaborate with others and use benchmarking to drive the quality of the care they provide. Tracking of data related to these quality metrics is just beginning. Teams' data contributions (kept anonymous from other teams) will help determine the performance benchmarking goals necessary to begin the quality improvement phase of this work.[30] Preliminary data have been published,[72] and the process is ongoing.[7]

In addition, quality assurance may be implemented through continuing education both internally and externally. **Transport programs must create individualized internal training programs that effectively provide current and continuous education to ensure maintenance of appropriate skills for high-quality perinatal transport. A similar program must be adapted to provide educational resources to the referring hospital where training in pre-transport resuscitation and stabilization is imperative.** Ensuring competence in these areas has the potential to improve short-term and long-term morbidity of sick infants, offsetting the negative effects of de-regionalization and distance between interhospital transfer facilities.[54] **Building strong relationships of trust within network delivery hospitals will facilitate this process.** Independent of the level of care, these hospitals will deliver emergency sick preterm and term infants; it is therefore imperative that local health care teams develop the expertise to resuscitate and stabilize these infants before transport if necessary. **The regional subspecialty perinatal care center is responsible for working with these hospitals to ensure they develop adequate 24/7 resuscitation and stabilization teams;** the use of scheduled team skills training with simulation and the implementation of real-time communication through advanced technologies like telemedicine will support achieving this goal.

BOX 3.1 GAMUT QUALITY IMPROVEMENT COLLABORATIVE CONSENSUS METRICS

- Ventilator use in neonates with advanced airways
- Average (mean) bedside time and average scene time at transport
- Unintended neonatal hypothermia
- Blood glucose check
- Waveform capnography for ventilated patients
- First attempt tracheal tube success
- First-attempt establishment of airway without neonatal hypoxia/hypotension
- Verification of tracheal tube placement
- Number of patients transported without hospital admission
- Medication errors on transport
- Percent of neonates undergoing rapid sequence intubation where all elements of the protocol are used
- Appropriate management of blood pressure for aortic emergencies
- Unplanned dislodgement of therapeutic devices
- Rate of serious reportable events
- Incidence of hypoxia during transport
- Management of hypertension in hemorrhagic stroke
- Percent of transported patients with accurately interpreted 12-lead ECGs
- Appropriate management of hemorrhagic shock
- Medical equipment failure
- Adverse drug event during transport
- Patient near-miss or precursor adverse events
- Reliable pain assessments
- Average mobilization time of the transport team
- Rate of transport-related patient injuries
- Rate of CPR performed during transport
- Rate of transport-related crew injury
- Use of a standardized patient care hand-off

CPR, Cardiopulmonary resuscitation; *ECG*, electrocardiogram.
Modified from GAMUT Quality Improvement Collaborative Consensus Quality Metrics, version 5/16/2016. Available at: http://gamutqi.org?GAMUT%20Metrics_version%205.16.2016.pdf. Accessed February 5, 2019.

High-Risk Maternal Referral

The most effective method to decrease mortality and morbidity during the perinatal and neonatal period is the timely and appropriate referral of mothers with high-risk pregnancies to medical centers in which both the human and technical resources are available to address complications.[20,27] As better clinical outcomes for very low-birth-weight (VLBW) infants (birth weight <1500 g) have been associated with birth and early care at level III centers,[17] early identification of maternal transport candidates is needed. Delivery of a VLBW infant at a level I or II center often leads to the need for neonatal transport. Robles et al. conducted a retrospective cohort study to assess the frequency of VLBW infants born at non-level III hospitals.[73] Using discharge data from 2008 to 2010 for VLBW infants, the study showed that mothers with an antepartum stay of greater than 1 day between admission and delivery occurred in 14.0% and 26.9% of VLBW births in level I and level II hospitals, respectively. Clearly opportunities for maternal transport still remain.[73]

In situations in which the risk to the mother outweighs the benefit of her transfer during active labor, the timely dispatch of the neonatal transport team from the regional perinatal center for resuscitation and stabilization of the high-risk neonate may be considered the optimal approach to delivery of care when it occurs in a timely manner.

Adequate referral of high-risk perinatal patients begins with high-quality antepartum surveillance.[74] **Indications for referral to a regional center are shown in** Box 3.2. Early identification of factors that can affect pregnancy outcome is important in developing appropriate diagnostic and treatment plans. Optimal perinatal care implies having well-trained and up-to-date obstetricians at all levels of care during both the antepartum and intrapartum period. These physicians should be experts in identifying maternal-fetal risk factors and complications through their knowledge, clinical skills, and expertise in prenatal ultrasonography and fetal monitoring.[1,22,39,66] In situations in which this level of expertise is not available, **medical and nursing personnel should be specifically trained to identify high-risk pregnancies with the objective of pursuing early referral.** Consultation and referral decisions for the high-risk mother should be based on the results of a thorough evaluation of each patient and specific guidelines. The ACOG has established a classification system for levels of maternal care. These guidelines help women receive care at centers that are prepared to provide the level of specialized care each requires.[57,73] Communication between the referral center and the regional perinatal center may be facilitated through the use of video-medicine technology.[28]

BOX 3.2 INDICATIONS FOR REFERRAL TO A REGIONAL PERINATAL CENTER

A. **Prenatal Diagnosis**
   1. Complex fetal genetic or congenital anomalies
   2. Severe intrauterine growth restriction[57]
   3. Hydrops fetalis
   4. Severe oligohydramnios and polyhydramnios
   5. Fetal airway anomalies

B. **Maternal Medical Complications**
   1. Advanced or uncontrolled diabetes mellitus
   2. Severe organic heart or lung disease
   3. Severe renal disease
   4. Maternal infection that can affect the fetus
   5. Thyrotoxicosis

C. **Maternal Surgical Complications**
   1. Acute abdominal emergency
   2. Trauma requiring intensive care
   3. Thoracic emergency requiring intensive care

D. **Obstetric Complications**
   1. Premature onset of labor
   2. Premature rupture of membranes
   3. Third trimester bleeding
   4. Severe preeclampsia or hypertension
   5. Multiple gestations
   6. Rh isoimmunization

Neonatal Referral

Despite efforts to identify high-risk perinatal patients during the antepartum period, as many as 30% to 50% of infants who ultimately require additional neonatal care may not be recognized until the late intrapartum or early neonatal period.[47] For this reason, **all hospitals that provide obstetric services must be prepared for the birth, resuscitation, stabilization, and treatment of premature or term sick infants.** The Neonatal Resuscitation Program (NRP)[66,87] sponsored by the American

BOX 3.3 S.T.A.B.L.E. PRETRANSPORT STABILIZATION OF THE NEWBORN©

Sugar and safe care
Temperature
Airway
Blood pressure
Lab work
Emotional support for the family

Modified from Karlsen K. *The S.T.A.B.L.E Program: Post-resuscitation/Pre-Transport Stabilization Care of Sick Infants—Guidelines for Neonatal Healthcare Providers.* 6th ed. Park City, Utah: S.T.A.B.L.E; 2013.

Heart Association and the American Academy of Pediatrics is an excellent resource for training individuals and maintaining resuscitation skills in both a regional program and an individual hospital setting. **Certification (and renewal) of NRP training should be a universal standard for all delivery room and nursery staff.** The frequency of renewal will depend on the average number of resuscitations that occur on a yearly basis in each institution. Institutions with a low average number of deliveries should renew their skills training more frequently to maintain their individual and team resuscitation and stabilization skills. Beyond the immediate delivery room setting, supportive care should be offered and maintained until the transport team has arrived and assumed care (Box 3.3). The S.T.A.B.L.E. program is the only neonatal continuing education program to focus exclusively on the post-resuscitation and/or pre-transport stabilization care of neonates.[37,40]

NEONATAL TRANSPORT

Stabilization of patients and preparation for transport should begin immediately on identification of a need for transport and before the transport team arrives. The S.T.A.B.L.E. curriculum provides a comprehensive set of generalized guidelines for the assessment and stabilization of sick infants in the postresuscitation/pretransport stabilization period. The "S.T.A.B.L.E." mnemonic was created to assist with information recall and to standardize and organize care in the pretransport/postresuscitation stabilization period. Prevention of adverse events and delivery of safe patient care are stressed throughout the program.[37] In consultation, the referring center (physician) and transport medical control officer (MCO) may address additional areas of attention based on specific patient clinical assessment and presumptive diagnosis. Although the reasons for neonatal referral may be quite diverse and based on needs of infants relative to the capabilities of the referring center, the most common indication is respiratory distress of the neonate.[37] Other common indications include prematurity, congenital anomalies (surgical and nonsurgical), and suspected congenital heart disease. Stabilization and support of these infants may require frequent interhospital communication (referring physician and transport MCO) to identify specific medical interventions. The importance of this form of continuing dialogue with respect to accuracy in diagnosis, management, and changes in patient status cannot be stressed enough. Again, the use of video-telemedicine may facilitate the accuracy of these interactions.[28]

Assumption of care of the neonate is a complex issue without a straightforward answer. However, transition of care should be seamless. **Many health care professionals can have medical responsibility for a single patient at one time. The fact that one person has acquired medical responsibility does not automatically release someone else. On arrival of the transport team, collaborative management is of utmost importance.** While the patient remains in the referring facility, the referring physician cannot hand off the patient and proceed as if the patient has left the facility and his or her care. The referring facility allows the specialty team to provide care under the supervision and authority of the referring physician. **The specialty team leads the effort to prepare the patient for transport. However, leading does not command or infer sole medical responsibility.** The referring physician retains involvement and ultimate responsibility and signs the transfer certificate at the time of actual transfer. If at any time the referring physician deems it is in the best interest of the patient to intervene or cancel the transfer, it is the physician's right and responsibility to do so. **Simultaneously the transport team has a medical responsibility to the patient. A team approach is in the best interest of the patient and should involve all participants in the process.** Communication between the referring physician, the transport team, and the accepting physician is of great importance.[58] **As long as the transport team is in the referring hospital, the**

ultimate responsibility lies with the referring physician. On leaving the referring facility, the transport team and receiving facility assume responsibility and control for medical decision making.[80] In the event that a community emergency medical service (EMS) is used for transport, the referring physician retains medical control until the patient reaches the regional referral center.

Pediatric and neonatal interfacility transport teams are unique entities. Provision of intensive care in the transport environment incorporates the philosophies of neonatal and pediatric critical care, but in a mobile environment with physical and environmental constraints of staff, space, mobility, and equipment. It is important to recognize that **the physical requirements of team members are different from those who work solely in a hospital or clinic environment.** Team members will be required to lift patients or carry equipment often with little or no help. The ability to function within the confines of a moving vehicle is important. Personnel should not be unusually prone to motion sickness or have mastered the techniques to mitigate the effects of motion sickness. Weight restrictions are a consideration in regard to aircraft. Personnel with chronic illness or disability may not be able to perform all expected duties. Pregnancy may pose a temporary limitation, and medical clearance should be provided by the member's obstetrician at a minimum. In the event a team member is unable to function, patient and crew safety may be compromised because there are few options should a team member be incapacitated while on duty. For this reason, team members with certain medical conditions may be at least temporarily precluded from participation on a transport. Policies developed with human resources and legal counsel should be put into place and address the physical requirements for team members.[58]

Interfacility transport teams are a part of the continuum of care provided by the system of emergency medical services for neonates and children. Transition of care should be seamless without compromise of level of care or monitoring. Neonatal-pediatric interfacility transport teams do not "scoop and run" or "swoop and scoop" (limited evaluation at the scene with rapid stabilization and transport to an advanced care environment as the primary goal) as may be appropriate for the prehospital transport from an accident scene. **Patients transported by neonatal-pediatric interfacility teams benefit from organized, coordinated, controlled transport that does not prioritize speed over thorough stabilization described as a "stay and play" philosophy.** The exception to this principle is the patient whose outcome will be compromised without access to care not available at the referring hospital or in the transport environment.[60]

Team Composition and Configuration

Transport teams may be composed of a variety of medical personnel, including physicians, neonatal nurse practitioners, physician assistants, registered nurses (RNs), respiratory therapists (RTs), paramedics, and emergency medical technicians.[38,48,49] Karlsen et al. conducted a Web-based national survey of 335 neonatal transport teams to describe the United States Neonatal Transport Team workforce.[38] Published in 2011, variations in aspects of neonatal transport teams were described including team composition. There were a total of 26 compositions reported.[38] **The most common composition among unit-based and dedicated teams was the RN-RT composition; the same finding as a more recent survey where 30% were RN-RT.**[82] Another recent survey of transport teams listed by the AAP found that most transport teams are nurse-led and consist of an RN and one other team member (i.e., another RN, medic, RT). Many teams adjust composition based on the neonate's acuity.[64] Interfacility transport should be accomplished in the most efficient and safe manner by qualified personnel. **The composition of a neonatal-pediatric transport team should be tailored to meet the specific needs and resources of its patients and referral region.**[58] Factors that can influence team composition include program resources, program design, unit-based versus dedicated teams, transport volume, and transport mode, as well as local, state, and regional regulation agencies.[80] **As a general guideline, a transported infant or child should receive the same level of care en route as will be provided in the unit to which he or she will be admitted.**[58]

There is considerable debate regarding the presence of physicians on transport. Traditionally pediatric teams have included a resident or attending physician, but in a recent survey, less than 5% of pediatric teams used a physician for transport.[82] There is little evidence to support that such a

composition results in more favorable outcomes. **Many neonatal teams have been led by nurse practitioners or advanced practice nurses,** as described by Karlsen et al.[38] Nurse-led teams have been shown (1) to provide better continuity of care, improved documentation, better maintenance of transport equipment, improved team availability, and stronger liaisons with referring hospitals and (2) to reduce overall operating costs.[54] Leslie and Stephenson evaluated physiologic parameters of infants stabilized and transported by neonatal nurse practitioners versus physicians.[50] Though stabilization of the infants by the nurse practitioners took longer, physiologic conditions were improved for pH and Pao_2 in the pretransport period, and temperature and oxygen saturations were improved in the post-transport period when transported by nurse practitioners. King et al. reported on the effects on patient outcomes when team composition was changed from RN-physician team to nurse only.[42] There was no difference found in mortality rates between groups, and team response times were significantly shorter for the RN team.[42] Limited research has demonstrated that providers such as RNs and RTs can function safely and effectively in the transport environment without the direct supervision of a physician.[58]

Team configuration has been categorized as *dedicated* and *unit based*. **Dedicated teams are those whose members perform neonatal transport on a full-time basis.** They generally are not assigned to any other major clinical responsibilities. However, between transports, team members may assist with procedures, attend deliveries, or have other responsibilities that do not involve patient care. Dedicated teams can be based in a receiving facility or in a freestanding transport service not affiliated with a hospital.[38] **Unit-based teams are composed of members who, although available for transport, are primarily involved with other clinical duties.** Institutional factors should drive the decision about which type of team to use. These factors often include the acuity of care level managed in the unit, annual volume of transports, financial support, and national, state, or local laws regulating the expanded role of nurses and respiratory therapists in health care.[58] **Regardless of the team composition, the team must have the cumulative expertise to resuscitate, stabilize, and provide critical care throughout the transport.**

Dedicated transport teams originated in the 1970s to 1980s, when regionalized perinatal care was established[38] and large metropolitan hospitals began to experience an increase in the demand for neonatal transport. **These teams often are composed of a nurse designated as team leader and a respiratory therapist as a partner, with a physician or nurse practitioner added to the team when a neonate is critically ill and more advanced procedures may be anticipated.[42,49]** The principal advantage for dedicated teams includes their immediate around-the-clock availability and their advanced training in neonatal resuscitation and stabilization procedures. However, the additional personnel necessary for dedicated teams may make them expensive to maintain. Dedicated neonatal teams were found to transport greater distances, to have larger transport volumes, were more likely to use all modes of transport, and were more rigorous with regard to orientation, annual skills maintenance, use of protocols, and quality assurance activities.[38]

Unit-based teams **usually are made up of staff nurses and respiratory therapists within the neonatal intensive care unit (NICU).[49]** The advantage to having a unit-based, nondedicated transport team is the large pool of trained personnel available around the clock. Qualifications of team members can be based on their daily bedside critical care experience and supplemental education, such as certification as a neonatal resuscitation provider. **The primary disadvantage to this team design is that the transport nurse's patient assignments must be absorbed by the unit nursing staff until he or she returns.** However, unit-based teams are usually very cost-effective because critical care skills are maintained during regular patient care, advanced skill training may be more focused, and administrative oversight duties are diminished.[49]

The American Academy of Pediatrics' Section of Transport Medicine article "Pediatric and Neonatal Interfacility Transport: Results from a National Consensus Conference"[80] describes an additional method of categorizing transport teams. **Four types of transport systems are described: hospital based, community based, EMS based, and a hybrid (mix of the previous three systems).** Hospital-based teams are owned and operated by sponsoring institutions and serve the needs of these institutions. These systems often operate at a net loss. Indirect revenue is generated providing an

overall profit. Community-based teams are most often owned and operated by private companies and are dependent on a mix of adult transports, high volumes, and low expenses. EMS-based teams are typically subsidized by local, regional, and state government funding, including taxpayer revenue. Hybrid teams are gaining popularity with an increased awareness of cost and resource sharing and increased collaboration.[80]

Transport Education and Training

The goal for training of transport teams should be the development of a program that ensures that members will have the combined expertise to effectively assess and manage actual and potential problems in the transport environment. The training program should enable team members to demonstrate their abilities to plan, implement, and evaluate ongoing stabilization efforts and interventions during transport. The scope of this training program should reflect the team member's job description, transport responsibilities, patient population, and modalities of travel.[60,83] Training is often begun during an orientation period but must continue throughout the career of the transport team member. Orientation is accomplished through participation on transport under the supervision of an experienced team member, as well as with the use of didactic and process curricula.[58,80] Cognitive knowledge should be demonstrated in transport and medical content areas.[58] **Team members should be able to recognize and manage life-threatening conditions as appropriate for their transport population.** New team members will need training designed to enhance their current knowledge base and will need to learn and interpret certain assessments, techniques, studies, and procedures not usually expected in their standard or previous positions.[58]

Procedural skills required by transport teams will be defined by patient population, program guidelines, and legal scope of practice. Suggested skills and procedures are described by the AAP.[58] Resourcefulness is required for the development of opportunities to attain and maintain the necessary skills. Laboratory simulations are available for certain skills. Electronic computer-linked simulators are additional resources but are limited by their availability and expense to purchase and maintain. Resources exist within the hospital for attainment and maintenance of procedures and skills and include the operating room, NICU, delivery room, pediatric intensive care unit, and emergency department. Each area provides unique opportunities for skill and knowledge development.[58]

Continual education for transport team members is vitally important because as technology changes, therapies will change. Procedural skills must be maintained because some skills are only performed occasionally if ever in actual practice. Continual learning of rare conditions allows team members to be prepared to initiate appropriate management of these conditions.[58] Multiple modalities are used for continuing education and can include quality improvement initiatives, case conferences, didactics, skills laboratory sessions, case simulation, literature review, computer-based activities, and peer performance.[64,80]

Research related to simulation in health care is supporting the idea that didactic and experiential learning alone is not enough to fully prepare teams to transport patients.[15] Transport teams must maintain competency of many skills and procedures of which some may not be used frequently or at all. Simulation training can be used as an adjunct to transport team education to reinforce knowledge and skills.[15,23] The most recent survey of transport teams found that 80% use simulation as part of their education programs.[64] Procedures can be performed in a safe, controlled environment. Patient care environments (transport vehicle workspace) can be simulated. Simulation training should include interprofessional team members, providing the opportunity to learn collaboration skills and prepare teams to achieve high reliability.[15] Scenarios can be created to assess not only resuscitation skills but also team dynamics. Debriefing is a vital component to simulation. Through facilitated discussions, participants review and critique their experiences.[80]

The use of specialty-specific models has been shown to improve outcomes, collaboration, and care delivery.[34,83] The Circle of Caring Model for Neonatal Transport focuses on collaboration and evaluation, noting that teamwork is a critical component throughout the transport process. Although the model is linear for clarity, the process is very fluid and dynamic.[83] Based on experience, knowledge base, and intuition, the team must collaborate and work through complex thought processes using critical thinking skills to make patient care decisions.

This model serves as a tool to help clarify and improve the transport process, leading to safe and consistent care.[83]

Variability among neonatal transport teams exists related to length of orientation, readiness for independent transport, orientation content, procedures performed, and skills maintenance.[23,38,58,64,82] Competency assessment, based on the medical education model, has also been recommended, thus allowing teams to evaluate individual personnel, focus on educational needs, and ensure acquisition of necessary knowledge and skills.[58,80]

A minimum of 2 years of level III neonatal critical care staff experience is a basic requirement for the nursing and respiratory therapy components of most neonatal transport services. Nurses and respiratory therapists who specialize in neonatal transport should have a basic understanding of neonatal pathophysiology, resuscitation and stabilization techniques, ventilatory management, and radiographic interpretation. In the event of a critically ill patient, a nurse practitioner or physician may serve as team leader with respect to high-level procedures and patient management.[41,42]

Programs using air transport should ensure that all providers, including physicians who may be involved occasionally, have education on air safety, survival methods, and flight physiology (including air transport effects of barometric pressure, g-force, humidity change, potential temperature loss, noise, and vibration).[54,77]

Mode of Transport

The optimal transport of a neonatal or pediatric patient is facilitated by the appropriate use of resources, including staff, equipment, and vehicles. Vehicles used in transport include surface (ground) and air (rotor-wing or fixed-wing) ambulances. A fully integrated transport system would include all three modalities.[58] When initiating a neonatal transport program, the first step should be to identify the geographic catchment area, total number and location of perinatal resources, distance in miles/kilometers, and duration of transport time (ground versus air) between the different levels of care. An important factor is the particular characteristics of the topography of the catchment area, which will help determine the ratio of ground-to-air transport resources required. In areas with good roads and low traffic volume, ground transport may be the only transport system required.[20,33,54,81]

Selecting the proper mode of transport (ground ambulance, helicopter, or fixed-wing aircraft) depends on many variables. However, the safety of the patient and crew must be the foremost consideration when determining the mode of transport. Careful consideration of risks should be made before any patient transport is initiated. **Variables that affect mode of transport and benefits of ground versus helicopter include clinical status of the patient, medical care required by the patient before and during transport, urgency of the transport, and other logistical considerations.** By shortening response time and transport time in a clinically unstable patient, the selection of one mode of transport over another may be lifesaving. Logistical concerns affect the appropriate selection of mode of transport and can include distance, weather, traffic, and accessibility of area.[58]

Potential advantages and disadvantages of the available modes of transport should be considered. Ground ambulances are the most common means for interfacility transport of neonatal and pediatric patients. Ground ambulances offer many advantages over air transport. Ground ambulances are routinely available, can operate in weather conditions that restrict safe air operations, may be more user-friendly and functional with regard to the transport environment, and provide door-to-door service without need for helipad, landing zone, or runway. There are limitations to ground transport. There is a high potential for a rough ride, as well as the possibility of motion sickness for the patient, team members, or family. Ground ambulances have significant time, distance, and access constraints.[58]

Helicopters have strengths and weaknesses as well. Speed of travel is one of the unique characteristics of air transport. There is no need for a runway, and helicopters are able to avoid common traffic delays and ground obstacles and fly into areas that are otherwise inaccessible to other modes of transport. The disadvantages associated with helicopter transport include limitation in cabin size, landing zone requirements, and weather considerations.[58]

Fixed-wing aircraft travel at a greater speed and cover a greater service area compared with ground ambulances and helicopters. Other advantages include a larger patient cabin than that of a helicopter and the ability to fly above or around inclement weather. The greatest limitation of fixed-wing

aircraft is the need for an airport landing that may be a distance from the referral and receiving facilities. Ground transport is needed between referral and receiving facilities and the airport.[58]

Selection of the appropriate mode of transport is not a simple decision, and no single vehicle is ideal for all patients or transport teams. The risks, benefits, advantages, and disadvantages of each mode should be considered, as well as the mission of the team and needs of the patient.[58] In general, when transport time exceeds 2 hours, air transport is more appropriate.[54] However, local ground transport capabilities to and from a referring hospital and airport must be known when fixed-wing air transport is used.

Equipment and Medications

Transport teams should be self-sufficient with dedicated, organized supplies for quick, efficient access.[58] The equipment and medications necessary for neonatal transport are similar to those used in the NICU. Equipment must be light, compact, durable, and motion and g-force tolerant. All electronic equipment should have its own independent power supply (AC/DC capability), adequate visual and audio alarms, and lack of electromagnetic interference.[20,54] Compatibility of all equipment is of vital importance to prevent potential interruption in therapy. Maintenance of equipment should be scheduled on a routine basis and be performed by competent, well-trained biomedical technicians. Equipment should be secured in all transport vehicles by approved methods.[58]

Storage packs should be organized, maintained, and checked on a routine basis by transport team members. It should not be standard practice to rely on or plan to borrow equipment or medications from referral facilities.[58]

Medication storage is of the utmost importance for the delivery of safe care. Special considerations are needed for certain medications such as surfactant and prostaglandins that require refrigeration. Security of controlled substances must be maintained as mandated by institutional, state, and federal regulations.[58]

Sample supply lists for equipment and medications needed for ground and fixed-wing transports of neonates and pediatric patients are available.[58] Table 3.2 **provides a list of common transport equipment and medications.**

Novel Interventions

Because the objective of the perinatal transport team is to bring the intensive care environment to the newborn infant, it is also important **that initial resuscitation and stabilization of the infant be performed by skilled practitioners; this will enhance the role of the transport team to successfully continue to offer appropriate high-quality intensive care during the transport of the baby.** Level II centers should be equipped with surfactant, nasal continuous positive airway pressure (NCPAP) systems, and oxygen-air blenders to give prompt and effective respiratory support while maintaining blood saturation levels within acceptable limits awaiting the arrival of the transport team. Adequate management of the premature infant with surfactant deficiency will include supporting adequate recruitment of the lung and minimizing barotrauma. **It is essential that practitioners have the skills needed for noninvasive surfactant administration and appropriate intubation so they can administer early NCPAP to improve morbidity and mortality and decrease the need for mechanical ventilation.* These requisite skills are necessary in situations in which duration of transport may be prolonged for hours because of unforeseen delays. The use of early NCPAP in the delivery room for infants with respiratory distress is recommended for the management of premature infants with respiratory distress syndrome and term infants with mild to moderate respiratory failure.**[5] Because surfactant is an expensive medication, level II centers can maintain one or two ampules in their pharmacy to be restocked as needed. The use of NCPAP during transport has been evaluated and has been shown to be a safe and efficacious intervention for respiratory support.[59]

The use of a resuscitation device such as the T-piece infant resuscitator (Neopuff Infant Resuscitator, Fisher & Paykel Healthcare, Auckland, NZ) may help decrease the variability of pressures administered to the neonate during resuscitation, stabilization, or administration of surfactant. This device also has the potential to minimize lung damage while supporting lung recruitment with the use of positive end-expiratory pressure.[10,63] This system can also temporarily replace the need for mechanical ventilation if NCPAP is unsuccessful in maintaining respiratory stability.

*References 5, 16, 18, 21, 26, 58, 69, 88.

TABLE 3.2 EQUIPMENT AND MEDICATIONS FOR NEONATAL TRANSPORT*

PHYSIOLOGIC MONITORING AND SAFETY	AIRWAY AND SUCTION EQUIPMENT	RESPIRATORY EQUIPMENT	PROCEDURE EQUIPMENT	IV FLUID AND ACCESS	MEDICATIONS	REFRIGERATED MEDICATION
BP cuffs, #2–#4 (2 each)* Electrodes (2 of each available size) Pulse oximeter probes (2) Dispensable thermometers (2) Skin temperature probes (8) Rectal probe (1) Warming pad portable: chemical (2) 4×4 gauze pads (2) Nonstick gauze pads (2) Bowel bag (1) Sterile rolled gauze (2) Ear protectors (2) Hats (2) Flashlight (2) Tape measures (2)	Laryngoscope (2) Laryngoscope blades (2 of each size) Laryngoscope light bulbs (3) AA batteries (4) Endotracheal tubes (3 of each size) Stylets (4) CO_2 detector (2 self-contained, sterile) Closed suction catheter (2 of each size) Meconium aspiration device (2) Bulb suction (2) Suction catheters (2 of each size) Saline bullets (4) Replogle (2 of each size) Orogastric tubes (2 of each size)	Anesthesia bags (2 per T-PICU infant resuscitator) Self-inflating bag (2) Oxygen mask (2) Facemasks (2 of each size) Infant nasal cannula (2) CPAP prongs (2 of each size) Neonatal flow sensor (2) CPAP circuit (1) Ventilator circuit (1) Point-of-care blood gas equipment (1–2)	Sterile towels (1) UAC tray (1) Single-lumen umbilical catheters (2 of each size) Double-lumen umbilical catheters (2 of each size) Umbilical tape (2) Povidone-iodine (3) Scalpels #11 and #15 (1 each) 4.0 silk suture (4) Dressing for umbilical line (2) Needle aspiration/chest tube kit (2) Transducer (2) Chest tubes, 10 Fr/12 Fr (2 of each size) Heimlich valve (2) Sterile gloves (5 of each size)	D_5W 50 mL (2) NS 250 mL (1) $D_{10}W$ 500 mL (1) $D_{50}W$ 50 mL (1) Heparin sodium 1000 mcg/mL vial (3) Syringes, 3 mL/1 mL (6 each) IV catheter, #22 and #24 gauge (5 each) Access kit, including dressing, tourniquet (2) Butterfly needle (3 of each size) Arm board (2) Heel warmers (2) Lancets (2 of infant and preemie size) Syringes (5 of each size)	Epinephrine 1:10,000 (2) Naloxone 1 mg/1 mL (2) 4.2% sodium bicarbonate (2) Dopamine (2) Dobutamine (2) Acyclovir (1) Ampicillin (2) Gentamicin (2) Vitamin K for injection (1) Eye ointment (2) Lidocaine HCl (1) Adenosine (1) Vecuronium (1) Sterile saline for injection (2) Abboject needle (2) Fentanyl (2) Midazolam (2) Phenobarbital (2)	Exogenous surfactant (1) PGE (2)

*( ) designates numbers of pieces of equipment to be carried in transport kit.

BP, Blood pressure; *CPAP*, continuous positive airway pressure; *NS*, normal saline; *PGE*, prostaglandin E; *UAC*, umbilical artery catheter; *T-PICU*, T-piece infant care unit.

Early mobilization of the transport team for an impending premature delivery or delivery of a sick neonate allows for earlier implementation of tertiary care in the community. There has been a change in philosophy regarding departure of the transport team. The patient need not be born to mobilize a team. Close monitoring of aborted or prolonged transports is necessary to avoid inappropriate use of resources in a region. Time spent awaiting the delivery must also be monitored.

Neonatal transport brings ICU care to the patient including many of the same modes of ventilation as in the NICU. Conventional ventilation as well as high-frequency ventilation can be used to transport infants. During the past 10 to 15 years, **the use of noninvasive respiratory support on transport has increased for all gestational ages.** Multiple reasons may have contributed to this including: increased use of antenatal steroids, surfactant replacement therapy, improved resuscitation protocols, and improved knowledge and availability of noninvasive modes.[61] Nasal cannula, nasal CPAP, and high-frequency nasal ventilation are all examples of noninvasive modes being used (see Chapter 23).

Another important intervention for perinatal transport is the **administration of prostaglandin E_1 (PGE_1) for patients in whom a suspicion of**

cyanotic congenital heart diseases is supported with a positive hyperoxia test and measurement of upper and lower extremity blood pressures. Adequate knowledge of dosing and preparation is fundamental to the successful use of this medication, which can prevent patients with ductal dependent lesions from becoming clinically unstable and developing severe hypoxemia and metabolic acidosis before the arrival of the transport team. The need for intubation and ventilator support to prevent apnea varies depending on the anticipated length of transfer and the dose of PGE_1 necessary to maintain the infant asymptomatic.[13,29] A recent retrospective chart review found that apnea began within 1 hour of initiation of the PGE_1 infusion in neonates diagnosed prenatally with ductal-dependent heart disease. Beginning the transport after the first hour of infusion may make prophylactic intubation unnecessary.[76] Knowledge by the referring physician of the performance and interpretation of the hyperoxia test will facilitate the decision to start PGE_1 and should be part of the maintenance-of-skills program. Level II nurseries should maintain a vial of PGE_1 in stock.

Inhaled nitric oxide (iNO) is used during transport to support term and near-term infants with hypoxemic respiratory failure that does not respond to conventional mechanical ventilation.[14,55] The use of iNO can be lifesaving and may decrease associated morbidities. Use of pre- and post-ductal saturations facilitates the identification of neonates who can benefit from this therapy. During transport, certain adaptations for both ground and air transport must be made to use iNO safely and effectively.

Therapeutic hypothermia is only offered at high-level NICUs and is neuroprotective for infants with moderate to severe hypoxic ischemic encephalopathy (HIE). Passive cooling can be initiated by turning off external heating devices and can be continued on transport.[6] However a 10-year retrospective study of passive cooling found that the therapeutic temperature zone was met in only 52.6% of the neonates during transport.[46] A recent retrospective study evaluated both passive and active cooling on transport and concluded that active cooling increased the odds that the infant would arrive at the receiving center within the therapeutic temperature range.[79] These and other researchers suggest that if cooling is considered on transport, active servo-controlled therapeutic hypothermia be used.[2,53,79] Other considerations while actively or passively cooling a patient during transport include: mode and length of transportation, external temperatures, and the inclusion of ice packs on the transport equipment list.

Neonates managed during transport with other more complex interventions, such as high-frequency jet ventilation (HFJV) and extracorporeal membrane oxygenation (ECMO), have been reported. Mobile ECMO units in Sweden,[12] France,[71] and Italy[24] found that although ECMO during transport is safe, many complications are possible, thus a highly skilled ECMO team is required. The use of HFJV during transport is feasible and has resulted in safe transport of infants needing ECMO[56] and those with congenital diaphragmatic hernia.[91] Use for routine transport cannot be recommended, because of the complexity of training, equipment, and logistics required for HFJV and ECMO. Every country and regional perinatal center must determine its priorities for transport based on epidemiologic studies conducted in its catchment area to support the demand with appropriate resources for adequate perinatal transport.

FAMILY-CENTERED CARE FOR TRANSPORT

Separation of the infant and mother is often a consequence of neonatal transport. This physical separation affects both bonding and attachment, increasing the stress surrounding the delivery of an ill infant.* Creative ways to minimize the negative effects of this separation must be incorporated into the transport process. Whenever possible, transport should allow for the presence of a family member.[58]

Principles of family-centered care used in the inpatient setting should apply to the transport environment. Despite the evidence of benefits, there is no universal acceptance or implementation of family-centered care in transport. Transport members cite multiple reasons for excluding parents, including anticipated difficulty caring for the patient if the parent needs attention, potential difficulty dealing with distraught parents, difficulty controlling the child with the parent present, and general team member anxiety in providing care with parent(s) watching.[58] **Before departure from the referring facility, the transport team**

*References 3, 32, 40, 43, 44, 45, 60,62.

should meet with the parents of the infant, communicating the plan for transport, providing information with regard to the receiving hospital (including phone numbers, directions, and unit-specific guidelines), and answering any questions the parents may have. The transport team should identify a phone number that may be used to communicate with the parents once the infant is transported. In addition, **the transport team should enable the parents to see and touch the infant before departure and should provide the parents with a photograph of their infant.**[54]

Enabling parents to be present during provision of critical care is the cornerstone of family-centered care. The presence of the family during resuscitation continues to gain support. The presence of the family allows them to continue to act as allies in the care of their child and enables them to see firsthand that team members did their best and treated their child with respect, dignity, and empathy.[58]

With the presence of the family during transport, safety should remain the priority. All vehicle occupants should wear appropriate restraints. Family members should be educated if it is unsafe for them to ride in the transport vehicle or in a particular location in the transport vehicle. **The transport team has the responsibility to define a standard of family-centered care during the transport of sick neonates and pediatric patients.**[58]

If family is unable to accompany the child during transport, **upon arrival at the receiving medical center, a transport team member should call the parents to update them on the condition and the safe arrival of their child in the receiving facility.** At this time, the transport team should give the parents the names of those who will be responsible for the care of the infant. Once the infant is admitted into the receiving unit, the receiving physician should communicate directly with the parents and referring physician. Engaging the parents in the caregiving process as soon as possible empowers parents and assists the health care team in devising a care plan that will be mutually acceptable and in the best interest of the infant.

Facilitation of bonding between parents and infant may be improved with the use of webcam technology in the NICU.[75] Webcam technology provides virtual visitation with the infant for the family regardless of the geographic distance between them at the time.

FUTURE OF NEONATAL TRANSPORT

Research, innovation, and enhancement of regionalization networks represent the future for perinatal transport. The mandate for highly motivated leadership able to apply epidemiologic, research, and quality-improvement methodology to the area of perinatal transport is essential for progress. The development and evaluation of new interventions, as well as the evaluation of what we consider "standard therapies," are imperative to more favorable outcomes. An example of the need for further evaluation is the excessive physical strain of the transport process on VLBW infants who are at high risk for intraventricular hemorrhage and specifically looking at ways to decrease sound and vibration during ground and air transport.[8,70] The inclusion of continuous quality improvement at the top leadership level of the organizational structure of the perinatal transport system and the systematic collection of relevant data within an identified perinatal region represents the backbone for research in standing and new technologies. The use of evidenced-based practices is crucial to the improvement of survival without severe morbidity, especially for very preterm infants. A recent prospective multinational population-based observational study found that the combined and simultaneous use of four practices for infants born before 28 weeks of gestation lowered in-hospital mortality and morbidity, corresponding to an estimated 18% decrease in all deaths without an increase in severe morbidity.[90] These evidence-based practices include: (1) delivery in a maternity unit with appropriate level of neonatal care, (2) administration of antenatal corticosteroids, (3) prevention of hypothermia, and (4) surfactant administration within 2 hours of birth and/or early nasal continuous positive pressure.

Special attention must be focused on the referral community to improve resuscitation and stabilization efforts. In addition, benchmarking with regard to morbidity and mortality outcomes for transported patients will provide clarity for evaluation of the transport experience. The ultimate focus of this effort is to improve maternal and neonatal outcomes. Ultimate success will depend on the level of multidisciplinary participation of government, community, and private industry stakeholders.

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4 CARE AT BIRTH

SUSAN NIERMEYER AND SUSAN B. CLARKE

A GOLDEN OPPORTUNITY

The initial evaluation and management of the newly born infant focus on promoting normal adaptation to extrauterine life and integration of the mother–baby dyad as well as detecting significant medical problems so that they can be evaluated and treated appropriately. In adjusting to extrauterine life, the newly born infant experiences a complex series of physical and physiologic changes. These changes result from a variety of processes, including perinatal surges in hormones, labor, delivery, ventilation and oxygenation of the lungs, umbilical cord occlusion, decreased environmental temperature, and activation of the sympathoadrenal system.

Such complex changes are essential for survival. **Every infant must successfully complete this transition in order to survive in the extrauterine environment.** For a small percentage of infants, transition is never achieved; for a slightly larger number, transition is delayed or complicated; however, for most infants, transition is so smooth it appears uneventful.[2] It has been estimated that in **approximately 10% of live births, the active intervention of a skilled individual or team is necessary to ensure a successful transition.**[34] Consequently, the optimum care of the neonatal patient during this period needs to be prospective and anticipatory.

The purpose of immediate care after birth is to support the normal physiologic changes in a newborn's respiratory and circulatory transition from fetal to neonatal life. Normal physiologic changes at birth include expansion of the lungs with air, initiation of gas exchange across the alveolar membrane, and closure of circulatory shunts that were necessary during intrauterine life. **When delivery is complicated by perinatal conditions leading to perinatal depression, the aim of resuscitation is to reverse hypoxia, hypercarbia, and acidosis.** The survival and outcome of distressed newborns depend on timely and effective intervention in the first few minutes after birth.

All resuscitation efforts begin with the basic techniques of drying, providing warmth, and stimulating, with clearing of the airway only as needed.[3,81] Advanced resuscitation includes assessment of oxygenation, supplemental oxygen administration (if needed), bag-and-mask ventilation, endotracheal intubation, chest compressions, and the use of epinephrine and volume expansion. Emergencies at birth may require resuscitation, as well as more advanced procedures during stabilization in the delivery area and transition to the neonatal care unit. **Finally, truly successful resuscitation depends on care of the family, collaborative perinatal decision making, and teamwork and communication among health care professionals.**

PHYSIOLOGY

At birth, a rapid physiologic transition must occur from the intrauterine to extrauterine environment.[43,67] **Effective, regular respirations should begin within the first minute after delivery.**[2,24] Environmental factors, such as a relatively cool ambient temperature and tactile stimulation, assist in initiating respiration. The changes in Pao_2 and $Paco_2$ during birth affect chemoreceptors and aid in the reflexive initiation of respiration. **The initial breath may generate from 20 to 70 cm H_2O**

BLUE type highlights content that is particularly applicable to clinical settings.

of negative intrathoracic pressure to replace lung liquid with air inside the alveoli.[69] A rapid decrease in pulmonary vascular resistance and an increase in pulmonary blood flow occur after expansion of the lungs with air and filling of the pulmonary circuit with blood. This results in increased pulmonary perfusion and oxygenation.[68] Resorption of fetal lung liquid across the respiratory epithelium accelerates during labor, resulting in net clearance of liquid from the potential airspaces.[12] Colloid osmotic pressure and the relatively lower postnatal hydrostatic pressure of blood within the pulmonary circuit assist in absorbing alveolar fluid after delivery. During this process, fetal right-to-left shunts through the ductus arteriosus and foramen ovale gradually close[23] (Fig. 4.1; Table 4.1).

ASPHYXIA AND APNEA

***Asphyxia* is defined as inadequate tissue perfusion that fails to meet the metabolic demands of the tissues for oxygen uptake and waste removal. Asphyxia is characterized by progressive hypoxemia (↓Po_2), hypercarbia (↑Pco_2), and acidosis (↓pH).** Hypoxic tissues convert from aerobic metabolism to anaerobic glycolysis, producing lactate and metabolic acidosis that is initially buffered by bicarbonate.[17] When the buffering capacity is exhausted, acidosis occurs. Acidosis and hypoxemia initially result in reflexive, compensatory cardiovascular changes. After early tachycardia, cardiac output decreases, and generalized peripheral vasoconstriction occurs to maintain a blood pressure adequate for perfusion of the heart and brain. **Prolonged asphyxia results in eventual bradycardia and hypotension as severe acidosis and cardiac failure develop.**

Asphyxia may occur in utero or postnatally. In either circumstance, a well-defined series of respiratory events follows (Fig. 4.2).[17] During ***primary apnea*, respiratory movements cease after a brief period of rapid breathing.** At the same time, the heart rate falls, and neuromuscular tone diminishes. Intrapartum-related events may result in the passage of meconium before birth. If the hypoxic-ischemic event continues, the heart rate falls further, blood pressure falls, hypotonia worsens, and a series of spontaneous deep gasps occurs. Gasping continues but becomes weaker and more irregular and then finally ceases. **After the last gasp, a period of *secondary apnea* begins.**[17,81] Another

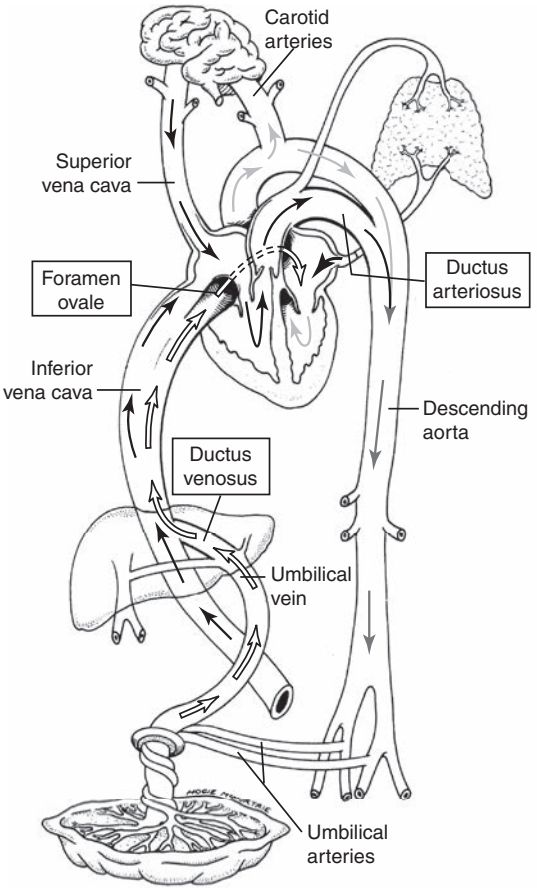


FIGURE 4.1 **Circulatory pattern before birth.** (From Goldsmith JP. Delivery room resuscitation of the newborn. In: Martin RJ, Fanaroff AA, Walsh MC, eds. *Fanaroff and Martin's Neonatal-Perinatal Medicine*. 9th ed. St. Louis: Elsevier Mosby; 2011.)

simple, **functional definition of asphyxia used by the World Health Organization is the failure to establish effective breathing at birth.**[71]

Delivery may occur at any point during an intrapartum-related hypoxic event and the progression to biochemical asphyxia. **If an infant is born during primary apnea, stimulation will usually induce respirations. If delivery occurs during secondary apnea, the infant will not respond to stimulation. Spontaneous respirations will not resume until resuscitation is initiated with assisted ventilation.**[17,81] **In the clinical setting of birth, primary and secondary apnea are essentially indistinguishable.** The infant who is not breathing may have a heart rate of less than 100

TABLE 4.1 COMPARISON OF VASCULAR AND PULMONARY FUNCTIONS BEFORE AND AFTER BIRTH

BODY STRUCTURE	FETAL FUNCTION	EXTRAUTERINE FUNCTION
Aorta	Carries oxygenated blood from left ventricle and deoxygenated blood from pulmonary arteries to fetal organs and placenta	Carries oxygenated blood from left ventricle into systemic circulation
Ductus venosus	Shunts most of the oxygenated blood from placenta to inferior vena cava	Disappears within 2 weeks after birth; becomes ligamentum venosum
Foramen ovale	Connects right and left atria; permits oxygenated blood from right atrium to bypass right ventricle and pulmonary circuit and go directly into left atrium	Functionally closes soon after birth; anatomically seals during childhood
Ductus arteriosus	Shunts blood from pulmonary artery directly into aorta	Functionally closes soon after birth; eventually becomes ligamentum arteriosum
Umbilical arteries and vein	Carry blood to and from placenta, the organ of respiration before birth	Clamped at birth, obliterating placental connections; become ligaments
Lungs	Distended with fluid; minimal pulmonary circulation; fetal respiratory movements	Expanded and aerated; pulmonary circulation allows CO_2 and O_2 exchange; organ of respiration

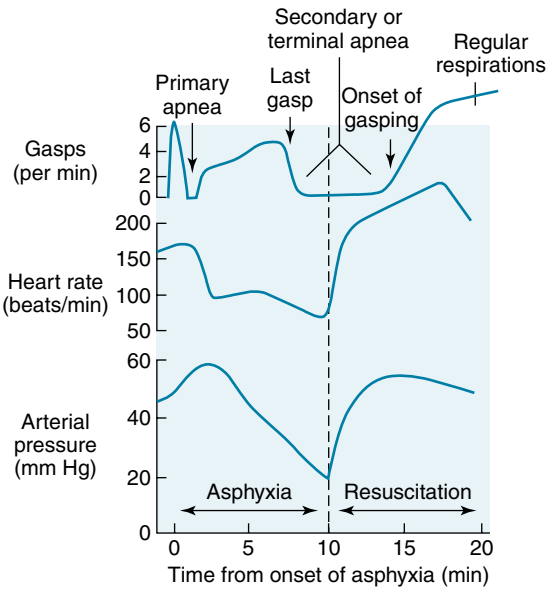


FIGURE 4.2 Changes in physiologic parameters during asphyxiation and resuscitation of rhesus monkey fetus at birth. (From Dawes GS. *Foetal and Neonatal Physiology: A Comparative Study of the Changes at Birth.* St. Louis: Mosby; 1968.)

beats/min and may be hypotonic. **Thus, any infant who is apneic at delivery must be assumed to be in secondary apnea, and intervention should begin immediately.**

The longer the initiation of ventilation is delayed after an infant's last gasp in secondary apnea, the longer the time necessary during resuscitation for the return of the infant's spontaneous respiration. **For every 1-minute delay, the time to the first gasp increases by about 2 minutes, and the time to the onset of spontaneous breathing is prolonged by more than 4 minutes.**[17] In the absence of effective resuscitation after delivery, apnea and decreased cardiac output result in progressive biochemical deterioration.[17]

Severe fetal and neonatal asphyxia impair the physiologic transitions to extrauterine life. The normally high fetal pulmonary vascular resistance may not decrease in the presence of pulmonary hypoexpansion, persistent acidosis, and hypoxemia. As part of persistent pulmonary hypertension of the newborn, pulmonary blood flow and oxygen transfer are impeded, perpetuating hypoxemia, and normal closure of fetal shunts is delayed.[68] This results in persistent right-to-left shunting through the ductus arteriosus and foramen ovale. Lung fluid clearance also may be delayed because of poor lung

inflation or pulmonary hypoperfusion and hypoxemia. In addition, intraalveolar fluid may accumulate as a result of leakage from damaged pulmonary capillaries, resulting in pulmonary edema. **With worsening hypoxemia and acidosis, myocardial function begins to fail, cardiac output falls, and systemic perfusion decreases to the brain, kidney, and intestine, setting the stage for postasphyxial injury of these organs.**[6]

CLAMPING OF THE UMBILICAL CORD

The optimal timing for cord clamping remains a subject for debate, as it has been for decades, but only recently has **management of the umbilical circulation been considered as part of stabilization or resuscitation of the newly born infant.**[58] The approach to the timing of cord clamping is variable worldwide; however, **practice guidelines now generally recommend a delay in cord clamping of 1 to 3 minutes as the standard of care.**[5,87] Maintaining placental circulation during the onset of spontaneous respirations and inflation of the lungs with air smooths the immediate cardiovascular transition. Until pulmonary blood flow increases to supply left ventricular preload, cardiac output and systemic circulation depend on umbilical flow to the right atrium and streaming across the foramen ovale to the left atrium. Premature disruption of the umbilical circulation can result in bradycardia and fluctuations in systemic blood flow and pressure.[11]

Placental transfusion, the amount of blood that flows from the placenta to the infant at birth before cord clamping or cessation of cord pulsations, mediates blood volume as a second major aspect of cardiovascular transition.[27] **A delay in clamping the cord for 30 to 120 seconds after birth facilitates the transfer of an additional 30 to 150 mL of blood from the placenta to the newborn,** with most of the transfer occurring in the first minute.[31] The maximal mean volume of placental transfusion has been reported between 24 and 32 mL/kg of body weight or an additional 30% to 40% of blood volume in the first 3 minutes after birth.[44] **Immediate clamping of the umbilical cord after delivery blocks the normal transfer of blood from the placenta to the infant, resulting in a deficit of as much as 25% of normal blood volume.**[55] The quantity of blood transferred to the infant appears to be influenced by the route of delivery (vaginal, cesarean), the timing of cord clamping, the initiation of respiration and cry, the position of the newborn relative to the placenta (gravity), manipulation of the cord (milking), and the intensity of uterine contractions at the end of the second stage of labor.[52,54,58] **Experimental evidence suggests that the onset of respirations is crucial in optimizing placental transfusion, and the physiologic sequence of delayed cord clamping (DCC) is clamping after the onset of respirations.**[11]

Studies conducted in term infants suggest that early cord clamping (ECC), compared with DCC, results in a greater risk of anemia in infancy.[54] **Late clamping acts as a low-cost intervention to reduce anemia during the first 6 months of life.**[32,36] Despite concerns that the increase in neonatal blood volume with DCC may result in neonatal jaundice and polycythemia, randomized trials in term infants have not substantiated an increased need for special care related to these diagnoses.[44] In fact, **a recent meta-analysis of trials in preterm infants showed a reduction in mortality with DCC.**[30] **Several recent reviews evaluating the potential benefits and risks of late versus early cord clamping in the preterm and term population summarize the evidence that DCC after birth is beneficial to both preterm and term infants.**[31,44,54,65] **In preterm infants, these studies report benefits in terms of improved physiologic stability and reduction in the relative risk of intraventricular hemorrhage and the need for transfusion.**

Although there may be physiologic benefits to delayed clamping, few studies have examined the timing of cord clamping with respect to the need for or response to resuscitation at birth.[9,46] In the event of fetal distress and neonatal depression, immediate clamping of the cord has usually been performed so that the infant can be resuscitated. Ongoing large, randomized clinical trials are examining resuscitation with the cord intact.[13,84] **Clinicians who are charged with the care of the newborn at delivery and thereafter should be part of the decision making around the time of cord clamping, document the time of cord clamping as part of the resuscitation record, and be aware of the implications of either early or delayed clamping for subsequent care.**

RESUSCITATION OF THE NEWBORN

Preparation for Resuscitation

Immediate, effective resuscitation of the newborn infant can reduce or prevent morbidity and mortality. **Much of neonatal resuscitation focuses on accurate assessment and initiation of ventilation. Basic interventions are often all that is necessary to successfully resuscitate a depressed infant.**[35,56,62] **However, effective resuscitation requires anticipation, adequate preparation of equipment and personnel, and teamwork.**[29,83]

In the mid-1980s, the American Heart Association and the American Academy of Pediatrics addressed the need for a national training program for neonatal resuscitation in the United States by developing the **Neonatal Resuscitation Program (NRP). The NRP provides the training necessary for health care professionals to put into practice the scientific consensus established and updated periodically by the International Liaison Committee on Resuscitation (ILCOR).** The ILCOR Consensus on Science is revised according to a rigorous process of evidence evaluation.[63] Changes are then incorporated into regional guidelines and the *Textbook of Neonatal Resuscitation*.[81,88] **The program's widespread acceptance ensures consistent awareness of current scientific consensus, use of proper equipment, and preparation of personnel to work as a team using shared knowledge and performance skills.** *Helping Babies Breathe,* a program for basic resuscitation in resource-limited settings, shares the same evidence base as the NRP; however, it emphasizes the initial steps of resuscitation through bag-and-mask ventilation with air for resource-limited settings where both mother and baby may be cared for by a single birth attendant and advanced interventions are not universally available.[2,57]

The seventh edition of the NRP recommends the following guidelines.[81]

At every delivery, there should be at least one person capable of initiating resuscitation whose only responsibility is the baby. Either this person or another who is immediately available should have the skills necessary to perform a complete resuscitation, including endotracheal intubation and administration of medications.

When a high-risk delivery is anticipated, two persons whose sole responsibility is resuscitation of the infant should be present, and their roles should be designated in advance. Multiple births require a full team of personnel with complete equipment for each newborn.

Care providers responsible for the newborn must be familiar with the prenatal and intrapartum history of the mother and fetus because this information guides preparation for resuscitation. Preterm/postterm gestation; multiple gestation; meconium-stained amniotic fluid; and risk factors in the medical, obstetric, intrapartum, and social history may identify the infant who may require skilled resuscitation at delivery (Box 4.1).[1,8,90] However, **any normal pregnancy may become high risk at the onset of previously unexpected or undetected intrapartum complications, including maternal hemorrhage, cord prolapse, and meconium staining of the amniotic fluid.** Although prevention,

BOX 4.1 CONDITIONS THAT MAY REQUIRE AVAILABILITY OF SKILLED RESUSCITATION AT DELIVERY

Intrapartum Problems

- Fetal distress
  - Persistent late decelerations
  - Severe variable decelerations without baseline variability
  - Bradycardia
  - Meconium-stained amniotic fluid
  - Cord prolapse
- Prolonged, unusual, or difficult labor
- Emergency operative or assisted delivery
- Breech presentation with vaginal delivery
- Narcotic administration to mother within 4 hours of delivery

Medical/Obstetric/Genetic Problems

- Diabetes mellitus
- Suspected or confirmed maternal infection
- Preeclampsia
- Abnormal amniotic fluid volume
- Multiple gestation
- Fetal growth deviations
- Prematurity
- Isoimmunization/hydrops
- Fetal congenital anomalies

BOX 4.2 EQUIPMENT USED DURING NEONATAL RESUSCITATION

Thermal Management
- Radiant warmer
- Warmed blankets or towels
- Infant stocking cap
- Food-grade plastic wrap or polyethylene bags
- Chemically activated warming pad

Airway
- Bulb syringe
- Mechanical suction
- Suction catheters—5 to 6, 8, 10, and 14 Fr
- 8-Fr feeding tube and 20-mL syringe
- Meconium aspirator/suction device
- Shoulder roll

Breathing
- Bag-and-mask ventilation
  - Oxygen source with flowmeter and tubing
  - Neonatal resuscitation bag with 21% to 100% oxygen capability and manometer or pressure release valve and/or T-piece device
  - Facemasks—newborn and premature sizes
  - Oral airways—newborn and premature sizes
  - Pulse oximeter with neonatal probe
  - Oxygen blender and compressed air source
- Intubation
  - Laryngoscope with extra batteries
  - Straight blades—No. 0 and No. 1 with extra bulbs
  - Endotracheal tubes—2.5-, 3.0-, 3.5-, and 4.0-mm internal diameter
  - Stylet
  - Tape, skin preparation
  - Scissors
  - CO_2 detector
  - Laryngeal mask airway

Circulation
- Stethoscope
- Wall clock or stopwatch
- Cord clamp
- Medications (epinephrine, normal saline)
- Sterile gloves
- Chlorhexidine sponges, povidone-iodine solution
- Umbilical vessel catheterization tray
- Umbilical catheters—3.5 and 5 Fr
- Three-way stopcocks
- Umbilical tape
- Suture material
- Intravenous catheters, tubing, fluid
- Needles—25, 23, 22, 20, and 18 gauge
- Syringes—1, 3, 5, 10, 20 or 30, 50, or 60 mL
- Cardiorespiratory monitor and temperature probe (for prolonged stabilization)
- Procedure light

detection, and treatment of fetal asphyxia are the responsibilities of the obstetric team, coordination between obstetric and neonatal services in a "prebriefing" before delivery is vital to ensure timely and effective resuscitation.

Resuscitation equipment, supplies, and drugs (Box 4.2) should always be readily available, functional, and assembled for immediate use in a designated location—ideally in a specific area of the delivery/birthing room or on a radiant warmer/intensive care bed equipped with easily accessible storage (Figs. 4.3 and 4.4).

Prepare to facilitate normal transition or provide neonatal resuscitation by performing the following:

- **Conduct a prebriefing** (Gestation? Amniotic fluid clear? Expected number of babies? Other risk factors?) and **designate roles among the resuscitation team.**
- **Prepare the mother for skin-to-skin care and DCC.**
- **Preheat the radiant warmer.**
- **Assemble basic supplies:** warm linens, head covering for infant, suction device, cord clamp, and appropriate personal protection.
- **Check suction device and equipment for function;** set the vacuum regulator control not to exceed 100 mm Hg.
- **Turn on the air/oxygen flow to the ventilation bag or T-piece device, and check all connections, flow-control valves, the pressure-release valve, and manometer function to enable the ventilation device to deliver a pressure of up to 30 to 40 cm H_2O.** Select the appropriate oxygen concentration for initiation of positive-pressure ventilation. Prepare an appropriate-size facemask and a pulse oximeter with a neonatal probe.

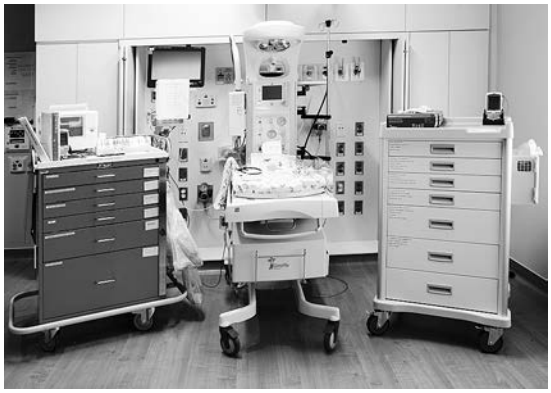


FIGURE 4.3 Labor/delivery/recovery (LDR) room resuscitation area prepared for high-risk delivery. Blended oxygen is available from wall outlets via T-piece device incorporated into the radiant warmer. Flow-inflating bag and manometer are prepared with self-inflating bag as backup. Bulb suction device and catheter for use with wall suction are available. Other supplies for airway suctioning and intubation are stored in the drawers of the supply cart. Resuscitation drugs and umbilical catheterization trays are kept in a separate resuscitation cart accessible from all LDR rooms. (Photo courtesy of Children's Hospital Colorado, Maternal Fetal Care Unit. Photo by Tia Brayman.)

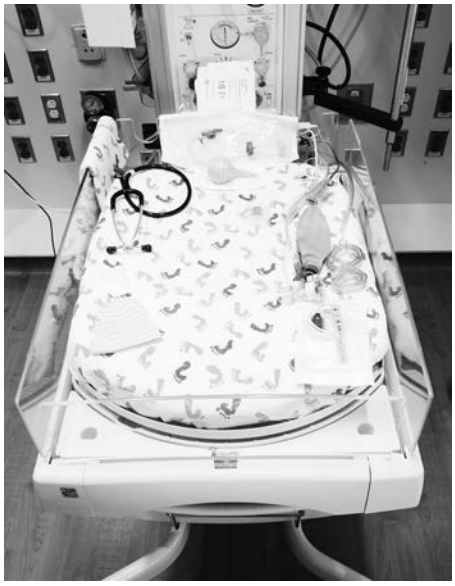


FIGURE 4.4 Patient area of radiant warmer prepared for a delivery. Supplies needed for initial steps and ventilation include warm blankets *(left rear)* for drying, overhead heater for warmth, head covering, suction devices, ventilation bag and masks, pulse oximetry probe and patient connector, stethoscope, and cord clamp. Temperature probe and cardiorespiratory monitor connector are available for prolonged stabilization. (Photo courtesy of Children's Hospital Colorado, Maternal Fetal Care Unit. Photo by Tia Brayman.)

- **Check the laryngoscope** for a bright light source and appropriate blades (size 0 for premature infants and size 1 for term infants); tighten the bulb.
- **Check the availability of appropriate-size endotracheal tubes** (2.5 to 3.5 mm internal diameter).
- **Locate a stethoscope** of appropriate size and confirm that it is functioning properly.
- **Identify a cardiac monitor and leads** for use if positive-pressure ventilation is necessary.
- **Check the ancillary equipment** (e.g., umbilical catheter supplies, intravenous solutions, unexpired resuscitation drugs, alternative airway).
- **If the clinical situation warrants, draw up and label emergency medications** for ready administration, using the estimated fetal weight, and obtain O-negative packed red blood cells for emergency transfusion.

The steps of transition and neonatal resuscitation follow the standard ABCs of resuscitation:

A—Airway
B—Breathing
C—Circulation

With the ABCs as an overall framework for neonatal resuscitation, the components of the procedure can be examined sequentially:

A—Establish an airway:

Position the infant.
Clear secretions from the mouth and nose as needed.
Perform endotracheal intubation or use alternative airway, such as a laryngeal mask, if necessary.

B—Initiate breathing:

Dry thoroughly.
Provide specific tactile stimulation to breathe, if necessary.
Provide free-flow oxygen or positive-pressure ventilation with oxygen based on gestational age and time-specific oxygenation targets (Table 4.2).

C—Maintain circulation:

Delay umbilical cord clamping for at least 1 minute in term and preterm infants. Take steps to establish respirations before umbilical cord clamping.
Provide chest compressions.
Administer epinephrine and volume expander, if indicated.

Each step of the resuscitation procedure, whether uncomplicated or extended, is guided by

TABLE 4.2 TIME-SPECIFIC SATURATION TARGETS AFTER BIRTH

TIME AFTER BIRTH (MINUTES)	SATURATION (%)
1	60–64
2	65–69
3	70–74
4	75–79
5	80–84
10	85–95

Adapted from Weiner GM, ed. *Textbook of Neonatal Resuscitation.* 7th ed. Elk Grove Village, IL: American Academy of Pediatrics and American Heart Association; 2016:77.

the evaluation/decision/action cycle. Evaluation includes assessment of respirations, heart rate, and oxygen saturation (Fig. 4.5).[81] The importance of providing warmth, establishing an airway, drying, and stimulating the newly born to initiate breathing cannot be overemphasized in neonatal resuscitation. **Expansion of the lungs with air and adequate ventilation are the keys to successful resuscitation.** Successful performance of these steps often obviates the need for further intervention, but **inadequate lung expansion and ventilation cannot be overcome by performing chest compressions or administering medications.**

Apgar Score

The Apgar score provides a comprehensive, objective measure of the infant's condition in the first minutes after birth (Fig. 4.6). **The Apgar score does not serve as an indicator of the need for resuscitation; rather, it quantifies an infant's response to the extrauterine environment and resuscitative measures.** In term and preterm infants, the Apgar score remains a valuable predictor of infants who will need ongoing support in the immediate perinatal period and those who are at higher mortality risk in the neonatal period.[16]

Although perinatal asphyxia may be associated with low Apgar scores, it is possible for an infant to have a low Apgar score without having asphyxia.[50] For example, an infant born to a mother who received general anesthesia may be flaccid and have depressed reflexes and poor respiratory efforts. Such infants usually respond

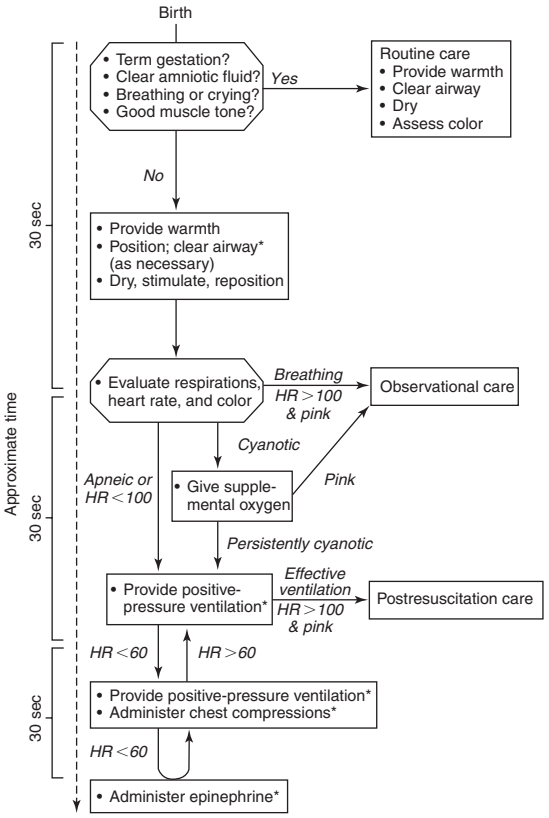


FIGURE 4.5 Throughout resuscitation, the infant's respirations, heart rate (HR), and oxygen saturations are evaluated as a basis for decisions and actions. (From Weiner GM, ed. *Textbook of Neonatal Resuscitation.* 7th ed. Elk Grove Village, IL: American Academy of Pediatrics and American Heart Association; 2016:9.)

rapidly to bag-and-mask ventilation, and no further intervention is necessary. However, an infant may have an equally low Apgar score as a result of intrauterine asphyxia and may require prolonged resuscitative efforts. An infant with a midrange Apgar score between 6 and 7 may be using homeostatic mechanisms to maintain adequate central blood pressure and cardiac output. **Apgar scores should be assigned at 1 and 5 minutes and every 5 minutes thereafter until the score is 7 or greater.** A complete description of the timing and nature of resuscitative measures is vital to interpreting a low Apgar score.[4]

Although the Apgar score is not used to guide resuscitation, **the experienced clinician performs a rapid visual assessment of an infant at the**

Sign	0	1	2	1 min	5 min	10 min	15 min	20 min
Color	Blue or pale	Acrocyanotic	Completely pink					
Heart rate	Absent	Less than 100 min	Greater than 100 min					
Reflex irritability	No response	Grimace	Cry or active withdrawal					
Muscle tone	Limp	Some flexion	Active motion					
Respiration	Absent	Weak cry, hypoventilation	Good,crying					
			Total					

Comments:	Resuscitation					
	Min	1	5	10	15	20
	Oxygen					
	PPV/NCPAP					
	ETT					
	Chest compressions					
	Epinephrine					

FIGURE 4.6 Expanded Apgar score. (From American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 333: The Apgar score. *Obstet Gynecol.* 2005;106:1141.)

moment of birth. This rapid assessment incorporates two elements from the Apgar score, as well as a key question that influences the overall conduct of the resuscitation.

Rapid Assessment after Birth

In the first few seconds after birth, a rapid visual assessment of the baby should be performed to answer the following questions[88]:

- Is the baby term?
- Is the baby breathing or crying (respiratory effort)?
- Is there good muscle tone?

If the answer to all of these questions is "yes," the baby can remain with the mother in skin-to-skin contact to receive routine care as described in the Routine Care and Initial Steps of Resuscitation section that follows.

If the answer to any of the questions is "no," the infant will need further evaluation.[80]

Routine Care and Initial Steps of Resuscitation

The care of every infant at birth includes (1) drying, (2) providing warmth, (3) clearing the airway (positioning and suctioning if needed), and (4) support of breathing with tactile stimulation as necessary.

Whether part of routine care or during the initial steps of resuscitation, many of the actions can be performed simultaneously, especially if more than one person is caring for the infant.

DRY AND PROVIDE WARMTH

- Dry the infant thoroughly, remove wet linens, and place him or her directly on the mother's abdomen; cover both with warm linens during a delay in clamping the cord (routine care).

  or
- If the infant requires positive-pressure ventilation, dry thoroughly and clamp and cut the cord, and place the infant under a radiant heat source.

  or
- Wrap preterm infants less than 32 weeks of gestation in a polyethylene sheet or bag of food-grade plastic from the shoulders to the toes (without drying), with the right arm exposed for pulse oximetry probe placement; clamp and cut the cord; and place under a radiant heat source.[81,88]

POSITION AND CLEAR THE AIRWAY (AS NECESSARY)

- **Ensure that the infant's neck is slightly extended** when positioning him or her on the mother's chest; **wipe secretions from the mouth and nose or clear the airway with a bulb suction device if secretions are blocking the airway or the amniotic fluid contains meconium (routine care).**
  or
- **Position the infant on a flat surface with the neck slightly extended.**
- Turn the head (or the head and body) to the side to allow secretions to pool in the cheek, and then remove with a cloth or suction device. **Suction the mouth and then the nose to clear the airway. The mouth is suctioned first to clear the largest volume of secretions; when the nasopharynx is suctioned, a reflex cough, sneeze, or cry often results.** Deep pharyngeal suctioning in an infant not requiring positive-pressure ventilation or intubation should not be performed during the first few minutes after birth to avoid vagal stimulation, resultant bradycardia, and a delay in the rise of Pao_2.[14,26]

STIMULATE AND REPOSITION

- **Provide tactile stimulation by briefly rubbing** the back for infants who are not breathing or crying after drying.
  or
- **Continue gentle rubbing of trunk, extremities, or head to support early respiratory efforts** in the newborn.
- **Keep the head and neck in a slightly extended position to maintain an open airway.**

Evaluate the Infant

Evaluation of the infant is a continuous, ongoing process. Subsequent action is guided by evaluation during each step of resuscitation and decisions about whether the response is adequate.

EVALUATE RESPIRATIONS

- **Rate and depth of respirations** (chest wall movement, air exchange) must be adequate; **apnea and gasping respirations both require positive-pressure ventilation.**

EVALUATE HEART RATE

- **The heart rate should be greater than 100 beats/min.** Listen over the left side of the chest with a stethoscope to count the heart rate. Count the heart rate in 6 seconds and multiply by 10 for the beats per minute. Indicate each beat for other team members by tapping the forefinger on the bed or tapping the thumb and index finger together.
- **If the heart rate is <100 beats/min or the infant requires respiratory support, heart rate can be measured continuously with pulse oximetry or an electrocardiogram (ECG) monitor.**

EVALUATE OXYGENATION

- **Term, healthy babies may take more than 10 minutes to achieve a preductal oxygen saturation above 95%** and nearly an hour to achieve the same level in the postductal circulation.[19,39,66,73]
- **Give free-flow oxygen and place a pulse oximeter probe on the right hand/wrist if the infant is breathing but remains centrally cyanotic.** Peripheral cyanosis (acrocyanosis) is *not* an indication for supplemental oxygen. **The goal of oxygen administration should be normoxia based on time-specific oxygenation targets, not hyperoxia.**[19,63]

Respiratory Support With Positive Pressure

Consider continuous positive airway pressure (CPAP) for infants who have labored breathing and are unable to maintain SpO_2 within the target range despite increasing oxygen concentration.

Indications for positive-pressure ventilation in the newborn infant include the following:

- **Apnea or gasping respirations despite a brief period of tactile stimulation**
- **A heart rate of less than 100 beats/min**
- **Central cyanosis despite free-flow oxygen or oxygen administered with CPAP**

Prolonged tactile stimulation or administration of supplemental oxygen to a baby who is not breathing effectively or who has a heart rate of less than 100 beats/min only delays appropriate treatment. If supplemental oxygen is unavailable, positive-pressure ventilation should be provided with room air. **When supplemental oxygen is available, it should be administered with the goal of achieving normoxia and avoiding hyperoxia.**[19,63] **Research in animals and humans has demonstrated that room air is equivalent to 100% oxygen for positive-pressure ventilation**

in many newly born infants. The exclusive use of 100% oxygen for postnatal resuscitation, as previously recommended, can result in hyperoxia and changes induced by the generation of oxygen free radicals.[75,77] The concentration and duration of supplemental oxygen administration should be individualized to patient needs. Pulse oximetry, initiated as soon as feasible, can help guide oxygen administration.[18] The ability to administer oxygen in concentrations from 21% to 100% in the delivery setting is a standard of care that has special importance for preterm infants who are more vulnerable to oxygen injury yet may need concentrations greater than 21%.[26,47,61,78,81] Positive-pressure ventilation should be initiated with 21% oxygen for infants >35 weeks. Preterm infants <35 weeks may require 21% to 30% oxygen initially to achieve target saturations. Frequently, preterm infants who have received antenatal corticosteroids and resuscitation with low oxygen concentrations wean back to room air by admission to the neonatal intensive care unit (NICU).

IMPROVE VENTILATION

- The best indication of good mask seal and adequate lung inflation is a rising heart rate and bilateral breath sounds. Oxygen saturation should also rise, and chest movement should be seen with each inflation.
- If heart rate and oxygenation do not improve, take steps to improve ventilation by reapplying the mask and repositioning the head, suctioning mouth and nose and opening the mouth, increasing ventilation pressure, and considering an alternative airway (endotracheal tube or laryngeal mask airway).

Chest Compressions

- If, after 30 seconds of effective positive-pressure ventilation, the heart rate is less than 60 beats/min, intubate or insert an alternative airway, begin chest compressions (two-thumb technique), and increase the oxygen concentration to 100%. Call for help to prepare for possible umbilical venous catheter (UVC) placement and administration of emergency drugs.

Administration of Epinephrine and Volume Expansion

- If the heart rate remains below 60 beats/min despite ongoing positive-pressure ventilation and chest compressions, ensure that ventilation and chest compressions are being given effectively.
- If the heart rate remains below 60 beats/min after 45 to 60 seconds of coordinated chest compressions and effective ventilation, administer epinephrine.
- If the baby is not responding to resuscitation, including administration of epinephrine, and there is evidence of blood loss or hypovolemia, consider administration of a volume expander.

The initial steps in resuscitation should be accomplished rapidly so that the baby is breathing spontaneously or receiving positive-pressure ventilation by 1 minute after birth. The initial rapid assessment can be performed in the first few seconds after birth to determine whether routine care can be provided to the infant in skin-to-skin contact with the mother or whether more extensive evaluation and resuscitation will be necessary during the initial steps. The initial steps of resuscitation can be performed concurrently with evaluation of heart rate, respirations, and oxygen saturations, especially if more than one person is present to care for the infant. Positive-pressure ventilation should be performed for at least 30 seconds before moving to the next level of intervention. When oxygen concentrations of less than 100% are used with positive-pressure ventilation and an adequate response in heart rate does not occur, steps to improve lung inflation should be taken, and then the oxygen concentration can be increased before initiating chest compressions. Chest compressions should be continued for 60 seconds before pausing for assessment. If the resuscitation proceeds to the use of epinephrine, reassessment should occur after 60 seconds to allow the epinephrine to circulate.

An infant who has received more than the initial steps of resuscitation will require close monitoring for additional or recurrent problems during the postnatal transition and may need supportive care such as continued oxygen administration. Infants who require more than brief positive-pressure

ventilation should be monitored in a nursery setting in which they can receive ongoing care.[4]

Skills Necessary for Neonatal Resuscitation

INITIAL STEPS: SUCTIONING FOR MECONIUM-STAINED AMNIOTIC FLUID

Meconium-stained amniotic fluid may be seen in infants who are more than 34 weeks of gestational age and occurs most often in term and postterm neonates. Passage of meconium may be associated with asphyxia. Severe fetal acidosis can result in fetal gasping, leading to in utero aspiration of meconium.[10] Suctioning the mouth and hypopharynx at the delivery of the head and again after complete delivery was advocated in the past to help prevent meconium aspiration. Current evidence no longer advises routine intrapartum suctioning for infants with meconium-stained amniotic fluid.[63,74]

Resuscitation for infants with meconium-stained amniotic fluid should follow the same principles as for infants born through clear fluid. The NRP no longer recommends that any infant with meconium-stained amniotic fluid at birth receive routine tracheal intubation for suctioning because this may delay ventilation beyond 60 seconds after birth.

Nevertheless, **any infant born with meconium-stained amniotic fluid who develops signs of airway obstruction or ineffective positive-pressure ventilation should have tracheal intubation performed for suctioning of any meconium present.** For this reason, **newborns with meconium-stained amniotic fluid require notification and availability of an appropriately credentialed team with full resuscitation skills, including endotracheal intubation.**

ADMINISTRATION OF FREE-FLOW OXYGEN

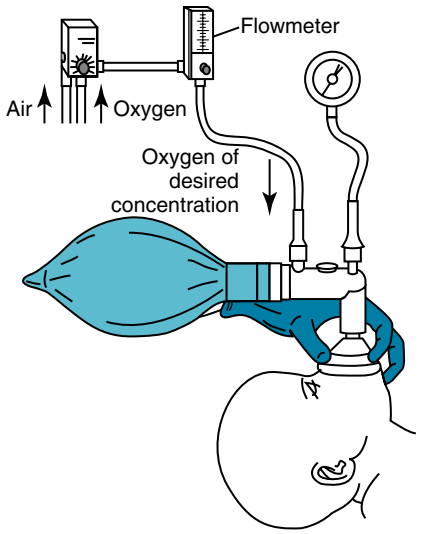
Supplemental oxygen should be administered after the initial steps if the infant remains centrally cyanotic.[88] The administration of oxygen is guided by pulse oximetry to achieve time-specific saturation targets (see **Table 4.2**).[20,91] Oxygen delivered at a flow rate of 5 L/min may be administered by mask or by holding the oxygen tubing in a cupped hand over the infant's face. The delivered oxygen concentration decreases rapidly as the tubing or mask is withdrawn from the face.

Once the target oxygen saturations are achieved, gradually withdraw the oxygen tubing or the mask from the infant's face. If cyanosis persists, reevaluate the quality of respirations and the heart rate, perform a brief physical examination, and consider bag-and-mask ventilation or intubation if there is evidence of respiratory distress.

BAG-AND-MASK VENTILATION

The indications for bag-and-mask ventilation include (1) apnea unresponsive to brief stimulation or gasping respirations, (2) heart rate less than 100 beats/min, and (3) persistently low oxygen saturation despite free-flow oxygen or CPAP with increasing oxygen concentration. The equipment for bag-and-mask ventilation can be either a self-inflating bag with an oxygen reservoir and pressure-release valve or pressure gauge, a flow-inflating bag (anesthesia bag) with a flow-control valve and pressure gauge, or a T-piece resuscitation device.

Although used widely, *self-inflating bags* **do not deliver consistent tidal volumes or inflation pressures, even in the hands of providers who resuscitate frequently.** Some data suggest, however, that self-inflating bags may offer advantages over flow-inflating bags in the hands of inexperienced operators.[41] **Self-inflating bags cannot be used reliably to deliver free-flow oxygen, and they require a special adapter to deliver CPAP** (Fig. 4.7). Ideally, they would be fitted with a CPAP device and a manometer for use with newborns. *Flow-inflating bags* **require a complete seal between mask and face to deliver a tidal volume. They offer the capability to achieve high peak pressures, deliver positive end-expiratory pressure (PEEP) and CPAP, and administer free-flow oxygen.** The volume of the bag should generally be between 200 and 750 mL.[81] Larger bags are more difficult to handle and predispose to overly large tidal volumes, especially for preterm infants. A *T-piece resuscitation device,* as opposed to a bag, can **achieve desired inflation pressures and respiratory times more consistently (at least in mechanical models) but requires setting the inspiratory pressure and PEEP before use and may be more difficult to adjust during resuscitation** (see Fig. 4.7).[20,28,41]



Flow-inflating bags. Flow-inflating bags contain an inflatable gas reservoir that must be connected to a compressed gas source to refill between breaths.

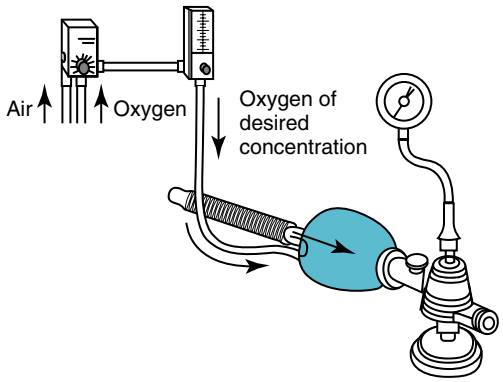
Advantages:

- Ability to deliver 21% to 100% oxygen, depending on the source
- Ability to maintain a positive end-expiratory pressure and measure with manometer
- Easy to determine when there is a seal around the neonate's face
- Ability to deliver free-flow oxygen at concentrations up to 100% depending on the source

Disadvantages:

- Requires an external compressed gas source to inflate
- Requires a tight seal between mask and face to remain inflated
- Requires use of pressure gauge (manometer) to monitor pressure delivered with each breath.

A



Self-inflating bags. Self-inflating bags fill with ambient air and are independent on an external oxygen or compressed air source.

Advantages:

- Will always refill after being squeezed, even with no compressed gas source
- Pressure-release valve makes overinflation less likely

Disadvantages:

- Will inflate even if there is not a seal between the mask and the neonate's face
- Requires an oxygen reservoir to provide high concentration of oxygen
- Cannot be used to deliver free-flow oxygen reliably through the mask
- Cannot be used to deliver continuous positive airway pressure (CPAP) and can deliver positive end-expiratory pressure (PEEP) only when a PEEP valve is added and pressurized gas is entering the bag

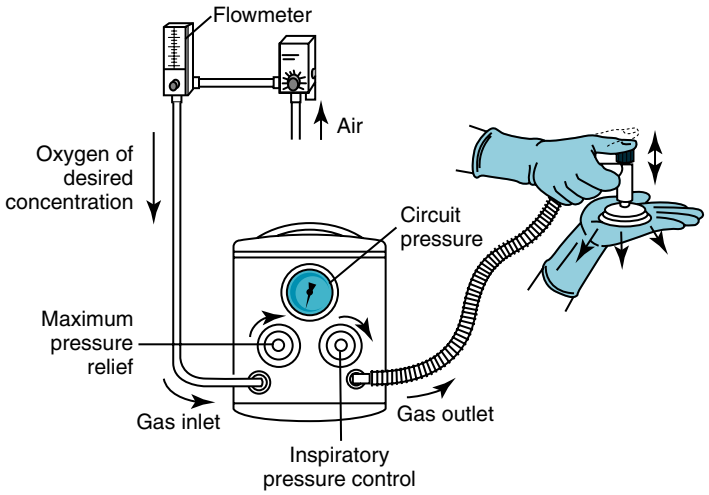
B

FIGURE 4.7 **A**, Flow-inflating bag. **B**, Self-inflating bag. **C**, T-piece resuscitator. (From Weiner GM, ed. *Textbook of Neonatal Resuscitation.* 7th ed. Elk Grove Village, IL: American Academy of Pediatrics and American Heart Association; 2016.)

The facemask should be selected to ensure that it is the appropriate size to cover the chin, mouth, and nose but not the eyes. Masks are commonly available in term and premature sizes to fit even very low-birth-weight infants. **Flexible, translucent masks with a cushioned rim generally provide the best seal with minimal trauma and allow monitoring of mouth position and secretions.**[85,86]

Perform the following steps:

- **Set the flowmeter to deliver 5 to 10 L/min.** Flow rates at the higher end of the range are necessary to achieve higher pressures and faster ventilation rates with a flow-inflating bag.
- **Test equipment before use.** Equipment failure can cause resuscitation failure!
- **Position the infant with the neck slightly extended, place the mask on the chin, and roll it over the mouth and nose (but not the eyes) to make a firm seal.**[86] Avoid compression of the soft tissues of the neck by holding the mask to the face with the thumb and index finger and providing gentle upward pressure with the third finger under the chin.



T-piece resuscitator.
Advantages:
- Consistent pressure
- Reliable control of peak inspiratory pressure (PIP) and positive end-expiratory pressure (PEEP)
- Reliable delivery of 100% oxygen
- Operator does not become fatigued from bagging

Disadvantages:
- Requires compressed gas supply
- Requires pressures to be set prior to use
- Changing inflation pressure during resuscitation is more difficult
- Risk of prolonged inspiratory time

C

FIGURE 4.7, cont'd

- **Ventilate at a rate of 40 to 60 breaths/min with pressures of 15 to 20 cm H_2O for normal lungs or up to 20 to 40 cm H_2O for diseased lungs.** Most apneic preterm infants respond to initial inflation pressures of 20 to 25 cm H_2O.[81] Pressure as high as 30 to 40 cm H_2O may be necessary in term infants not breathing spontaneously. When surfactant is administered immediately after birth, rapid compliance changes may require equally rapid adjustment of ventilation pressures and oxygen concentration.
- **Place ECG leads and connect to a cardiac monitor.** Check the heart rate after 15 seconds of positive-pressure ventilation. Prompt improvement in heart rate is the best indicator of adequate ventilation. If the heart rate is <100 beats/min and chest rise is adequate, continue ventilation. If the chest is not rising, perform the corrective steps of MR SOPA: (1) **reapply the facemask** for a better seal, (2) **reposition** the head, (3) suction **secretions**, (4) **open** the infant's mouth slightly, (5) increase **pressure**, and (6) consider an **alternative** airway.[81]
- **Reevaluate respirations, heart rate, and oxygen saturation after 30 seconds of positive-pressure ventilation.** If the heart rate is <100 beats/min, call for additional help and prepare for intubation or insertion of laryngeal mask airway.
- **Provide CPAP after spontaneous respirations have returned.** End-expiratory pressure decreases lung injury and improves compliance and gas exchange.[45,72] CPAP may have a role in maintaining lung volumes in premature infants and aiding the absorption of lung fluid.[56]
- **Insert an orogastric catheter** (8-Fr feeding tube) after several minutes of bag-and-mask

ventilation or CPAP or if there is evidence of gastric distention.

- **Measure the insertion depth of the catheter** by holding the tip at the bridge of the nose and measuring to the earlobe and then midway between the xiphoid and the umbilicus.[81]
- **Insert the catheter through the mouth,** not the nose, because newborns are obligate nose-breathers.
- **Aspirate gastric contents with a 20-mL syringe and leave the catheter open.**
- **Tape the catheter to the infant's cheek.**

The adequacy of bag-and-mask ventilation must be continuously assessed by monitoring of heart rate, auscultation of breath sounds, visualization of chest wall movement, and oxygen saturations. Peak inspiratory pressure should be limited to that necessary to see an improvement in heart rate and chest wall movement and to hear good air exchange on auscultation of the chest. Inspiratory pressures cannot be judged clinically; bags fitted with in-line pressure manometers or T-piece devices are recommended in the delivery room.[81] Devices that more easily and consistently deliver targeted volumes during positive-pressure ventilation are the focus of much recent research.[70] Strategies to avoid intubation, especially CPAP with limited oxygen concentration, offer the promise of a reduction in the severity of chronic lung disease.[21] Further clinical trials will help establish the optimal method(s) for achieving lung expansion while minimizing the complications of positive-pressure ventilation.[64,78]

Potential complications of bag-and-mask ventilation include trauma to the eyes or face from an improper size or position of the mask, lung injury (especially in preterm infants), air leak (pneumothorax, subcutaneous air), gastric distention elevating the diaphragm, and direct lung compression in the case of a diaphragmatic hernia (Table 4.3). Complications can be minimized by using gentle technique and equipment of the correct size, careful monitoring of pressures, and insertion of an orogastric tube when indicated.

ENDOTRACHEAL INTUBATION

Endotracheal intubation may be performed at several points during neonatal resuscitation.[81] Intubation is indicated when bag-and-mask ventilation is ineffective or prolonged positive-pressure ventilation is needed and when chest compressions are necessary. Additional indications for endotracheal intubation include surfactant administration, suspected diaphragmatic hernia, and direct tracheal suction for obstructive secretions. Equipment for intubation is listed in the "Airway" and "Breathing" sections in Box 4.2.

Select an uncuffed, uniform-diameter endotracheal tube of the correct size (Table 4.4). A variety of sizes (2.5- to 3.5-mm internal diameter) should be available because estimated weights may be inaccurate or airway anomalies may exist. **Orotracheal intubation is preferable to nasotracheal intubation during acute resuscitation because it can be performed rapidly and without additional equipment.**

Perform the following steps:

- Shorten the selected endotracheal tube to 13 cm (or the length appropriate for the fixation method used), and **prepare the laryngoscope, tape, suction, oxygen, bag, and mask.**
- **Position the infant with the neck slightly extended.**
- **Provide free-flow oxygen** as needed to achieve target saturations.
- **Hold the laryngoscope with the left hand;** open the mouth with the right index finger and gently insert the blade.
- **Lift the laryngoscope upward and away so that the blade is nearly parallel to the surface beneath the infant.**
- **Visualize landmarks;** identify the epiglottis, vocal cords, and glottis (Fig. 4.8). If the esophagus is seen, withdraw the blade until the epiglottis drops down. If only the tongue is visible, advance the blade further until it enters the vallecula or passes under the epiglottis.
- **Apply gentle external pressure over the cricoid, which may help visualize the vocal cords.** Pressure may be applied with the little finger of the hand holding the laryngoscope or by an assistant.
- **Insert the endotracheal tube from the right corner of the mouth to just beyond the vocal cord guideline at the tip of the tube,** or measure from the tragus of the ear to nasal septum and add 1 cm to confirm the depth of insertion. Gestational age can also be used to predict insertion depth (see Table 4.4).
- **Limit each intubation attempt to 30 seconds to avoid hypoxia.**

TABLE 4.3 COMPLICATIONS DURING RESUSCITATION AND STABILIZATION

PROBLEM	CAUSE	DIAGNOSIS	REMEDIES
Persistent cyanosis	Inadequate oxygenation		
	• Inadequate Fio_2	Check pulse oximetry saturation and blender setting	Always have available blended O_2
	• Disconnected O_2 line	Check all connections	Reconnect line
	• Empty O_2 cylinder	Check O_2 source	Replace O_2 cylinder
	Inadequate ventilation		
	• Inadequate face mask seal	Diminished breath sounds; little chest wall movement; air leak around mask	Readjust facemask; seal tightly against skin
	• Compression of airway	Diminished breath sounds; little chest wall movement	Apply upward force to mandible to counteract downward force holding facemask in place; extend neck slightly
	• Insufficient insufflation pressure	Diminished breath sounds; little chest wall movement	Increase insufflation pressure until breath sounds are audible and chest movement seen
	• Compression of lungs by distended stomach	Diminished breath sounds; little chest wall movement; visibly distended stomach	Place orogastric tube
	• Malpositioned ET tube	Check tube position with laryngoscope Check breath sounds	Reinsert into trachea Withdraw until breath sounds are bilaterally equal Tape ET tube in place
	Pneumothorax	Check breath sounds Check for chest asymmetry Transillumination Chest x-ray examination	Decompress tension pneumothorax
Bradycardia	Same as for persistent cyanosis	Auscultation of precordium or palpation of umbilical cord base; pulse oximeter or cardiac monitor	Same as for persistent cyanosis External cardiac compression if heart rate less than 60 beats/min after 30 sec of effective ventilation
	Vagal stimulation Perinatal myocardial ischemia	Lack of response to oxygenation, ventilation, and chest compressions	Stop oropharyngeal suctioning Emergency epinephrine/volume expander administration
Hypothermia	Evaporative heat loss; conductive heat loss	Specific signs overlap those of asphyxia and shock Low core temperature	Dry infant; remove wet linen Use polyethylene bags/warming mattress Cover wet hair Keep under radiant warmer
Hyperthermia	Excessive warming Maternal fever	Apnea High core temperature	Servocontrol of warming devices Removal of warming mattress
Hypoglycemia	Glucose stores used before birth or during resuscitation	Specific symptoms overlap those of asphyxia and shock Low blood sugar	Bolus 2 mL/kg of $D_{10}W$ Maintenance infusion of $D_{10}W$
Hemorrhage	Inadequately secured umbilical arterial or venous line	Pallor Poor capillary refilling Leakage of blood	Keep all intravascular tubing connection sites in plain view Tape UAC/UVC in place in addition to suturing lines
	Liver laceration		Perform chest compressions with correct position/depth

ET, Endotracheal; *UAC,* umbilical artery catheter; *UVC,* umbilical venous catheter.

TABLE 4.4 ENDOTRACHEAL TUBE SIZE AND DEPTH OF INSERTION

WEIGHT (G)	GESTATIONAL AGE (wk)	TUBE SIZE (mm) (INSIDE DIAMETER)	DEPTH OF INSERTION (cm FROM UPPER LIP)
<1000	<28	2.5	<7
1000-2000	28-34	3.0	7
2000-3000	>34	3.5	8
>3000	>40	3.5	9

Adapted from Weiner GM, ed. *Textbook of Neonatal Resuscitation.* 7th ed. Elk Grove Village, IL: American Academy of Pediatrics and American Heart Association; 2016.

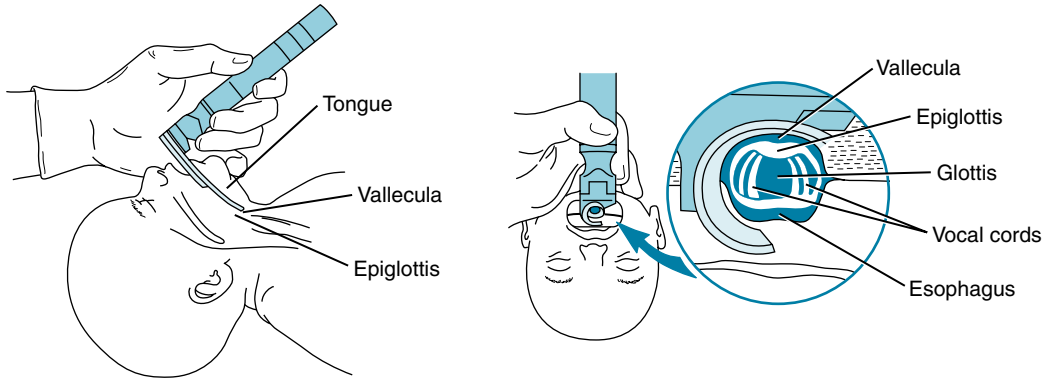


FIGURE 4.8 Anatomic landmarks that relate to intubation. (From Weiner GM, ed. *Textbook of Neonatal Resuscitation.* 7th ed. Elk Grove Village, IL: American Academy of Pediatrics and American Heart Association; 2016.)

- **Confirm endotracheal tube position by exhaled CO_2 detector and by auscultation for bilaterally equal breath sounds in the axillae and absence of breath sounds over the stomach. Observe chest wall movement. Note the centimeter marking at the lip** (see Table 4.4).
- **Secure the endotracheal tube and obtain a chest radiograph.**
- Shorten the endotracheal tube to 4 cm beyond the lips, if necessary.

Complications of intubation include hypoxia caused by prolonged intubation attempts or lack of supplemental oxygen; tube malposition; apnea or bradycardia caused by hypoxia or vagal stimulation; and trauma to the oropharynx, trachea, vocal cords, or esophagus (see Table 4.3). Exhaled CO_2 detection devices may be helpful even in newborn infants weighing less than 2 kg.[89] Color change in detection devices may be delayed in extremely preterm infants, especially if cardiac output is low, as during bradycardia. To prevent complications, provide free-flow oxygen during intubation, use gentle technique, and limit each intubation attempt to 30 seconds.

CHEST COMPRESSIONS

Indications for chest compressions include a heart rate of less than 60 beats/min despite effective positive-pressure ventilation for 30 seconds. Follow the sequence of (A) airway, (B) breathing, and (C) circulation in providing resuscitative support. **Even if the heart rate is less than 60 beats/min shortly after delivery, the airway should be cleared, and positive-pressure ventilation should be given for 30 seconds before beginning chest compressions. Often, adequate ventilation alone will result in a rapid increase in heart rate.**[62] Beginning chest compressions too early may interfere with the effectiveness of positive-pressure ventilation and actually delay an

infant's response to resuscitation.

Perform the following steps:

- **Attach ECG leads and intubate** if not already done.
- **Position the infant** with the neck slightly extended.
- **Provide firm support for the back.**
- **Increase oxygen concentration to 100%**
- **Perform compressions from the head of the bed using the two-thumb technique** (Fig. 4.9). The person providing ventilation moves to the side of the warmer once the intubation is complete and the tube is secured.
  - *Position:* Lower third of sternum[88]
  - *Rate:* 90 times/min
  - *Depth:* One third of the anterior-posterior diameter of the chest
  - *Support:* Encircling fingers
- Provide **90 compressions/min and interpose 30 breaths/min with a 3:1 ratio of compressions to breaths (120 events/min).**[88]
- **Evaluate the heart rate after 60 seconds** by ECG monitoring.
- **Continue chest compressions until the heart rate is greater than 60 beats/min.**
- Administer epinephrine if the heart rate remains less than 60 beats/min **after 60 seconds of coordinated and effective chest compressions with 100% oxygen.**

When the response to positive-pressure ventilation and chest compressions is poor, reevaluate for technical problems and conditions interfering with ventilation. Confirm that oxygen is connected properly and that oxygen has been increased to 100% (see Table 4.3). Ventilate with pressures to expand the chest and breaths interposed between compressions. Evaluate the infant for pneumothorax, diaphragmatic hernia, or hypovolemia (see **Delivery Room Emergencies** later in this chapter).

Complications of chest compressions include liver laceration, rib fractures, and pneumothorax. To prevent complications, check the position of compressions, maintain contact with the chest during the release portion of the compression cycle, and avoid excessive force during compressions.

MEDICATIONS

The indications for drug administration during newborn resuscitation include the following:

- **Epinephrine:** Heart rate less than 60 beats/min despite 60 seconds of coordinated ventilation via endotracheal tube and chest compressions
- **Volume expanders:** Evidence of acute bleeding or signs of hypovolemia; poor response to other resuscitative measures

Perform the following steps:

- **Calculate the correct dosage** of each drug based on the newborn's (estimated) weight.
- **Prepare each drug for administration,** draw up the appropriate concentration and volume, and label the syringe.
- **Administer each drug by the correct route** and at the **proper rate.**
- **Reevaluate for desired effect** and take follow-up action.

Epinephrine increases the rate and strength of cardiac contractions. Perhaps more important during resuscitation is its action as a peripheral vasoconstrictor, directing cardiac output to the central circulation and increasing coronary perfusion pressure.[82] **Epinephrine is most effective when administered by umbilical venous catheter in a dose of 0.1 to 0.3 mL/kg (0.01 to 0.03 mg/kg). Endotracheal administration in a one-time dose of 0.5 to 1 mL/kg (0.05 to 0.1 mg/kg) can be considered while obtaining venous access.** Expansion of plasma and blood volume may also be necessary to maintain cardiac output, blood pressure, and peripheral perfusion.

Volume expansion should be considered when there is evidence of acute blood loss (e.g., placental abruption, bleeding from placenta previa, fetal-maternal hemorrhage, umbilical cord tear, acute neonatal hemorrhage) or poor response to resuscitation (e.g., pallor, bradycardia, exaggerated tachycardia). **Normal saline is the preferred solution for volume expansion in a dose of 10 mL/kg by umbilical venous catheter.**

Complications of drug administration include extravasation with intravascular administration, hepatic injury with low umbilical venous catheters, and unpredictable absorption with endotracheal administration. The use of resuscitation drugs also may result in complications from their adverse pharmacologic effects. Epinephrine, administered in high doses, increases the risk for significant hypertension and a hyperadrenergic state, which may result in germinal matrix hemorrhage or myocardial damage. Absorption of epinephrine after

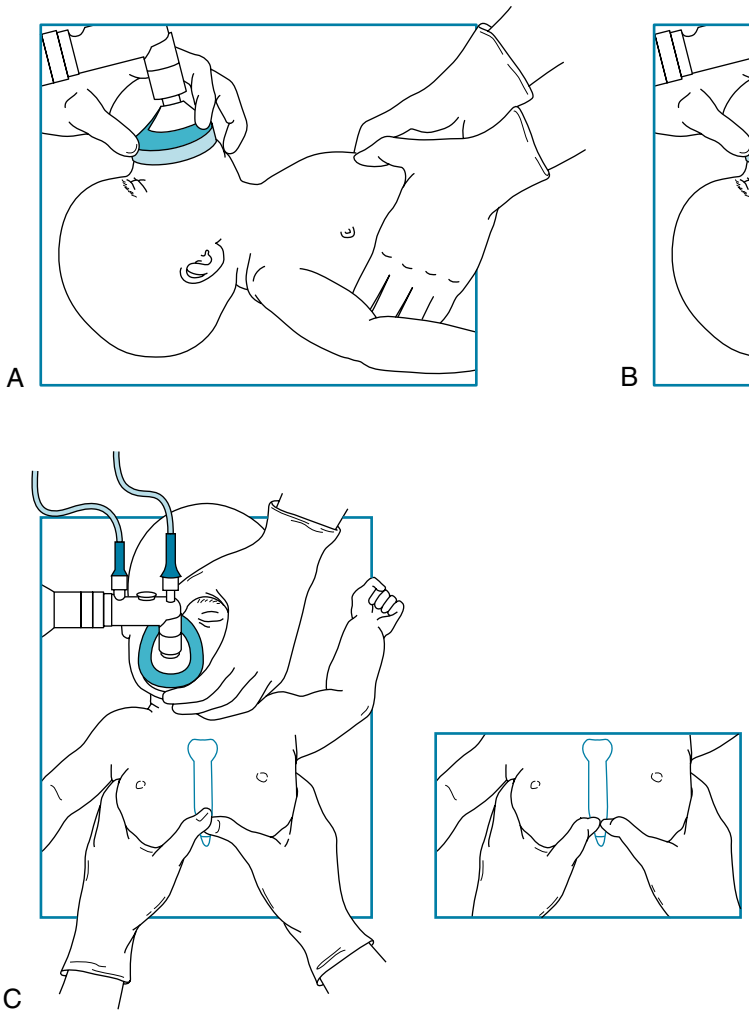


FIGURE 4.9 Two-thumb method of chest compression. Two thumbs placed one over the other or side by side (depending on the size of the baby) compress the sternum; the fingers support the spine. Providing chest compressions from the head of the bed facilitates emergency UVC placement. (From Weiner GM, ed. *Textbook of Neonatal Resuscitation.* 7th ed. Elk Grove Village, IL: American Academy of Pediatrics and American Heart Association; 2016.)

endotracheal administration is erratic.[82] Volume overload may result from administration of repeated doses of volume expanders. Rapid volume expansion, resulting in acute elevation of systolic blood pressure, has been associated with intraventricular hemorrhage.[33]

Distressed newborns have impaired autoregulation of cerebral blood flow, with blood flow directly related to the systolic blood pressure. Increased cerebral blood flow and elevated systolic pressures may be responsible for intraventricular hemorrhage in the presence of a capillary bed insulted by acidosis and hypoxia.[53] Autopsy studies also suggest that increased cerebral venous capillary pressure can initiate intraventricular hemorrhage. **Volume**

expansion should be performed cautiously in preterm or asphyxiated infants, infusing 10 mL/kg aliquots of fluid over a 5- to 10-minute period and evaluating the response before administering repeated aliquots of fluid. The exception to this rule is the infant who has experienced acute perinatal hemorrhage with hypovolemia. These infants should have the circulatory fluid volume restored as rapidly as possible. Complications of medication administration can be prevented by choosing the correct dose, rate, and route of administration and positioning umbilical lines carefully. The infant should be evaluated for adverse effects and response to fluid volume after each medication/volume dose.

Sodium bicarbonate is no longer recommended for use during resuscitation immediately after birth. Although acidosis frequently persists after a prolonged resuscitation, many infants correct an acidosis spontaneously once the asphyxiating circumstances are relieved and adequate ventilation is established. Metabolic correction of pH is a slow process that takes several hours, and treatment with sodium bicarbonate is not necessary. Sodium bicarbonate results in worsened acidosis in the setting of impaired ventilation; bicarbonate also may worsen intracellular acidosis. Furthermore, bicarbonate adds a high sodium load, which may directly depress myocardial performance.[7]

Naloxone hydrochloride is indicated during acute resuscitation only in the very specific circumstance of severe neonatal respiratory depression and narcotic administration to the mother in the last 4 hours. Naloxone is not part of the routine resuscitation of an apneic infant.[81] Establishment of gas exchange with positive-pressure ventilation is the first priority for any infant who does not have adequate spontaneous respirations after birth. Furthermore, naloxone hydrochloride is contraindicated in infants of narcotic-addicted mothers because administration can result in severe abstinence syndrome, including seizures.

Calcium and atropine have little role in delivery room settings. Calcium is indicated for hypocalcemia or hyperkalemia, both of which are infrequent problems in the delivery room. Atropine may mask hypoxia-related bradycardia.

DELIVERY ROOM EMERGENCIES

Certain conditions can present as emergencies in the delivery room (Table 4.5). These conditions may require extensive resuscitation or result in a poor response to resuscitation. **Some situations require special intervention immediately; most merit the involvement of a neonatal nurse practitioner, pediatrician, and/or neonatologist for management.** Coordinated teamwork, with techniques and communication skills acquired through simulation training, can help ensure rapid and effective stabilization.[37,83] Surgical intervention is necessary to complete the treatment of diaphragmatic hernia, abdominal wall defects, and neural tube defects. See Box 4.3 for an outline of emergency procedures in the delivery room setting.

CARE DURING THE TRANSITION FROM THE DELIVERY ROOM TO THE NURSERY

After the infant is stabilized and vigorous, perform elective procedures, such as clamping and shortening the umbilical cord, footprinting, and identification. A head covering prevents heat loss from the large surface area of the head and wet hair. **A vigorous, stable infant may remain in skin-to-skin contact with the mother and breastfeed immediately. The stable infant may complete the transition period with the parents under appropriate observation.**

The infant who has required more extensive resuscitation in the delivery room should be transferred to a special care or intensive care nursery when the infant has been dried and protected from excessive heat loss, adequate spontaneous or controlled ventilation has been established, and the heart rate is greater than 100 beats/min. Note the time of the infant's first respiratory effort and when sustained, regular respirations occur. **Transfer the infant in a warmed transport incubator with necessary support measures, such as supplemental oxygen or positive-pressure ventilation and pulse oximetry monitoring of heart rate and oxygen saturations.[42] Delay elective procedures until the infant is physiologically**

TABLE 4.5 DELIVERY ROOM EMERGENCIES

CONDITION	SIGNS AND SYMPTOMS	ONGOING PROBLEMS	INITIAL RESPONSES
Pneumothorax	Cyanosis, respiratory distress, unequal breath sounds, bradycardia, displaced heart sounds	Continuing asphyxia, shock (poor venous return)	Transilluminate chest, perform needle thoracentesis, evaluate chest tube placement
Choanal atresia; oral/pharyngeal airway anomalies	Noisy respirations, pink when crying but cyanotic when quiet, cannot pass suction catheter per nares	Respiratory distress, intermittent hypoxemia and bradycardia	Supplemental oxygen, oral airway, and prone positioning; or intubation (lower airway anomalies may require emergency tracheostomy)
Extreme prematurity	Respiratory distress	Continuing hypoxemia, hypothermia, possible sepsis, hypovolemia	Intubate, place umbilical lines, evaluate for artificial surfactant, begin antibiotics, consider transport to neonatal center
Sepsis	Respiratory distress, hypotonia, poor perfusion, foul odor	Continuing hypoxemia, shock	Intubate, place umbilical lines, administer antibiotics
Severe asphyxia	Prolonged apnea, bradycardia, poor perfusion, pallor, hypotonia, seizures	Hypoxemia, shock, multiorgan system injury	Intubate, place umbilical lines, give volume expander and vasopressors for shock, consider transport to neonatal center
Hydrops fetalis	Body wall edema, ascites, pallor, poor perfusion, respiratory distress, possibly unequal breath sounds (pneumothorax), distant heart sounds (pericardial effusion)	Hypoxemia, anemia, shock, potential for multiorgan system injury	Intubate, perform posterolateral needle thoracentesis bilaterally if unable to ventilate; consider paracentesis if ascites compromises ventilation; place chest tube for pneumothorax, place umbilical lines, evaluate need for partial exchange transfusion, consider transport to neonatal center
Pulmonary hypoplasia and oligohydramnios	Respiratory distress; flattened, deviated nose; infraorbital creases; low-set, crumpled ears; small chin; deformities of the extremities	Hypoxemia, pneumothorax, pulmonary hypoplasia	Intubate, place umbilical lines, monitor closely for pulmonary air leak, consider transport to neonatal center
Congenital diaphragmatic hernia	Respiratory distress with asymmetric breath sounds, barrel chest and scaphoid abdomen, point of maximal cardiac intensity shifted to side opposite hernia	Hypoxemia, pulmonary hypertension, contralateral pneumothorax	Intubate, decompress bowel with orogastric tube to low intermittent suction, place umbilical lines, arrange transport to neonatal center
Abdominal wall defect	Midline abdominal wall defect at base of umbilical cord (omphalocele) or lateral to cord insertion (gastroschisis) with externalization of abdominal contents	Hypovolemia, respiratory distress, hypothermia, ischemic injury to externalized abdominal contents, infection	Protect exposed tissue with evaporative barrier; begin parenteral fluids at 1.5 times maintenance; place an orogastric tube to low intermittent suction, position infant side-lying with support of exposed organs, monitor temperature and urine output, arrange transport to a neonatal center with pediatric surgery
Neural tube defects	Open spinal defect (myelomeningocele), cranial defect with outpouching brain tissue (occipital or frontal encephalocele), failure of formation of skull and brain (anencephaly)	Prolonged apnea, infection, hypothermia	Provide supportive care unless prenatal diagnosis of lethal anomaly has allowed formation of a plan for limited support; protect exposed tissue with gauze soaked in warmed saline and evaporative barrier; arrange transport to a neonatal center with specialists in spinal defects

BOX 4.3 EMERGENCY PROCEDURES IN THE DELIVERY ROOM

A. Umbilical vessel catheterization (see Chapter 7)
B. Thoracentesis and chest tube placement (see Chapter 23)
C. Partial exchange transfusion for anemia (see Chapter 20)
   1. Indications: Profound chronic anemia (hematocrit [Hct] <25%), as in the setting of hydrops. Distinct from situations of acute loss of blood volume, chronic anemia results in normal blood volume per kilogram, necessitating partial exchange transfusion to rapidly raise the hematocrit.
   2. Procedure
      a. Obtain O-negative packed red blood cells (PRBCs) by emergency release if necessary. PRBCs should be as fresh as possible to minimize risk for hyperkalemia.
      b. Insert a low umbilical vein catheter, and attach a four-way stopcock (exchange set).
      c. Perform an isovolumetric exchange by alternating withdrawal and infusion of 5- to 10-mL aliquots of patient blood and PRBCs to a total exchange volume of approximately 20 mL/kg. The formula is as follows:

$$\text{Exchange volume} = \text{Estimated dry wt} \times \text{Blood volume/kg} \times \frac{\text{desired Hct} - \text{current Hct}}{\text{Hct of PRBCs}}$$

      This equation can be used to estimate the rise in hematocrit for a given exchange volume and a given hematocrit of exchange blood.
      d. Alternatively, place both a low umbilical vein catheter (UVC) and an umbilical artery catheter (UAC). Withdraw from the UAC while infusing PRBCs per the UVC at the same rate to the total exchange volume.
   3. Risks
      a. Thrombotic, embolic events
      b. Infection
      c. Bleeding (from mechanical complications or depletion of clotting factors)
      d. Hyperkalemia (consider use of washed PRBCs for nonemergent partial volume exchanges)
D. Prophylactic administration of exogenous surfactant (see Chapter 23)
   1. Indications
      a. Prematurity
      b. Respiratory distress
      c. Presumed surfactant deficiency
   2. Procedure
      a. Calculate the appropriate dose of surfactant based on birth weight.
      b. Confirm correct endotracheal tube position by centimeter markings at the lip (see Table 4.4) and careful auscultation. Chest x-ray film confirmation is ideal if surfactant is administered during stabilization in the nursery.
      c. Suction the endotracheal tube to clear secretions.
      d. Monitor heart rate and oxygen saturation with pulse oximetry.
      e. Administer surfactant according to manufacturer's directions. Administration options include rapid bolus and gradual infusion combined with positioning of the infant and hand or mechanical ventilation.
      f. Refrain from suctioning for at least 4 hours after surfactant administration.
      g. Monitor chest wall rise, saturations, and arterial blood gases, and adjust ventilator support accordingly.
   3. Complications
      a. Hypoxemia
      b. Air leak
      c. Pulmonary hemorrhage

stable.[48] Depending on the level of care required by the infant and the level of care available in the institution, the infant may need to be transported from the birth setting to receive appropriate care after resuscitation (see Chapter 3).

In the intensive care nursery, place the infant on a preheated open warmer with servocontrol. Avoid overwarming because hyperthermia may be associated with respiratory depression and worsened neurologic outcome after asphyxial insults.[51,61] **Continue adequate cardiopulmonary monitoring, including electrocardiogram, respiratory rate and pattern, and monitoring of oxygen saturation with pulse oximetry** (see Chapter 7). **Obtain serum glucose by heelstick and blood pressure by a Doppler device and blood pressure cuff.** If a UVC was inserted during the initial resuscitation for medication administration, place a peripheral intravenous line and remove the low-lying UVC or replace it with a central umbilical line for maintenance fluid administration. **If blood glucose is low or volume expansion is indicated, begin a glucose infusion or volume expansion via either route.** Evaluate for placement of an arterial line for blood sampling and continuous arterial pressure monitoring. Confirm endotracheal tube and umbilical line placement with an x-ray examination.

Debriefing after resuscitation and stabilization of the infant in the NICU gives those

who attended the delivery an opportunity to have a conversation and reflect on their care, teamwork, and communication. Debriefing identifies aspects of the resuscitation that went well and those that could be improved, with the goal of practice and systems change for continuous improvement.

CARE OF THE FAMILY AND PERINATAL DECISION MAKING

Encouraging the presence of the father or another mature support person at birth is common obstetric practice and should not interfere with care after birth. Ideally, members of the obstetric and neonatal resuscitation team should introduce themselves to the parents/birth companion before the delivery. **Parents have a great deal of anxiety concerning procedures performed on their newborn; a few moments spent describing routine procedures will help allay their fears and avoid misinterpretation.** When problems are anticipated, a calm, professional explanation of neonatal assessment and life-support measures is necessary. **Parental awareness that the medical and nursing staff have anticipated and prepared for possible problems can partially relieve their anxieties.** Care must be taken, however, to avoid instilling undue alarm. Care providers should understand ethical principles and the impact of their personal moral and ethical beliefs on decisions made about resuscitation.[40]

If an infant requires resuscitation or prolonged assessment and support, the attending staff's primary obligation is to provide this care and communicate with the parents. **Parents should be encouraged to have contact with their baby, but the presence of the father or a support person should not interfere with or delay the delivery of care. The pediatric staff should tell the parents what is happening at the earliest possible opportunity because a lack of communication prolongs anxiety for the parents.** A few brief statements to explain the status of the baby and procedures can relieve the anguish of silence. **Especially when a difficult resuscitation is anticipated, it is ideal to designate, in advance, a team member who can keep parents informed.**

When severe perinatal problems are suspected prenatally and confirmed after birth, such as extreme prematurity (gestational age less than 23 weeks, birth weight less than 400 g), anencephaly, or other potentially lethal anomalies, **discussions may be held in advance with obstetric care providers and the family about limiting the extent of resuscitative measures** (see Chapter 32).[40,60] When problems are unanticipated, information is uncertain, or there has been no time for decision making before delivery, intervention in the delivery room may be warranted.[22] This approach allows time for complete information to be gathered and discussed with the family. **If appropriate, support measures can be withdrawn later in the nursery.** When an infant fails to respond to intensive resuscitative measures in the delivery room, a decision, in consultation with the parents, must be made as to when to stop support. **Survival is unlikely if no heart rate has been obtained after 10 minutes.[15,38,49] Discontinuation of resuscitation may be appropriate if, after 10 minutes of full resuscitative effort, there is no return of spontaneous circulation.** The data for infants who have an inadequate response to resuscitation remain less clear. **The probability of survival diminishes and the probability of cerebral palsy increases with the length of time during which Apgar scores remain below 4**. For example, if the Apgar score remains below 4 at 20 minutes, the probability of cerebral palsy in surviving infants is greater than 50%.[47] It is essential to rapidly identify remediable causes of poor response to resuscitation.

Anticipation and recognition of fetal and neonatal problems indicating delivery room resuscitation depend on a knowledgeable and prepared staff working as a team to effectively and efficiently communicate and respond in a critical situation. By applying current evidence in performing the skills necessary for neonatal resuscitation, evaluating the infant's response, and taking the time to discuss resuscitation options and outcomes with the parents and resuscitation team, successful delivery room care and stabilization of the newborn is more likely.

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5 IMMEDIATE NEWBORN CARE AFTER BIRTH

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A neonate must demonstrate a condition of well-being before being considered a normal, low-risk infant. **All neonatal intensive care professionals must understand the normal neonate to care for the sick neonate.** This chapter discusses the initial assessment, transitional period, and gestational age characteristics that are fundamental for providing quality initial care after.

Physical and physiologic changes occur so rapidly after birth that the assessment of the newly born can be divided into four distinctive periods: delivery, transition, the first 24 hours of life, and discharge. Each of these assessments has a specific purpose. These evaluations occur in relation to the age of the newborn infant (minutes, hours, days, and weeks) rather than the location of the mother and infant in the hospital or arbitrary nursery routines.

The evaluation at delivery is aimed at determining the condition of the infant at the time of birth and at detecting potentially life-threatening emergencies. The examination during the next few hours *(transitional period)* **is used to evaluate the infant's adjustment to extrauterine life. The complete newborn examination by a qualified health care provider should ideally be delayed until after initiation of breastfeeding, but completed by 12 to 24 hours.**[8] It is the most important examination, because many findings can be treated or complications can be avoided. Finally, the assessment/evaluation at discharge is of the utmost importance. Although it is not as detailed as the complete examination, it is aimed at **establishing the infant's readiness to leave the hospital and to be cared for by the mother.**

Both the initial complete examination and the discharge examination can be performed with parents present to demonstrate the baby's unique abilities and to answer the parents' questions. These are excellent opportunities to provide support and encouragement as the parents begin to incorporate the new member into their family.

ASSESSMENT AND CARE AT BIRTH

Before the birth, one should obtain pertinent facts about the pregnancy, such as parity, gravidity, fetal losses, estimated birth weight (BW) and gestational age (GA) of the fetus, and, of course, any problems present in the current pregnancy.[116] The results of prenatal screening tests should be available to the clinician at birth. Health care providers should note whether the mother was screened for group B streptococcus and whether she received any antibiotic treatment.[8,44]

During labor, one can observe the frequency and duration of contractions and the maternal and fetal reaction to contractions. Fetal distress, passage of meconium, prolonged rupture of membranes, malodorous fluid, and other signs will alert the attendants to impending problems.

At birth, the most common way to assess the infant's condition is to use the Apgar scoring system.[10] This score provides a comprehensive, objective measure of the state of an infant at given times after birth, traditionally at 1 and 5 minutes (see Chapter 4, Figure 4.7). **The Apgar score standardizes initial newborn assessment and continues to be a predictor of neonatal survival.**[10,146,182] The Apgar score should not be used as the primary indicator for resuscitation because it is not normally assigned until 1 minute of age. **Immediate assessment of respiratory effort is paramount to begin resuscitative**

BLUE type highlights content that is particularly applicable to clinical settings.

procedures if the infant is limp and not breathing (see Chapter 4). If the baby is vigorous, the care provider may place him or her on the mother's abdomen or in her arms; the first Apgar assessment can be done with the infant in skin-to-skin during the delay before umbilical cord clamping. Scoring is repeated at 5 minutes. **Between the 1- and 5-minute Apgar scores, one systematically evaluates the baby for potential or apparent medical emergencies.**

Most infants are vigorous, cry at birth, and breathe easily thereafter. A healthy, vigorous infant generally does not even need suctioning after birth. **With appropriate ongoing monitoring, most infants can be given directly to the mother for skin-to-skin care after birth without compromising the infant.**

Shortly after birth, a *quick estimate of GA* is done. Several tables, charts, and graphs have been developed over time to assist the clinician in performing this task. With practice and experience, the professional will be able to identify approximate GA from the physical appearance. Additional discussion on GA is presented later in this chapter. **Immediately following birth, *a brief but complete initial examination* should be performed on each newborn to assess the condition of the infant** and to ensure that there are no major anomalies or birth injuries, that the infant is pink, and that breathing is normal. **The entire body must be assessed, including overall size, proportionality and contour, respiratory pattern and presence of distress, posture, tone, and state of alertness.** This usually allows the clinician to reassure parents that their infant is well and appears normal. A more detailed evaluation/examination is described later.

The most severely ill neonates are usually apparent after birth. Most of them will have been identified prenatally (e.g., serious congenital anomalies, extreme prematurity), their presence anticipated, and a management plan is made before delivery (see Chapter 4).

EVALUATION AND CARE DURING THE TRANSITIONAL PERIOD

Physiologic Changes and Clinical Stages

The initial evaluation, assessment, and management of a newborn must be directed toward promoting and facilitating normal adaptation to extrauterine life and early detection of significant health problems so that they can be evaluated and treated promptly and appropriately.[91]

The obligatory change of environment at birth necessitates adjustment to the extrauterine environment in a complex series of changes essential for survival. Every infant must complete this process of transition successfully to survive in the extrauterine environment. For a small percentage of newborns, transition is never achieved; for a slightly larger number, transition is delayed or complicated. For most newborns, transition is so smooth it appears uneventful.

With the first breath, all neonates begin the transition from intrauterine to extrauterine life. Three major changes take place at birth. First, fluid in the alveoli is reabsorbed and air fills the alveoli, allowing for gas to diffuse into and out of the pulmonary blood vessels. Second, when the umbilical arteries and vein are clamped, the low-resistance placental circuit is gone and systemic blood pressure increases. Third, pulmonary vascular resistance decreases as a result of mechanical distention of the alveoli and increased alveolar oxygen content. Oxygen is a potent pulmonary vasodilator.

During the first few hours after birth, the normal newborn progresses through a fairly predictable sequence of events, recovering from the stress of birth and adapting to extrauterine life. Intrapartum and immediate neonatal events result in sympathetic discharges reflected in changes in heart rate, color, respiration, motor activity, gastrointestinal function, and temperature. **Awake and sleep states affect a neonate's behavior and ability to respond to the environment.** A newborn may go from one state to another quite frequently after birth and at home (see Critical Findings: Newborn States and Considerations for Caregiving in Chapter 13). Fig. 5.1 **shows the classic description by Desmond of the transitional period, which includes the three stages shown in** Box 5.1. Failure to establish this pattern of transition requires careful observation and investigation.

Management of the Newborn during Transition

Traditionally, "normal newborn" care was based on the optimistic assumption that most newborns have no difficulty with transition after birth and that

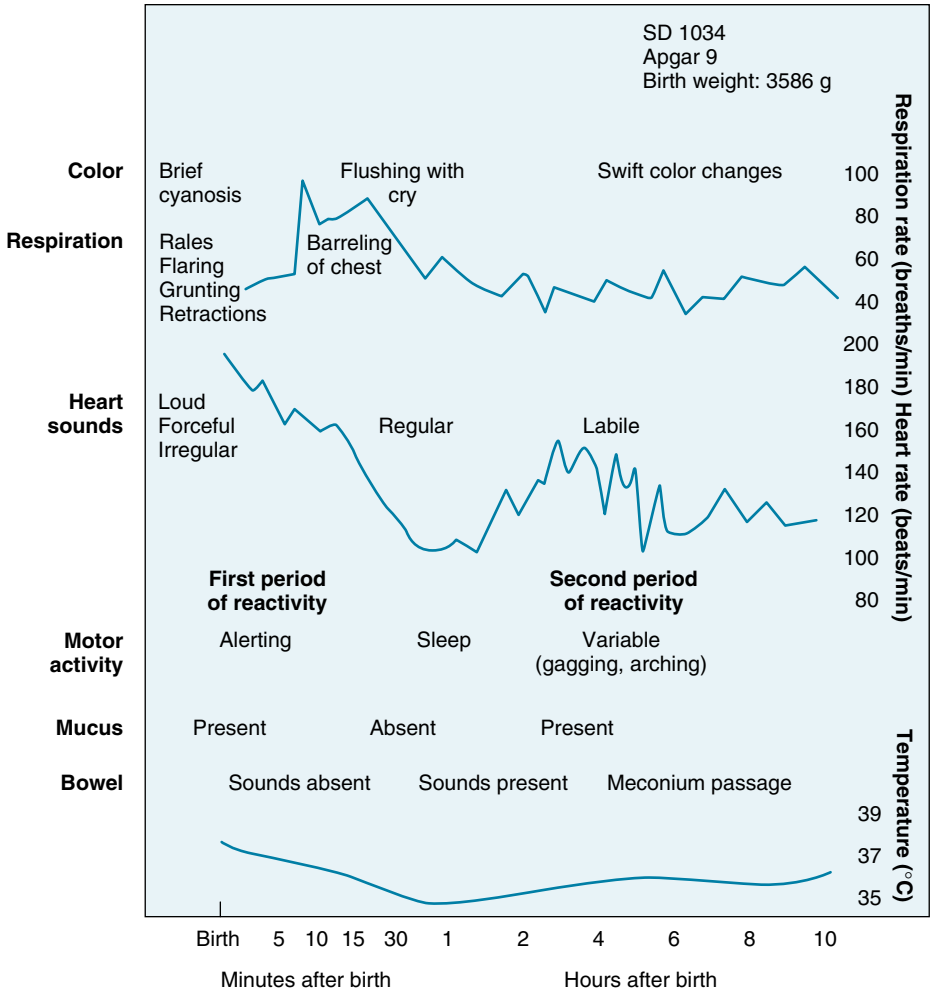

FIGURE 5.1 Critical findings: Neonatal transitional period. (From Desmond MM, Rudolph AJ, Phitaksphraiwan P, et al. The transitional care nursery: a mechanism for preventive medicine in the newborn, *Pediatr Clin North Am.* 1966;13:651.)

term infants, in particular, do exceedingly well.[91] Individualized newborn care recognizes the complexity of transitioning to extrauterine life, the need to support that transition, and the reality of serious disease, even in term newborns.

Newborn Should Be Treated as a Recovery Patient

SKILLED PROVIDERS SHOULD CARE FOR THE NEWBORN

Current standards of care[8] require skilled health care providers (24 hours/day) to care for newborns during the first minutes after birth (e.g., in the delivery room, at the birth center) and in the transitional period (e.g., in the birth room, mother-baby area, newborn nursery).[91] All personnel caring for the newborn must be familiar with the transitional changes after birth and deviations from normal transitional events. After a normal, low-risk pregnancy and birth, primary evaluation and care of the newborn must be provided by nurses with neonatal-perinatal competencies who consult advanced practice nurses and/or physician(s) when appropriate.[8,91]

BOX 5.1 TRANSITIONAL PERIOD

First Stage (0 to 30 Minutes) = First Period of Reactivity

- Rapid increase in heart rate to the range of 160 to 180 beats/min (0 to 15 min)
- Gradual decrease in heart rate over 30 minutes to baseline rate between 100 and 120 beats/min
- Irregular respirations (first 15 minutes), peak respiratory rates between 60 and 80 breaths/min
  - Rales present on auscultation
  - Grunting, flaring, and retractions may be noted, and brief periods of apnea (<10 seconds in duration)
  - Plethora
  - Alert with spontaneous startle reactions, gustatory movements, tremors, crying, and side-to-side head movements
  - Decrease in body temperature
  - Generalized increase in motor activity, with increased muscle tone
  - Bowel sounds absent, and abdomen distended
  - Production of saliva minimal

Second Stage (30 Minutes to 2 Hours) = Period of Decreased Responsiveness

- Newborn either sleeps or has a marked decrease in motor activity
- Muscle tone returns to normal, but responsiveness is diminished
- Fast, shallow, synchronous breathing (60 breaths/min) without dyspnea occurs
- Newborn's color is pale but pink with excellent perfusion and capillary refill
- Increase in anterior-posterior diameter (barreling) of the chest is usually present
- Heart rate decreases into the range of 100 to 120 beats/min or lower; the newborn is relatively less responsive to external stimuli
- Abdomen is rounded, and bowel sounds are audible; peristaltic waves may be visible, and meconium may be passed
- Oral mucus is absent
- Spontaneous jerks and twitches are common, but the newborn quickly returns to rest

Third Stage (2 to 8 Hours) = Second Period of Reactivity

- Return of and possible exaggeration of responsiveness
- Labile heart rate: periods of tachycardia
- Brief periods of rapid respirations: At 2 hours of age: median respiratory rates: 46 breaths/min; 95th percentile respiratory rates of 65 breaths/min; 5th percentile: respiratory rates 30 to 32 breaths/min.[186] Rates higher when awake, rather than asleep, boys higher than girls, and after heavy meconium staining of amniotic fluid; no difference in rate between vaginal versus cesarean birth.[186]
- Abrupt changes in tone, color, and bowel sounds
- Possible prominence of oral mucus; gagging and vomiting not unusual
- Possible clearing of meconium from the bowel
- Increased responsiveness to endogenous and exogenous stimuli
- Newborn hunger cues; quiet alert periods when maternal bonding is established

Modified from Hernandez JA, Thilo E. Routine care of the full-term newborn. In: Osborn LC, DeWitt TG, First LR, et al, eds. *Pediatrics.* St Louis, MO: Mosby; 2005.

STANDARDS FOR ROUTINE CARE AND PHYSIOLOGIC MONITORING DURING TRANSITION MUST BE MAINTAINED

Parent-infant bonding, skin-to-skin care, early breastfeeding, and careful neonatal monitoring during the transitional period should be addressed in delivery/birth room and other facility routines. After birth, the stable, pink newborn whose Apgar score is greater than 7 at 5 minutes can remain skin-to-skin with the mother.[148] **Immediate skin-to-skin contact in the first hours after birth facilitates early initiation of breastfeeding in the setting of a stable neonate under continuous monitoring. After birth, at 15-minute intervals, *every* newborn must be assessed for general condition, respiratory effort, color, muscle tone, and temperature; all assessments must be documented.[91] The mother and infant should not be left alone in the first hours after birth.**

Skin-to-skin care benefits parents, premature neonates, and full-term neonates after vaginal, operative vaginal, and cesarean birth (see Table 5.1 and Fig. 5.2). Skin-to-skin care not only prevents hypothermia[26] but also is effective in treating hypothermia.[131] In a randomized study of skin-to-skin versus incubator care for rewarming low-risk hypothermic neonates, **skin-to-skin care** was shown to be more effective (90%) than incubator care (60%)[51] (see Chapter 6).

Even newly born, **low-birth-weight (LBW) infants (1500 to 2500 g) transitioned by skin-to-skin care with their mothers have been shown to stabilize their cardiorespiratory function better than LBW infants cared for in incubators.** This randomized controlled trial (RCT) also found that

TABLE 5.1 BENEFITS OF SKIN-TO-SKIN CARE FOR PARENTS AND NEWBORNS AFTER VAGINAL AND CESAREAN SECTION BIRTHS

BENEFITS AFTER VAGINAL BIRTH	BENEFITS AFTER CESAREAN BIRTH
Psychological (Parental)	***Psychological (Parental)***
Promotes maternal and paternal infant bonding as a result of increased release of oxytocin[47,58,143,148]	Enhances family bonding, attachment, and satisfaction[174]
Facilitates the process of becoming a parent; either restores or drains energy[12,13]	Increases vocal interaction with newborn[192]
Increases positive activities with the newborn and growing infant[148]	
Decreases expense because infant formula does not have to be purchased	
Psychological (Maternal)	***Psychological (Maternal)***
Enhances birth experience[93]	Enhances perception of own health, quality of life, and satisfaction with birth experience[79]
Increases confidence and competence[148]	Decreases anxiety and pain;[148,198] decreases administration of medications for anxiety and pain[198]
Decreases postpartum cortisol levels, postpartum depression[28] and anxiety[58]	Rise in maternal salivary alpha-amylase directly after delivery when baby held skin-to-skin intraoperatively[107]
More positive maternal interactions at 1 week, 2 months, and 3 months of age[29]	Decreases maternal oxidative stress[207]
Decreases maternal pain during episiotomy repair[163]	Describes skin-to-skin care with father as the formation of the family[78]
	Prefers father to provide skin-to-skin if mother unable, rather than newborn be alone on a radiant warmer[78]
Psychological (Paternal)	***Psychological (Paternal)***
Promotes parental role attainment[164]	Increases conversation with mother[192]
Increases involvement and sensitivity toward newborn[191]	Facilitates more equal parenthood[139] because togetherness with infant enables the father to immediately and gradually change to "father" as he assumes the primary parenting responsibility and role with his newborn[70]
Exhibits more caring[191] and interactive behaviors[164]	No influence on initiation of breastfeeding or exclusive breastfeeding rates at 3 or 6 months of age when compared to maternal skin-to-skin contact.[85]
Increases confidence and comforting behaviors toward neonate	
Facilitates more equal parenthood[143]	
Decreases cortisol levels, stress, and anxiety[58,164]	
Decreases relationship problems with mother of baby[130]	
Physiologic (Maternal)	***Physiologic (Maternal)***
Decreases postpartum hemorrhage[157] as a result of increased oxytocin secretion[58,157] with breastfeeding	Significant reduction in blood pressure and respiratory rate[139]
Breastfeeding	**Breastfeeding**
Earlier initiation of breastfeeding[50,84,88,114,193] Increases incidence and duration[29,50,84,194]	Initiates earlier breastfeeding, infants were exclusively or predominantly breastfeeding at discharge, 3 months,[79,85] and 6 months of age.[85]
Assists in resolution of early breastfeeding problems such as latch-on[180]	More likely still breastfeeding at 1 month and 4 months of age/more successful[128]
Increases breastfeeding self-efficacy[5,138]	
Full Term Newborn	
Novel bioactive substances in human colostrum may assist in postnatal adaptation related to thermoregulation, vascular adaptation, glucose metabolism, lung function, and fluid homeostasis[32]	
Breastfeeding within the first hour of life decreases neonatal mortality by 33%[167]	
Higher breastfeeding rates[153] and breastfeeding exclusivity at 6 weeks,[128,163] 1 month,[115,128] 4 months,[128] and 6 months of age.[128]	
More likely to breastfeed successfully during first feeding[128]	
Enhances breastfeeding benefits: fewer postnatal infections (ear, gastrointestinal, and respiratory); decreased incidence of SIDS and chronic illnesses (obesity, diabetes, cardiovascular)[179]	
Dose-dependent relationship between the use of fentanyl administered by epidural and synthetic oxytocin and the inability of the newborn to initiate suckling in the first hour of life while skin-to-skin with mother.[34]	

Continued

TABLE 5.1 BENEFITS OF SKIN-TO-SKIN CARE FOR PARENTS AND NEWBORNS AFTER VAGINAL AND CESAREAN SECTION BIRTHS—CONT'D

BENEFITS AFTER VAGINAL BIRTH	BENEFITS AFTER CESAREAN BIRTH
Physiologic (Neonatal)	***Physiologic (Neonatal)***
Full-Term Newborn	**Full-Term Newborn**
Decreases cortisol levels resulting from less birth stress[122,181] and a larger decline in neurosteroid levels with more skin-to-skin contact[122]	Decreases newborn stress[159] resulting in less crying (within 15 minutes of starting skin-to-skin care with father),[71] calmer and better relaxation[71,144,192]
Improves thermal stability: less hypothermia, improved ability to remain in thermal neutrality[140,164,172,193]	Reaches drowsy state sooner (within 60 minutes after birth)[71]
Promotes earlier cardiopulmonary stabilization:[128,181] Higher Spo_2 and slower heart rate combined with a slower increase in the first 3 minutes; Less tachycardia and more bradycardia in the first minutes after birth[166]	Prefeeding behaviors facilitated[71]
Improves blood glucose regulation; higher blood glucose levels.[128]	Initiates vocalization with parents (within 15 minutes of initiating skin-to-skin care), which further promotes bonding and attachment[192]
Nonpharmacologic intervention for neonatal pain resulting in less crying and lower pain scores[1,83,164]	Thermal stability[22,79]
Premature Newborn	Lower transfer rates to NICU[150,158]
Improves physiologic stability: better temperatures, oxygen saturations, heart rate and blood glucose levels;[141] similar first body temperatures and blood glucose levels in moderately preterm infants (34–35 weeks gestational age) when compared to incubator care[110]	Fewer suspected neonatal infections[150]
Nonpharmacologic intervention for neonatal pain[141,142]	
Decreases late preterm infant's cortisol reactivity to handling, improves concordance between mother/infant salivary cortisol levels[130]	
Improves infant-to-parent bonding because of close proximity	

FIGURE 5.2 Skin-to-skin care and family bonding in the first hours after birth.

LBW infants transitioned with skin-to-skin care had less need for respiratory support, intravenous fluids, and antibiotics during their hospitalization.[49] Because of the extensive research evidence, the World Health Organization (WHO), American Academy of Breastfeeding Medicine (ABM),[2] American Academy of Pediatrics (AAP),[8,73] Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN).[13] International Childbirth Education Association (ICEA),[96] Neonatal Resuscitation

Program (NRP),[200] and Centers for Disease Control and Prevention (CDC)[45] recommend skin-to-skin contact for the term newborn after birth. **The AAP and ABM recommend that full-term neonates be placed in immediate skin-to-skin contact after birth and remain there until after the first breastfeeding.[2,8] The CDC[45] recommends that the full-term newborn remain skin-to-skin throughout the postpartum period as a strategy to facilitate breastfeeding.**

The triad of nearly continuous skin-to-skin care, exclusive breastfeeding, and close follow-up after discharge comprises kangaroo mother care (KMC) or kangaroo care (KC). Promoting universal KC, the International Network on Kangaroo Mother Care recommends KC as soon after birth as possible for as long as appropriate.[141] Even in the LBW infant, continuous KC that is initiated early results in a significantly higher proportion of exclusive breastfeeding at 6 months.[135] **Using skin-to-skin care after birth should be standard practice that is vigorously promoted by all maternal-neonatal health care providers.**[93,197] Skin-to-skin contact in the first hour of life is estimated to occur in only 1 of 4 newborn infants.[76] Globally breastfeeding within the first hour of life occurs in only 2 of 5 newborns.[187] Initiation of breastfeeding later than the first hour of life increases the risk of neonatal mortality by 33%, while initiation after 24 hours of life increases neonatal mortality by 50%.[187] Challenges to the implementation of early and prolonged skin-to-skin care and strategies to address these barriers are listed in Table 5.2.

Following a period of 60 to 90 minutes after birth, with close monitoring during skin-to-skin care and initiation of breastfeeding, routine care includes a complete physical examination and preventive interventions. Routine care can be provided at the mother's bedside. Elements include eye prophylaxis, administration of vitamin K_1, as well as glucose screening when indicated (see Table 5.3). **By 60 to 90 minutes of age, *every* newborn, regardless of where the baby is being cared for, must be examined by a nurse with neonatal-perinatal competencies. During the first 6 hours after birth, heart rate, respirations, blood pressure, degree of alertness, and color of skin and mucous membranes should be assessed frequently and the findings recorded.** This period is when clinical signs of the most threatening infections, cardiopulmonary diseases, and major congenital abnormalities appear. **Table 5.4 presents a useful scoring system for assessing the pattern of respirations for signs of respiratory distress; findings should be documented. The range of blood pressure in term infants during the first few hours of life is 65 to 95 mm Hg systolic and 30 to 60 mm Hg diastolic, with an average mean blood pressure of 50 to 55 mm Hg.** The blood pressure value will steadily increase from birth over the transitional period.[91]

Abnormal Transition

Regardless of GA or route of delivery, the sequence of clinical behavior just described is common to all well newborns. Preterm infants may exhibit variations in the duration of the transitional phases—shorter phase 1 or longer phase 2—but the patterns are similar. **Knowledge of the normal changes occurring during transition enables early recognition of a newborn who is not making a normal extrauterine adaptation.**[91]

Failure to make a normal transition to extrauterine life may result from obstetric anesthesia or analgesia, neonatal illness, or stress of intrapartum hypoxic-ischemic events. **If the infant's pulse, respirations, color, and activity have not stabilized within the normal ranges *after 1 hour of life,* a problem should be suspected and investigated.**

Observation for risk factors for abnormal transition is essential. A variety of conditions may result in significant deviation from the normal sequence of events during transition. Table 5.5 lists factors that may alter the sequence or pattern of changes expected to occur after birth and that result in either a healthy newborn or a newborn with significant illness. **The health care provider's challenge is to discriminate between signs of diseases that produce an ill newborn and the dynamic, rapidly changing features that accompany the physiologic adjustments of normal or altered transition but that still result in a healthy neonate.**[91] Box 5.2 lists clinical manifestations of abnormal transition.

PHYSICAL ASSESSMENT OF THE NEWBORN

Data Collection

HISTORY

Good perinatal care requires the identification of social, demographic, and medical-obstetric risk factors that correlate with fetal outcome. This must

TABLE 5.2 CHALLENGES TO THE IMPLEMENTATION OF EARLY AND PROLONGED SKIN-TO-SKIN CARE AFTER BIRTH

CHALLENGE/BARRIER	STRATEGY FOR CHANGE
Professional (level of education, years of experience, and primary practice settings)[197] and parental beliefs, attitudes, and knowledge about skin-to-skin care.	Professional education about parental and neonatal benefits, recommendations for use of skin-to-skin care and implementation strategies.* Parental education about the benefits of skin-to-skin care: (a) beginning in childbirth education classes and during clinic visits and (b) reinforced postpartally by all members of the health care team.[93,94,108,210]
Institutional culture that does not value skin-to-skin care as a standard of practice for all parents and newborns.	A written policy that establishes skin-to-skin care as the standard practice for the maternal-newborn department, as well as all departments providing services to mothers and their babies.[15,62,175] The policy defines expectations for use of skin-to-skin care, who is responsible, who is eligible, and how safe skin-to-skin care is to be provided.[63,73,93,108] Using an implementation algorithm to analyze the implementation of skin-to-skin care in the first hour after birth[33,41] Establishing universal use of skin-to-skin care as a quality improvement activity[30,129] Dedicating quality improvement champions to educate, promote, and advise colleagues on changing practice to improve the use of skin-to-skin care at birth and throughout inpatient care.[37,93,177] Institutional expectation that the entire maternal-neonatal health care team collaborate on educating, advocating for, and facilitating the use of skin-to-skin care with parents and other professionals such as anesthesia, laboratory, respiratory therapy, operating room, and recovery room staff.
Professional concerns about care of the newborn: (a) safety, (b) assessment, (c) maintenance of physiologic stability, and (d) loss of professional control.	A qualified neonatal /perinatal professional is responsible and controls newborn care after birth through (a) assessment of neonatal condition, (b) performance of routine care, and (c) provision of a supportive/stress-free environment that nurtures neonatal transition with skin-to-skin care.[73] Interruptions of early skin-to-skin contact interfere with early breastfeeding.[153] Parental presence during care does not remove control from the health care provider; rather it provides an opportunity for professionals to teach new parents about their newborn, how to read and interpret cues, and how to respond in a developmentally appropriate way. It is an opportunity to engage parents as partners in care of their neonate by modeling, role-modeling, and teaching them to care for and advocate for their baby.
Professional concerns about lack of time or inadequate staffing.[175]	If mothers and their newborns are recovered together after birth, the nurse caring for them must be able to provide the standard of neonatal as well as maternal care. Provision of neonatal care while the mother or father holds the newborn skin-to-skin is no different than caring for the newborn in a crib, except that the baby is more comfortable. Routine care during transition (see Table 5.3) does not differ whether the baby is being held skin-to-skin or is in a crib or radiant warmer. Parental proximity provides a more efficient opportunity for teaching and mentoring new parents, thus enabling them to begin providing care to their newborn with professional supervision.
Professional perceptions/misperceptions about willingness of parents to provide skin-to-skin care because of culture, ethnicity, or religion.[77]	Partner with parents to provide care. Individualize the experience of skin-to-skin care[93] by including parents in the decision of how it is to be done—after drying the baby; after clothing the baby; with baby wrapped in a blanket—any way the parents prefer to skin-to-skin with their baby is the "right way" to do it.
Interruptions of new mothers/families by visitors, large groups of visitors, and those who stay at the bedside of the new family for more than 1 hour.[80]	Initiation of a family bonding time (i.e., mothers/newborns resting together in their rooms, limiting interruptions to medically necessary procedures or upon the request of the mother) as a quality improvement project that significantly increased exclusive breastfeeding rates.[80]

*References 73, 93, 108, 175, 185, 197, 210.

TABLE 5.3 ROUTINE CARE DURING TRANSITION

ROUTINE CARE	TIME	DRUG/DOSE	COMMENTS
Glucose screening (see Chapter 15)	At 30–60 minutes of age	By POC glucometer device	Abnormal screen: glucose <40 mg/dL
Eye prophylaxis	Within 1 hour of age	Erythromycin (0.5%) or tetracycline (1%) eye ointment: apply ribbon in each conjunctival sac	Eye prophylaxis for ophthalmia neonatorum[188] Bactericidal effect depends on tissue concentration of drug and microorganisms.
Vitamin K_1	Within 1 hour of age	0.5–1 mg IM as a single dose for infants <1.5 kg or >1.5 kg *or*	Prophylaxis for hemorrhagic disease of the newborn. Vitamin K concentrations are physiologically low in breast milk so that exclusively breastfed infants are at increased risk for vitamin K deficiency, as are infants with fat malabsorption (e.g., biliary atresia, cystic fibrosis, α_1-antitrypsin deficiency), and prolonged treatment with antibiotics. Use sucrose, breastfeeding, kangaroo care, and topical analgesia for pain relief during injections (see Chapter 12)
		2 mg PO	Repeated oral dosing (e.g., first feed, 1 week, 4 weeks, 8 weeks) is necessary; increased risk for late-onset hemorrhagic disease when infant receives only one dose. Oral intake is contraindicated in preterm infants, sick infants with diarrhea or cholestasis, or those receiving antibiotics.

*Routine care is required wherever the newly born infant is cared for after birth (e.g., labor-delivery-recovery; labor-delivery-recovery-postpartum; birth center; mother-baby unit; nursery).
IM, Intramuscular; *PO,* orally; *POC,* point-of-care.
Modified from Hernandez JA, Thilo E. Routine care of the full-term newborn. In Osborn LC, DeWitt TG, First LR, et al, eds: *Pediatrics.* St Louis, MO: Mosby; 2005.

TABLE 5.4 CLINICAL RESPIRATORY DISTRESS SCORING SYSTEM*

	0	1	2
Respiratory rate (breaths/min)	60	60–80	>80 or apneic episode
Cyanosis	None	In room air	In 40% F_{IO_2}
Retractions	None	Mild	Moderate to severe
Grunting	None	Audible with stethoscope	Audible without stethoscope
Air entry†	Clear	Delayed or decreased	Barely audible

*The respiratory distress syndrome score is the sum of the individual scores for each of the five observations.
†Air entry represents the quality of inspiratory breath sounds as heard in the midaxillary line.
F_{IO_2}, Fraction of inspired oxygen; *RDS,* respiratory distress syndrome.
From Downes JJ, Vidyasager DD, Boggs TR, et al. Respiratory distress syndrome in newborn infants: I. New clinical scoring system (RDS score) with acid-base and blood-gas correlates. *Clin Pediatr.* 1970;9:325.

TABLE 5.5 MATERNAL, OBSTETRIC, AND NEONATAL CONDITIONS THAT INCREASE THE RISK OF ABNORMAL TRANSITION

Maternal Factors	Chronic hypertension Preeclampsia Diabetes mellitus Renal disease Infection Abuse of tobacco, alcohol, or illicit drugs Collagen vascular diseases Hemizygous hemoglobinopathies Certain maternal medications
Obstetric Factors	Rh or other isoimmunization Fetal growth restriction Decreased fetal movements Multiple gestation Oligohydramnios or polyhydramnios Premature rupture of membranes Third-trimester bleeding Delivery by cesarean section
Neonatal Factors	Prematurity (<37 weeks) Postmaturity (>42 weeks) Small for gestational age Large for gestational age Infection Metabolic abnormalities Birth trauma Major malformations Anemia Apgar 0-4 at 1 minute or need for resuscitation at delivery

From Hernandez JA, Thilo E. Routine care of the full-term newborn. In Osborn LC, DeWitt TG, First LR, et al, eds: *Pediatrics*. St Louis, MO: Mosby; 2005.

be an ongoing process, because high-risk patients may be identified on the first prenatal visit, during follow-up prenatal visits, or not until the intrapartum and postpartum periods. **Review of the perinatal history is important in determining significant factors for neonatal health management.** Identification of an at-risk maternal situation is essential to plan and organize care for an at-risk neonate. Review of the perinatal history includes antepartum and intrapartum events (see Chapter 2) and early neonatal events, both in the delivery room and during transition.

BOX 5.2 NEONATAL CLINICAL MANIFESTATIONS SIGNALING ABNORMAL TRANSITION

- Persistent tachypnea, flaring, grunting, and retractions (respiratory score >4; duration >first hour of life); fixed bradycardia
- Diffuse and persistent rales, retractions, flaring, and grunting (respiratory score >4; duration >first hour of life)
- Persistent cyanosis (persistent oxygen saturation <90% in room air) and prolonged requirements for supplemental oxygen (after 2 to 3 hours of age)
- Episodes of prolonged apnea (>20 seconds) and bradycardia (<80 beats/min)
- Marked pallor or ruddiness
- Temperature instability, persistently (after 2 to 3 hours of age) low temperature (<36.5°C)
- Poor capillary filling (>3 seconds) and blood pressure instability
- Unusual neurologic behavior (lethargy, decreased activity with marked and persistent hypotonia, irritability, excessive tremors and jitteriness)
- Excessive oral secretions, drooling, and choking/coughing spells, cyanosis

Modified from Hernandez JA, Thilo E. Routine care of the full-term newborn. In: Osborn LC, DeWitt TG, First LR, et al., eds. *Pediatrics*. St Louis, MO: Mosby; 2005.

SIGNS AND SYMPTOMS

Unlike the verbalizing adult patient, the nonverbal neonate communicates needs primarily by behavior. **Through objective observations and evaluations, the neonatal care provider interprets this behavior into information about the individual infant's condition. Initial newborn assessment includes the following:**

- Assessment of GA and fetal growth
- Newborn classification to estimate neonatal mortality and morbidity risk
- Physical and neurologic examination
- Assessment of neurobiologic development

ASSESSMENT OF GESTATIONAL AGE AND FETAL GROWTH

Optimal management of the pregnant woman and her fetus is entirely dependent on an accurate knowledge of the age of the fetus. **An assessment of GA should be done on *all* newborns to establish maturity and pattern of fetal growth at birth.**[116]

Pattern of Fetal Growth. With the use of anthropometric measurements, including weight, length, and head circumference, together with GA, fetal growth standards have been determined for different ref-

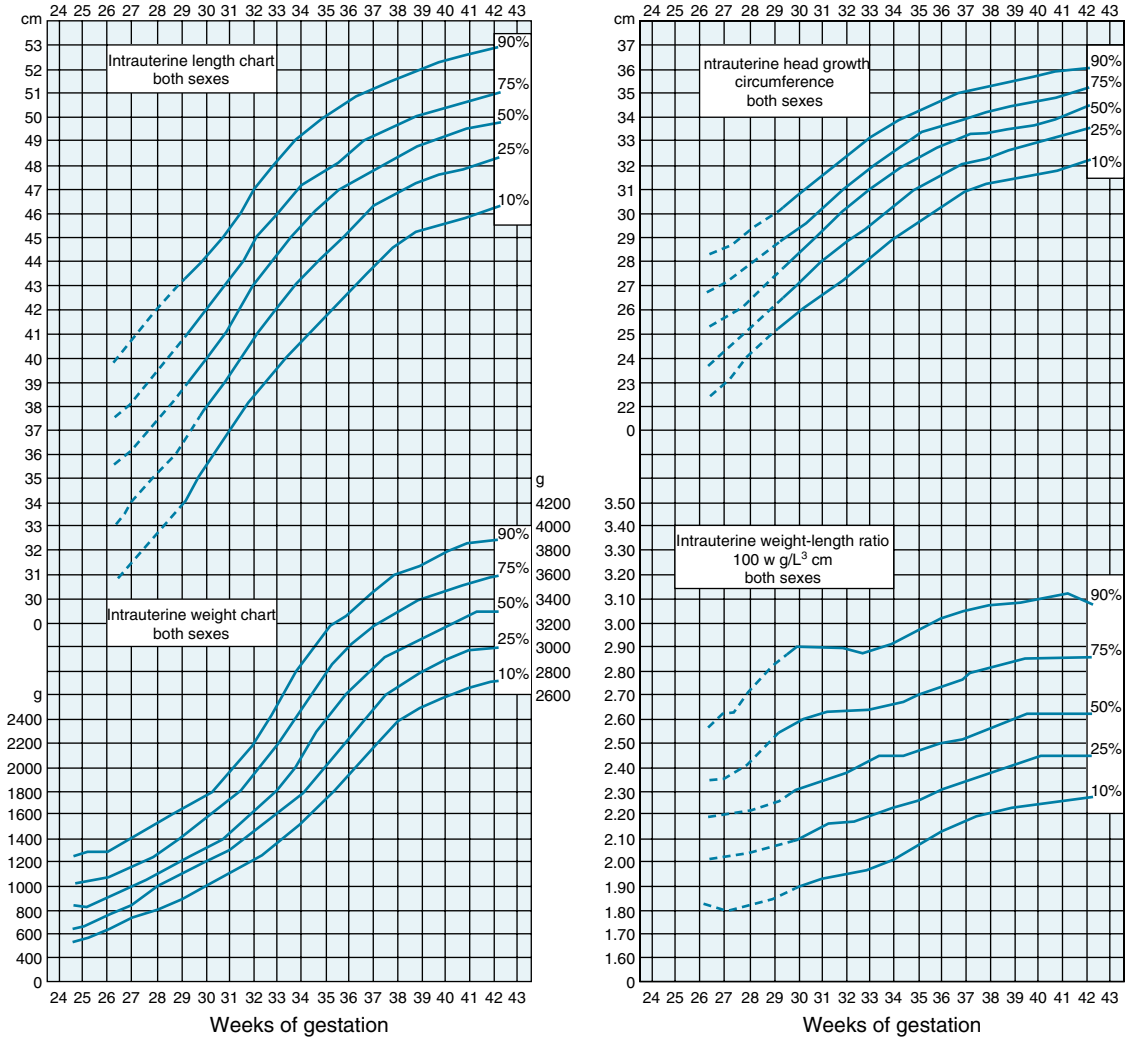

FIGURE 5.3 Colorado intrauterine growth charts. (From Lubchenco LO, Hansman C, Boyd E, et al. Intrauterine growth in weight, length and head circumference as estimated from live births at gestational ages from 26–43 weeks. *Pediatrics.* 1966;37:403.)

erence populations from various locations. From these data, it is apparent that there are variations in "normal" weight at any given GA from one locale to another. This variation is related to a number of factors, including sex, race, socioeconomic class, and even altitude. The Colorado intrauterine growth curves presented by Lubchenco and colleagues in the 1960s (Fig. 5.3) are unique in that each anthropometric measurement was related to GA. **The graphic display of this relationship provides a useful and simple method for determining the appropriateness of growth with respect to GA.** New fetal growth graphs include the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Fetal Growth Studies,[38,39] the INTERGROWTH-21st project,[145] and the WHO Multicentre Growth Reference Study.[105] Even though such curves differ in details, all demonstrate nearly linear growth between 20 and 38 weeks of gestation, with slowing thereafter. **In 1967, Battaglia and Lubchenco used the GA/BW relationship to categorize those infants whose BWs were less than the 10th percentile as *small for gestational age (SGA),* those weigh-**

ing more than the 90th percentile as ***large for gestational age (LGA),*** and the remaining 80% as ***appropriate for gestational age (AGA)*** (Fig. 5.4).[19]

Gestational Age. GA can be assessed by obstetric methods and by pediatric methods. **The most reliable antenatal method combines early ultrasound evaluation with information about the mother's last menstrual period (LMP).** Dating gestation based on the mother's LMP can be highly accurate if the mother is sure of the dates of her last menstrual period and the cycles are regular (see Chapter 2). Early antenatal ultrasonography appears to have 95% confidence intervals of less than 7 days.[199] Ultrasonography is preferred because it confirms conception, assesses gestation, and evaluates fetal growth.

Pediatric methods of determining GA are based on physical characteristics and neurologic examination. Within 2 hours after birth, every newborn should have an assessment of GA by physical characteristics.[8] Physical criteria are used because they progress in an orderly fashion with increasing gestation. Neurologic criteria involve the assessment of posture, passive and active tone, reflexes, and righting reaction. Numerous tables, charts, and graphs are available for determining GA. Some tables are more subjective and laborious than others, and each has proponents and detractors. **There is no perfect system, and all require the examiner to be familiar with and have experience in their use. At least one form should be adopted and consistently used by each nursery.**

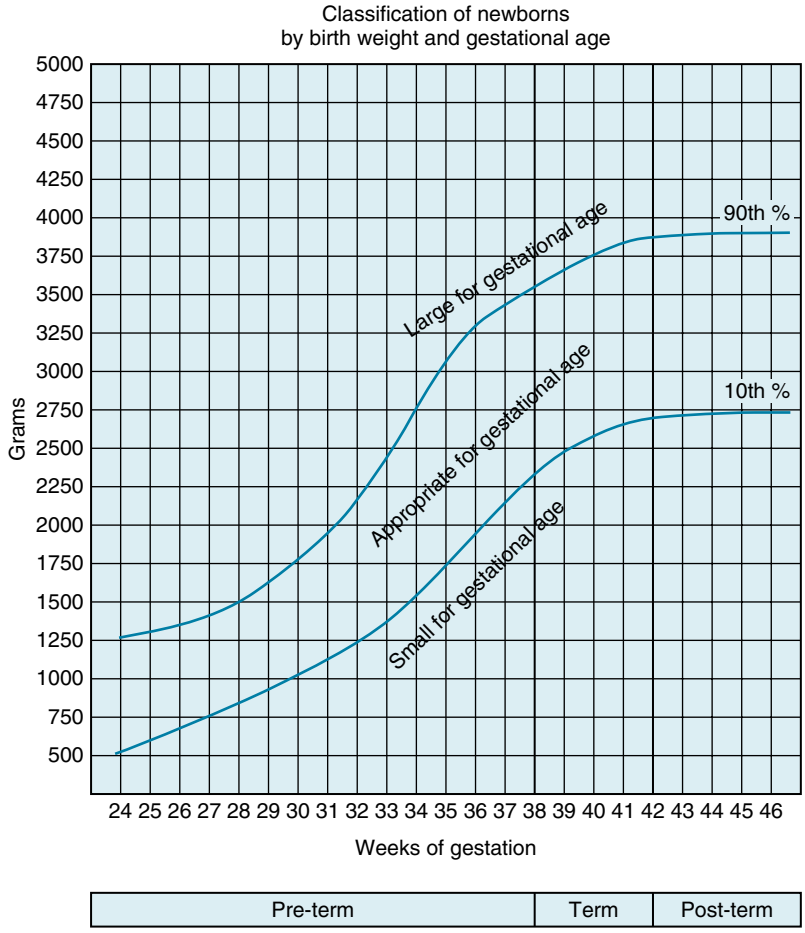

FIGURE 5.4 Classification of newborns by birth weight and gestational age. Birth weight of liveborn singleton white infants at gestational age from 24 to 42 weeks. (From Battaglia F, Lubchenco LO: A practical classification of newborn infants by weight and gestational age. *J Pediatr.* 1967;7:159.)

GA can be assessed most accurately by combining the physical criteria and the neurologic assessment. The revised Ballard system[9] displayed in Fig. 5.5 is a combined scoring system that is widely used. The Ballard system incorporates physical maturity (six characteristics) and neuromuscular maturity (six criteria) on an equal basis and includes assessment for extremely premature infants. The score for the neuromuscular and physical maturity is added and noted under the maturity rating column. Weeks of gestation are assigned according to the maturity rating score.

Assessment of Gestational Age in Very-Low-Birth-Weight and Extremely Premature Infants. Accuracy in estimation of GA is important because, for VLBW and extremely premature infants, small differences in GA result in large differences in outcome and may influence treatment and decision making by parents and professionals.[65] Research has shown that estimation of GA in very immature preterm infants is inaccurate. For preterm infants of 22 to 28 weeks of gestation, estimates of GA (by the scoring system shown in Fig. 5.5) exceeded the GA (by dates) by 1.3 to 3.3 weeks.[65] These inaccuracies must be considered in decision making, and better scoring systems are needed, particularly in the delivery room.

Neuromuscular maturity

	−1	0	1	2	3	4	5
Posture							
Square window (wrist)	>90°	90°	60°	45°	30°	0°	
Arm recoil		180°	140°–180°	110°–140°	90°–110°	ωωω90°	
Popliteal angle	180°	160°	140°	120°	100°	90°	<90°
Scarf sign							
Heel to ear							

Physical maturity

Skin	Sticky, friable, transparent	Gelatinous red, translucent	Smooth pink, visible veins	Superficial peeling and/or rash, few veins	Cracking pale areas, rare veins	Parchment deep, cracking, no vessels	Leathery, cracked, wrinkled
Lanugo	None	Sparse	Abundant	Thinning	Bald areas	Mostly bald	
Plantar surface	Heel-toe 40–50 mm: −1 <40 mm: −2	>50 mm no crease	Faint red marks	Anterior transverse crease only	Creases ant. 2/3	Creases over entire sole	
Breast	Imperceptible	Barely perceptible	Flat areola, no bud	Stippled areola 1–2 mm bud	Raised areola, 3–4 mm bud	Full areola, 5–10 mm bud	
Eye/ear	Lids fused loosely: −1 tightly: −2	Lids open; pinna flat, stays folded	Sl. curved pinna; soft, slow recoil	Well-curved pinna; soft but ready recoil	Formed and firm, instant recoil	Thick cartilage, ear stiff	
Genitals male	Scrotum flat, smooth	Scrotum empty, faint rugae	Testes in upper canal, rare rugae	Testes descending, few rugae	Testes down, good rugae	Testes pendulous, deep rugae	
Genitals female	Clitoris prominent, labia flat	Prominent clitoris, small labia minora	Prominent clitoris, enlarging minora	Majora and minora equally prominent	Majora large, minora small	Majora cover clitoris and minora	

Maturity rating

Score	Weeks
−10	20
−5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

FIGURE 5.5 Clinical estimation of gestational age. (From Ballard JL, Khoury JC, Wedig K, et al. New Ballard score, expanded to include extremely premature infants. *J Pediatr.* 1991;119:417.)

One quick and effective way to estimate GA in VLBW infants is by *measuring foot length*. **Foot length of AGA preterm infants has been correlated with GA (Table 5.6).** In short gestation (i.e., 24th to 34th week), there is a predictable increase in the mean foot length of 0.5 cm every 2 weeks. Measurement of foot length from the posterior prominence of the heel to the tip of the first (great) toe with a millimeter ruler is a rapid and simple method of assessing maturation of all newborns, even the very ill, VLBW, moderate intrauterine growth restricted (IUGR) infant. With this method, as with other physical measurements of GA, one must consider the standard deviation in interpreting results.

In areas where obstetric ultrasonography is not readily available and birth attendants do not estimate GA, research on other methods of determining GA is ongoing. Methods being investigated include DNA methylation in cord blood,[106] measurement of newborn fetal hemoglobin levels,[202] measurement of newborn metabolic markers,[154] and noninvasive measurement of cell-free RNA transcripts.[137]

TABLE 5.6 FOOT LENGTH BY GESTATIONAL AGE*

	FOOT LENGTH (cm)				
GESTATIONAL AGE (WEEKS)	NO. OF INFANTS	MEAN	MEDIAN	SD	RANGE
24	6	4.22	4.1	0.17	3.8–4.4
25	12	4.5	4.5	0.08	4.4–4.6
26	16	4.72	4.7	0.07	4.65–4.9
27	19	4.99	5.0	0.14	4.8–5.2
28	18	5.23	5.2	0.13	5.0–5.5
29	22	5.47	5.4	0.129	5.3–5.7
30	27	5.75	5.75	0.23	5.6–6.2
31	24	5.95	6.0	0.19	5.7–6.23
32	21	6.22	6.2	0.13	6.0–6.4
33	25	6.5	6.5	0.26	6.3–6.9
34	24	6.77	6.8	0.20	6.5–7.1
35	20	7.1	7.0	0.15	6.8–7.3
36	22	7.27	7.27	0.21	7.0–7.6
37	24	7.51	7.5	0.24	7.4–8.0
38	40	7.92	8.0	0.23	7.6–8.3
39	42	8.22	8.3	0.32	7.9–8.6
40	56	8.6	8.7	0.37	8.2–8.9
41	22	8.75	8.9	0.30	8.3–9.1
42	12	9.1	9.2	0.33	8.7–9.3
43	8	9.27	9.3	0.25	8.9–9.6

*Applies to both male and female infants

SD, Standard deviation.

From Hernandez JA, Lazarte R, Pisano D, et al. Foot length and gestational age in the very-low-birth-weight infant. The Children's Hospital Pediatric Update. September 1987; 4.

SIGNS OF PHYSICAL MATURITY

To use these charts accurately, the examiner must assess the following physical characteristics[116,189]:

Vernix. At 20 to 24 weeks, vernix is produced by sebaceous glands. Vernix is high in fat content and protects the skin from the aqueous amniotic fluid and bacteria. At 36 weeks, the white, cheeselike material begins to decrease and disappears by 41 weeks **Note the amount and distribution of vernix on the baby's skin (best done in the delivery room).**

Skin. **In early gestation, the skin of the fetus is very transparent, and veins are easily seen. As gestation progresses, the skin becomes tougher, thicker, and less transparent.** By 37 weeks, very few vessels are visible. From 36 weeks to delivery, fat deposits begin to form and grow. In a postterm infant, desquamation will be prominent at the ankles, wrists, and possibly palms and soles. As gestation progresses, the loss of vernix and subcutaneous tissue causes wrinkling. **Note skin turgor, color, texture, and the prominence of vessels, especially on the abdomen.**

Lanugo. At 20 weeks, fine, downy hair (lanugo) appears over the entire body of the fetus. At 28 weeks, it begins to disappear around the face and anterior trunk. At term, a few patches of lanugo may still be present over the shoulders. **Note the distribution of lanugo, first on the face and anterior trunk and then on the rest of the body.**

Hair on the Head. Hair appears on the head at 20 weeks. At 20 to 23 weeks, the eyelashes and eyebrows develop. From 28 to 36 weeks, the hair is fine and woolly and sticks together. It appears disheveled and sticks out in bunches from the head. At term, the hair lies flat on the head, it feels silky, and single strands are identifiable. **Note the quality and distribution of the hair, and feel its texture.** Scalp hair abnormalities (e.g., growth pattern, hypopigmentation, quantity, distribution, texture) may be external markers of genetic, metabolic, and neurologic disorders.

Sole Creases. Sole creases develop from toe to heel, progressing with GA. An infant with IUGR and early loss of vernix may have more sole creases than expected. **By 12 hours after birth, the skin has dried to a point that sole creases are no longer a valid indicator of GA.** Note the extent of sole creases (Fig. 5.6).

Eyes. In the third month of fetal life, the eyelids fuse; they reopen between 26 and 30 weeks. **In neonates of 27 to 34 weeks of gestation, examination of**

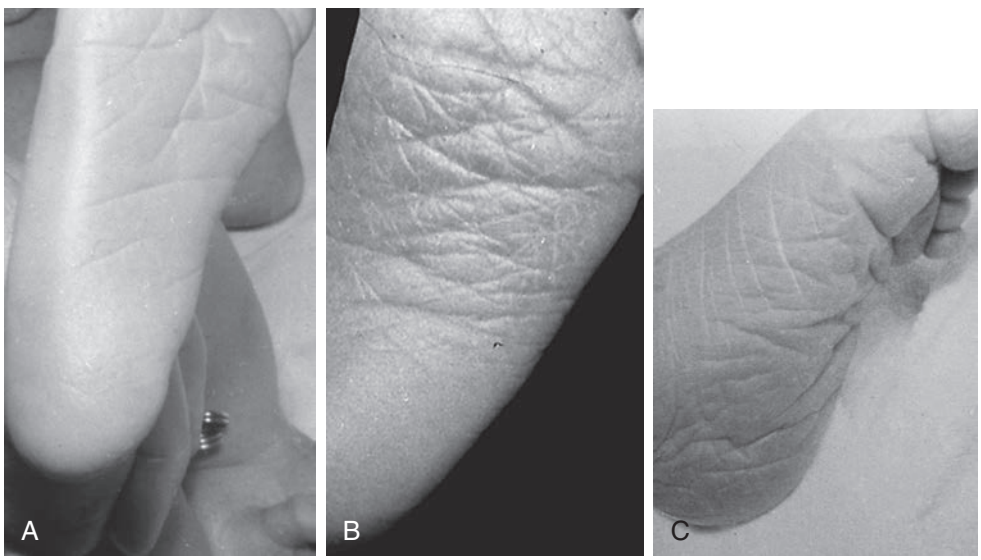

FIGURE 5.6 Sole creases at different gestational ages. **A**, Age 31 to 33 weeks of gestation. **B**, Age 34 to 38 weeks of gestation. **C**, Term.

the anterior vascular capsule of the lens is useful in assessing GA. GA is determined by assessing the level of remaining embryonic vessels on the lens (Fig. 5.7). Before 27 weeks, the hazy cornea prevents visualization of the vascular system. After 34 weeks, only remnants of the vascular system are visible. Because rapid atrophy occurs in the vascular system, an ophthalmoscopic examination should be performed during the first physical examination or within 24 to 48 hours after birth.

Ears. Before 34 weeks, the pinna of the ear is a slightly formed, cartilage-free double thickness of skin. When it is folded, it remains folded. **As gestation progresses, the pinna develops more cartilage, resulting in better form, so that it recoils when folded** (Fig. 5.8). Check ear recoil by folding the ear in half or into a three-corner-hat shape. Consistently folding it the same way helps the care provider develop a baseline for judging maturity. **Note the form and cartilage development of the ear. Examine both ears to be sure they are the same and without defects.**

Breast Development. Breast development is the result of the growth of glandular tissue related to high maternal estrogen levels and fat deposition. The areola is raised in an infant at 34 weeks of gestation. **Note the size, shape, and placement of both breasts.** Palpate the breast nodule, and determine its size. If the infant is growth restricted, breast size may be less than expected at term.

Genitalia

Male Genitalia. At 28 weeks, the testes begin to descend from the abdomen. By 37 weeks, they are high in the scrotum. By 40 weeks, the testes are completely descended, and the scrotum is covered with rugae. As gestation progresses, the scrotum becomes more pendulous (Fig. 5.9). **Note the presence of rugae on the scrotum and its size in relation to the position of the testes.** When examining the baby for descended testes, put the fingers of one hand over the inguinal canal to prevent the testes from ascending into the abdominal cavity, and palpate the scrotal sac with the other hand.

Female Genitalia. Early in the female's gestation, the clitoris is prominent with small and widely separated labia. By 40 weeks, the fat deposits have increased in size so that the labia majora completely cover the labia minora (Fig. 5.10). **Note the labial development in relation to the prominence of the clitoris.**

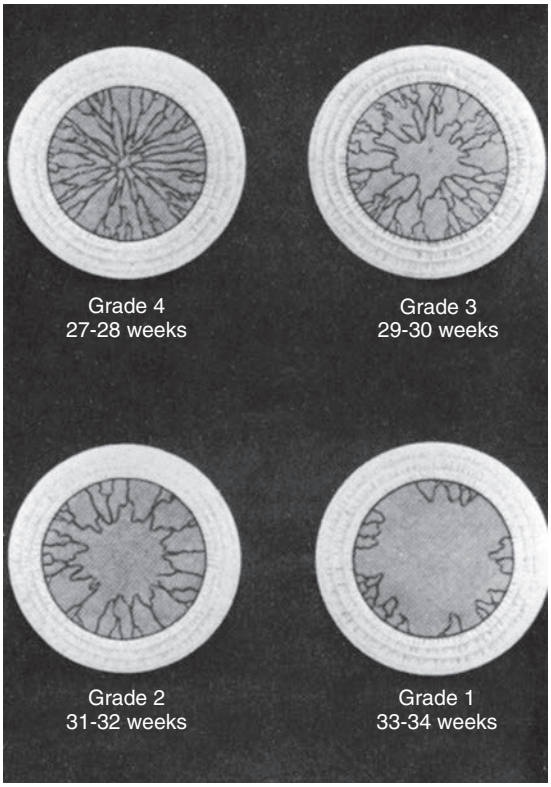

FIGURE 5.7 Anterior vascular capsule and gestational age. (From Hittner H, Hirsch NJ, Rudolph AJ. Assessment of gestational age by examination of the anterior vascular capsule of the lens. *J Pediatr.* 1977;91:455.)

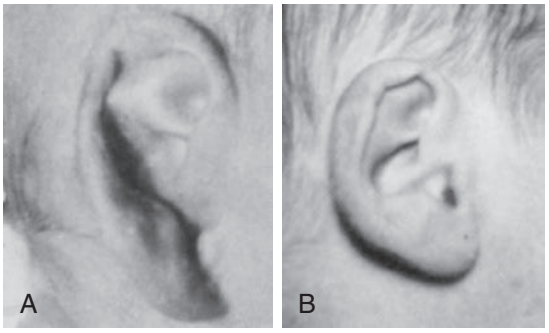

FIGURE 5.8 Ear form and gestational age. **A**, Age 34 to 38 weeks of gestation. **B**, Term.

NEWBORN CLASSIFICATION AND NEONATAL MORTALITY AND MORBIDITY RISKS

At birth, after establishing fetal maturity and pattern of fetal growth, the next step is to ensure appropriate assignment of a clinical newborn classification,

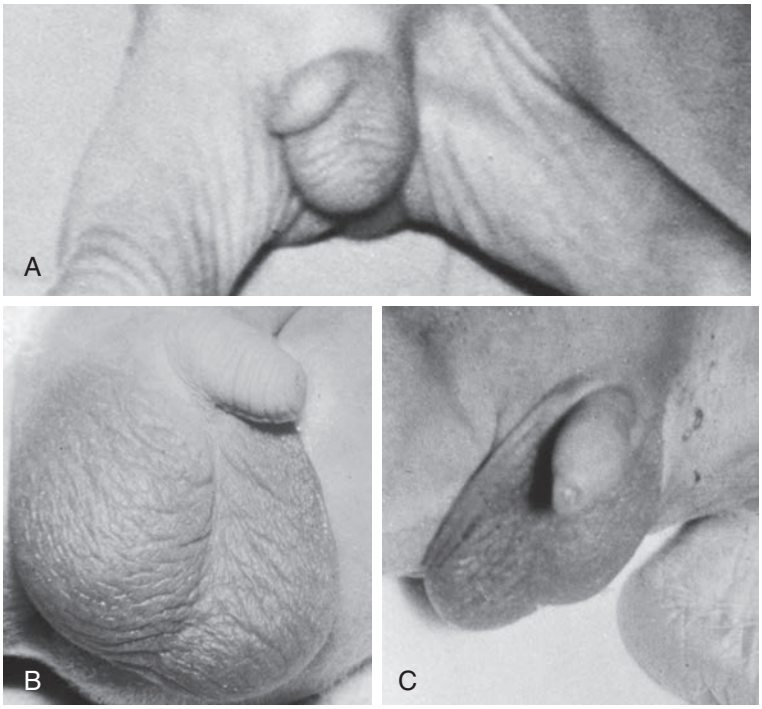

FIGURE 5.9 Male genitalia and gestational age. **A**, Age 28 to 35 weeks of gestation. **B**, Term. **C**, Age 42 or more weeks of gestation.

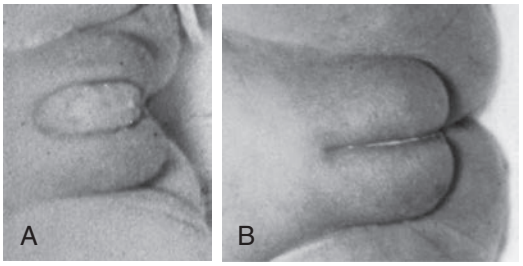

FIGURE 5.10 Female genitalia and gestational age. **A**, Age 30 to 36 weeks of gestation. **B**, Term.

determine neonatal mortality risk, generate a problem list of potential morbidities, and quickly initiate appropriate supportive care as well as screening procedures and/or interventions for recognized morbidities.

NEWBORN CLASSIFICATION

The neonatal population can be classified by the use of BW, GA, fetal growth pattern, and a combination of all of them into the following categories:

By Birth Weight.

- Normal birth weight (NBW): 2501 to 3999 g
- Excessive birth weight (EBW): 4000 g and above
- Low birth weight (LBW): 2500 g or less, with the following subcategories: moderate low birth weight (MLBW): 1501 to 2499 g, very low birth weight (VLBW): 1500 g or less, and extremely low birth weight (ELBW): 1000 g or less

By Gestational Age.

- Full-term (FT): 37 to $41^{6/7}$ weeks (259 to 293 days)
- Postterm (PoT): 42 or more weeks (294 or more days)
- Preterm (PT)[44]: Less than 37 weeks ($36^{6/7}$ weeks or less than 259 days), with the following subcategories: late preterm (LPT): $34^{0/7}$ to $36^{6/7}$ weeks (238 to 259 days), moderate-severe preterm (MSPT): 28 to $33^{6/7}$ weeks (196 to 237 days), and extreme preterm (EPT): $27^{6/7}$ or less weeks (less than 196 days)

By Fetal Growth Pattern. Using the intrauterine growth chart for the 10th and 90th percentiles, newborns can be classified as follows: those below the 10th percentile, SGA infants; those between the 10th and 90th percentiles, AGA infants; and those above the 90th percentile, LGA infants.[19]

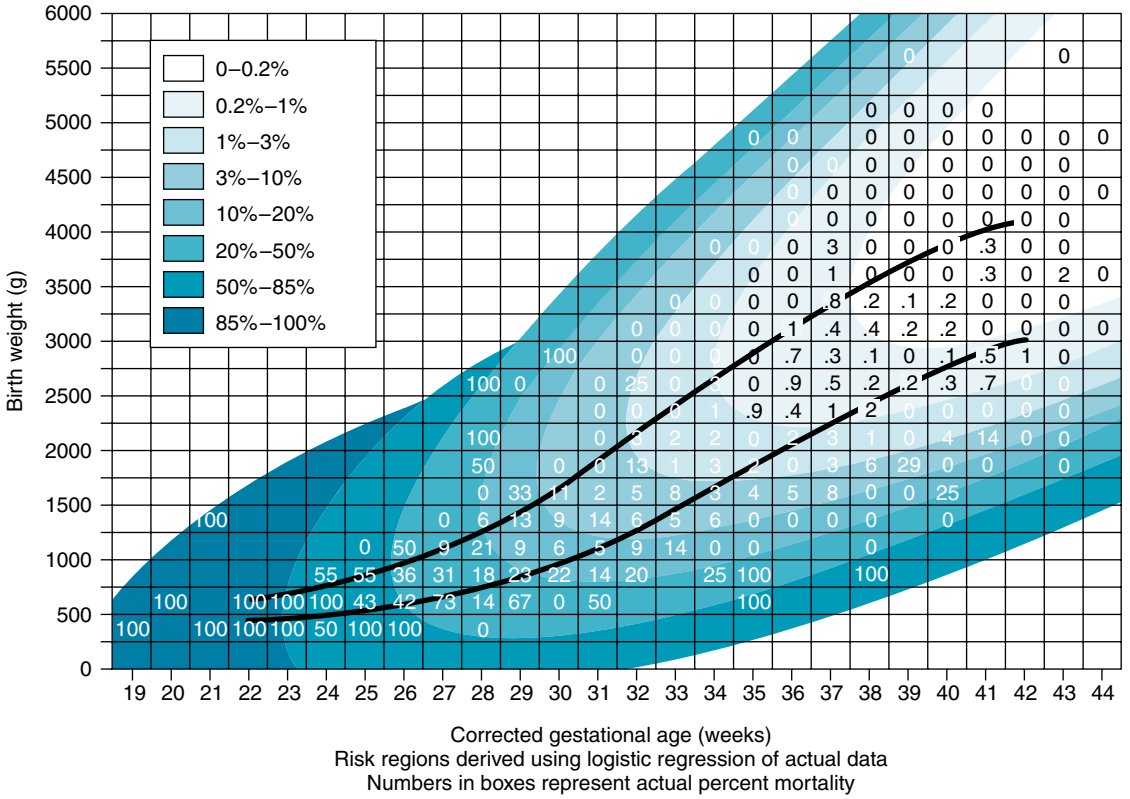

FIGURE 5.11 Neonatal mortality risk by birth weight and gestational age. (From Johnson JL, Merenstein G, Coll J, et al. Colorado intrauterine growth curve, 1980–1992: the new Lubchenco growth curve. *Pediatr Res.* 1994;35:274A.)

By combining GA in weeks, BW in grams, and intrauterine growth pattern, nine categories of newborns were thus defined (see Fig. 5.4). This type of classification allows clinicians to anticipate likely problems in the immediate neonatal period and potential morbidities in the long term.

NEONATAL MORTALITY RISK

Significant advances in obstetrics and perinatal-neonatal care during the past six decades have resulted in a remarkable decline in the rate of neonatal mortality (see Chapter 2). Although BW is considered to be the best predictor of neonatal survival, with exponential improvement evident with the achievement of optimum BW, it is apparent that **neonatal mortality risk could be predicted more accurately for any individual infant based on the relation of two factors: BW and GA.**[19,109]

Neonatal mortality risk (NMR), the chance of dying in the neonatal period, can be determined from mortality graphs based on BW and GA, such as that shown in Fig. 5.11. This figure was constructed based on the Lubchenco Perinatal Database, University of Colorado Hospital, 1980 to 1992. Mortality was calculated for each 100 g/1 week BW/GA block. On the chart, the area of least risk is the FT-AGA infant. Deviations from this area of least risk in relation to either weight or GA increase the newborn's mortality risk. **Further examination of NMR in Fig. 5.11 reveals that two infants with the same BW but with different GAs may have very different risks for death.** For example, infant A may have a BW of 2000 g and a GA of 33 weeks, and shows an NMR of 2%. Infant B, on the other hand, may also weigh 2000 g but have a GA of 39 weeks, and shows an NMR of 0.2%. Infant A thus has a mortality risk 10 times greater than that of infant B, even though they have the same BW.

Mortality risk has changed over time because an increasingly physiologic basis of care has been

used, coupled with sophisticated professional care, improved technology, new treatment modalities, transport systems, and aggressive management to handle increasingly at-risk populations. Consequently, these neonatal mortality risks need to be reviewed periodically.

Within the NICHD Neonatal Research Network, mortality rates for newborns weighing 501 to 1500 g decreased from 23% (1987 to 1988) to 17% (1993 to 1994) to 14% (1999 to 2000) to 12.4% (2000 to 2009). However, within each BW category, survival free of major morbidity (e.g., chronic lung disease/bronchopulmonary dysplasia, necrotizing enterocolitis, grade 3 or 4 intraventricular hemorrhage) did not change significantly. **Because mortality (and morbidity) rates are highest in infants of the lowest BW and GA, VLBW and ELBW infants would have more favorable outcomes when they are born in a facility that can provide the appropriate subspecialty care.[113,176,208] These research findings have prompted recommendations that high-risk mothers/infants (e.g., less than 32 weeks of GA) be delivered/born in a facility capable of providing the anticipated appropriate level of perinatal/neonatal care.[8,9]**

NEONATAL MORBIDITY RISK

Neonatal morbidity risk (Fig. 5.12) is determined by deviations of intrauterine growth and newborn classification. **Classification of the newborn assists in identification, observation, screening, and treatment of the most commonly occurring problems. For every newborn, formulate a problem list based on the morbidities common to the newborn classification. Observe, screen, intervene, and refer as necessary to prevent complications.**

SGA/IUGR infants are at increased risk for morbidities such as perinatal depression, hypothermia, hypoglycemia, polycythemia, and infection immediately after birth. Full-term SGA infants have higher morbidities, mortality (including stillbirth), and hospital charges when compared to other term infants.[72,127] LGA infants are at an increased risk for more morbidities, including hypoglycemia, polycythemia, and birth trauma.[126] There is also an association between size at birth, altered physiologic development, and long-term developmental and health problems (especially heart disease and stroke).[53]

LATE-PRETERM INFANT

In the United States, as a result of shifting distribution of GA among spontaneous live, singleton births, 39 weeks was found to be the most common length of gestation.[62] ***Preterm infants* are infants born before 37 completed weeks of gestation ($37^{0/7}$ weeks or day 259). *Late-preterm infants* refer to infants born between 34 completed ($34^{0/7}$ weeks or day 239) and less than 37 completed weeks ($36^{6/7}$ weeks or day 259).[69] *Early term infants* are infants born between $37^{0/7}$ weeks and $38^{6/7}$ weeks.[171]** In 2011, the prematurity rate in the United States was 11.7%,[81] and two-thirds (8.1%) of these were due to "late-preterm" births. From 2006 to 2014, birth rates for late preterm and early term births declined as a direct result of fewer clinician-initiated obstetric interventions.[152] However, in 2018 the CDC reported that the preterm birth rate in the United States increased from 9.57% to 9.85% from 2014 to 2016, mainly as a result of an increase in LPI, especially those at 36 weeks of gestation.[121] **Because late preterm and early term infants are at increased risk for health and developmental problems,[147] elective delivery before 39 weeks is considered a major public health concern.[95]**

A 2005 National Institutes of Health (NIH) meeting[136] adopted the description ***late-preterm* rather than *near-term* to reflect the increased morbidity (and mortality) rates of this group of biologically and physiologically immature neonates.[68]** These infants are larger than the usual premature infants, and they may be treated as mature infants, but they often manifest signs of physiologic immaturity in the neonatal period.

Morbidity and Mortality Outcomes in Late-Preterm Infants

Numerous studies have documented the high incidence of neonatal complications leading to neonatal intensive care unit (NICU) admission (30% to 59%) of LPIs.[64,69] A multicenter study found that 10% of LPIs admitted to mother-baby units required transfer to a higher level of care.[124] Table 5.7 shows a list of the most frequently encountered morbidities in LPIs. When spontaneous and medically indicated late preterm birth are compared, LPIs born because of a medical indication have **a higher incidence of respiratory complications,**

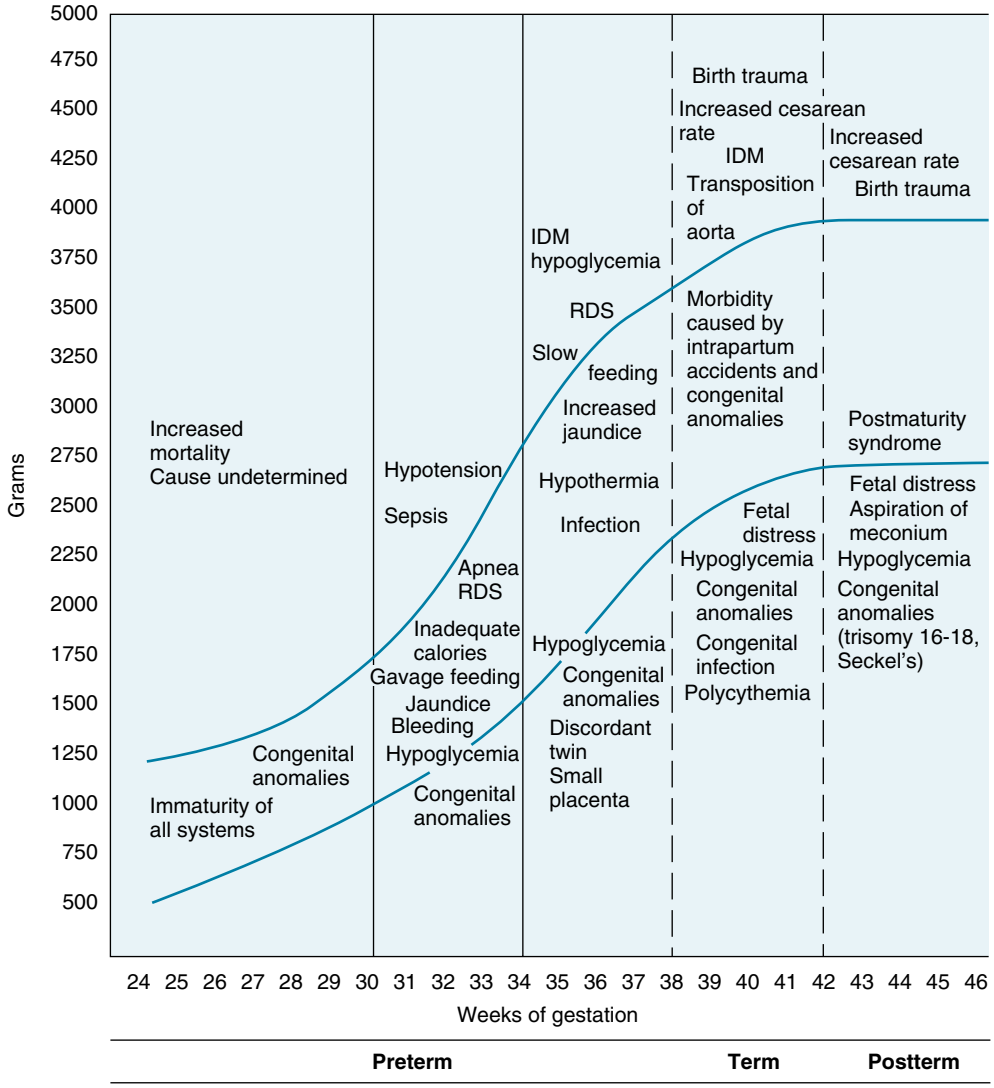

FIGURE 5.12 Specific neonatal morbidity by birth weight and gestational age based on statistics from Newborn and Premature Center at the University of Colorado Medical Center. *IDM,* Infant of diabetic mother; *RDS,* respiratory distress syndrome. (From Lubchenco LO. *The High-Risk Infant.* Philadelphia, PA: Saunders; 1976.)

such us transient tachypnea of the newborn, respiratory distress syndrome, persistent pulmonary hypertension of the newborn, respiratory failure, and respiratory depression requiring resuscitation at birth.[27,64,104,178] The incidence of these morbidities increases with decreasing GA. A single-center study showed that neonates born at 34 weeks of gestation had the highest risk for morbidities during neonatal transition to extrauterine life, including need for resuscitation at birth, hypothermia, hypoglycemia, and NICU admission.[64] This confirms the results of a previous study that also found 34-week GA LPIs with the highest morbidities.[196] **Each additional week of gestation decreases neonatal morbidity, mortality, and length of stay.**[64,119] With every additional week of gestation past 35 weeks, there is a decrease in specific and overall developmental delay in the first 2 years of life.[67]

TABLE 5.7 MORBIDITIES IN LATE-PRETERM VERSUS TERM INFANTS

	WANG ET AL. (2004)		LEONE ET AL. (2011)		VISRUTHAN ET AL. (2015)	
	FREQUENCY		FREQUENCY		FREQUENCY	
MORBIDITY	LATE PRETERM	FULL TERM	LATE PRETERM	FULL TERM	LATE PRETERM	FULL TERM
Temperature instability	10%	0%	2.5 %	0.6%	6.7%	0.2%
Hypoglycemia	15.6%	5.3%	14.3%	0.6%	46%	1%
Respiratory distress	28.9%	5.3%	34.7%	4.6%	5%* 31%†	0.1%* 3%†
Apnea/bradycardia	4.4%	0%				
Jaundice/hyperbilirubinemia	54.4%	37.9%	47.7%	3.4%	87%‡	8%†
Sepsis evaluation	36.7%	12.6%				
Poor feeding	76%	28.6%			39%	1.4%
Intravenous infusions	26.7%	5.3%			70%	3%

*Respiratory distress syndrome.
†Transient tachypnea of the newborn.
‡Requiring phototherapy.
Data from Wang M, Dorer D, Fleming M, et al. Clinical outcomes of near-term infants. *Pediatrics* 2004;114:372; Leone A, Ersfeld P, Adams M, et al. Neonatal mortality in singleton late preterm infants compared with full-term infants. *Acta Paediatr.* 2011;101:e6; Visruthan NK, Agarwal P, Sriram B, Rajadural VS. Neonatal outcome of the late preterm infant (34 to 36 weeks): the Singapore story. *Ann Acad Med Singapore* 2015;44(7):235.

LPIs not only have more morbidities but also have been shown to have *increased mortality risk.* A report from the Institute of Medicine in 2005 points out that whereas the mortality rates for full-term neonates were stable at 2.5 per 100,000 live births, the rate for moderately preterm neonates (32 to 36 weeks of gestation) rose from 8.9 to 9.2 per 100,000 live births from 2001 to 2002.[136] A more recent study compared overall and cause-specific mortality rates between singleton late-preterm and term infants.[184] This study concluded that **LPIs have higher mortality rates throughout infancy compared with term infants. LPI mortality rates were threefold higher than those of term infants (7.9 vs. 2.4 deaths per 1000 live births).**[184] In the first month of life, when evaluating deaths in the early (1 to 6 days) and late (7 to 27 days) neonatal periods, mortality rates were six and three times higher, respectively, for the LPI. Postneonatal deaths were twice as high as term infants. **During infancy, LPIs were approximately four times more likely than term infants to die.** In another study, neonatal mortality rates were significantly higher for LPIs (1.1, 1.5, and 0.5 per 1000 live births at 34, 35, and 36 weeks, respectively) compared with 0.2 per 1000 live births at 39 weeks.[123] A recent secondary analysis of the WHO multicountry survey on maternal and newborn health found that elective cesarean section was associated with reduced perinatal mortality and non-significantly associated with late preterm birth. However, labor induction was associated with increased late preterm birth and in less developed countries with an increase in perinatal mortality.[132] **Although the rate of mortality increases with decreasing GA,**[40] **two recent studies found the highest mortality occurring at 37 weeks of gestation.**[195,205]

BOX 5.3 LONG-TERM OUTCOMES OF LATE PRETERM INFANTS: RESEARCH FROM 2015 TO 2018

Growth

Higher risk for less weight gain and height in first year of life.[86] Faster head growth from 20 to 56 months of age associated with better adult neurocognitive function but not consistently associated with mental health outcomes.[155]

Higher Use of Health Care Resources

More hospital readmissions for jaundice, feeding difficulties, respiratory problems/infections, asthma, diarrhea, fever, and neurologic, and/or mental health problems from infancy[86,89,98,99,156] to adulthood.[98] More lower respiratory tract infections in preschool years, and more asthma at school age.[60] Reduction in measures of airway function.[182]

Developmental Delays

Being late preterm did not increase the risk of poorer neurocognitive functioning in adulthood. However being SGA and late preterm increases the risk of poorer neurodevelopmental outcomes.[90] No difference in IQ between LPI and full term infants.[133] Increased risk of lower cognitive ability in LPI when compared to early-term and full-term birth.[46]

At 4 and 8 Months CA[24]

- LPI at 4 months had lower fine motor scores
- LPI at 4 and 8 months had significantly lower communication and gross motor scores

At 9 Months CA[161]

- Less optimum developmental outcomes than full-term controls
- Delays not seen at 24 months CA
- Delays reemerged at preschool and kindergarten[204] (delays in reading and mathematics)

At 1 Year of Life

- Early intellectual delay (lower scores in adaptability, gross motor skills, and social competence) than full-term group[209]
- LPI admitted to an NICU increased the risk of developmental delay (i.e., communication and gross motor skills)[16]

At 18 Months CA[24]

- No significant difference in fine motor skills, gross motor skills, or communication delays seen at 4 and 8 months CA

At 2 Years CA

- Worse cognitive, language, and motor delays of moderate and LPIs compared to full term controls[48,170]
- Worse socioemotional competence of moderate and late preterm infants compared to full term controls[48]

At 3 Years CA

- Increased risk of emotional problems for girls born at late preterm and early term[173]

At 4 to 5 Years of Age

- Resolving communication problems and emerging motor problems that are comparable to early-preterm–born children but at a lower rate[92]

At 6 to 12 Years of Age

- Greater risk for emotional and behavioral problems and lower quality of life compared to full-term peers[149]

CA, Corrected age; *IQ*, intelligence quotient; *LPI*, late preterm infant; *SGA*, small for gestational age.

Long-Term Outcomes

Two large systematic reviews[18,134] comparing late-preterm infants (LPIs) with full-term infants found that the children and adults born late preterm fare worse than their full-term born peers in cognitive function, school outcomes, behavior problems, psychiatric disorders, and subtle intellectual and neuropsychological deficits. Box 5.3 lists long-term outcomes from more recent research studies not included in the systematic reviews. These retrospective reports in no way confirm causality. **Outcomes are not only the result of physiologic immaturity, but also of the biologic determinants of preterm birth interacting with GA.[36]** Neurodevelopmental follow-up of LPIs has been, until recently, a long neglected area of research. More research, including longitudinal, prospective studies, are needed to fully appreciate the impact of late-preterm birth, biologic determinants, and perinatal events on developmental and health outcomes in this population of at-risk infants.[36,151]

Clearly, LPIs are not term infants and need close observation, a high level of suspicion, assessment, and timely intervention by all care providers. Regardless of the setting of care for the LPI, these immature infants require more nursing time and care than do full-term infants. If the level of care cannot be provided in the birth setting, these infants should be transferred to a higher level of care (either in the same or a different facility) as soon as possible.

Physical and Neurologic Examination

The purpose of the physical examination is (1) to discover common variations of normal or obvious congenital defects, (2) to quickly initiate intervention or referral for deviations from normal, and (3) to establish a baseline for serial observations and comparisons. The best data are obtained from the neonate when the physical examination is organized to limit stress, maximize interaction with the examiner, and not overwhelm the newborn. **To maximize data and minimize stress, the physical examination should proceed in an orderly fashion from the least stressful to the more stressful aspects of the examination** (Box 5.4).

When one appreciates how stressful it is to the newborn to be undressed, it becomes obvious that as much as possible should be done without exposing the infant. Warm hands and instruments are essential, and a warm environment helps. Before touching the infant or removing any covers, observe the face, head, and hands as they appear.

OBSERVATION

Observation of the neonate provides pertinent data without touching him or her. General condition, anomalies, resting posture, and respirations should be observed.

GENERAL CONDITION

The general condition of the infant should be assessed by noting the color, activity, and neonatal state.

Color. **The color of the newborn is normally pink. Acrocyanosis, or peripheral cyanosis of the hands and feet, is commonly present in the first 24 hours of life and may be the result of immature circulation or cold stress.** Ecchymotic areas, especially on the presenting part, are common; however, they may be confused with cyanosis. To differentiate the two, apply pressure to the area. An ecchymotic area remains blue with pressure, whereas a cyanotic area will blanch.

General cyanosis and central cyanosis of the lips, mouth, and mucous membranes may indicate central nervous system (CNS), heart, or lung disease. Jaundice appearing at birth or within the first 24 hours of life is abnormal. Physiologic jaundice appears after 24 hours, but jaundice may indicate other abnormalities. **Pallor at or directly after birth is a sign of circulatory failure, anoxia, edema, or shock.** Pallor of anoxia is associated with bradycardia and the pallor of anemia with tachycardia. **Plethora, a beef-red color, may indicate polycythemia and is confirmed by hemoglobin and hematocrit determinations.** However, lack of plethora does not rule out polycythemia or hyperviscosity.

BOX 5.4 CRITICAL FINDINGS
PHYSICAL EXAMINATION OF THE NEWBORN

I. Observation Examination
- A. General condition
  - 1. Color
  - 2. Activity and neonatal state
- B. Crying
- C. Anomalies
- D. Resting posture
- E. Respirations

II. Quiet Examination
- A. Auscultation
  - 1. Heart
  - 2. Lungs
  - 3. Abdomen
- B. Palpation
  - 1. Fontanels
  - 2. Abdomen
- C. Inspection
  - 1. Eyes
  - 2. Blood pressure

III. Head-to-Toe Examination
- A. Skin
- B. Head
  - 1. Ears
  - 2. Nose
  - 3. Mouth
- C. Thorax
  - 1. Breast
  - 2. Clavicles
- D. Genitalia
- E. Rectum
- F. Back
- G. Extremities
  - 1. Upper
  - 2. Lower

Activity and Neonatal State. Activity and the neonatal state at the beginning of the examination and appropriate changes throughout the examination should be observed. If the infant is asleep, is it quiet or rapid-eye-movement (REM) sleep? Spontaneous, symmetric movements are normal. Tremors and twitching movements of short duration are normal in relation to states of coldness or startling or REM sleep. Good muscle tone is established with adequate oxygenation soon after birth.

Flaccidity, floppiness, or poor muscle tone should be noted. Spasticity, hyperactivity, opisthotonos, twitching, hypertonicity, tremors, or seizures may be indicative of CNS damage. **A lack of crying or evasive behavior in response to the manipulations of a physical examination is abnormal.**

Crying. Attempts to calm and console a crying infant during this part of the examination assist in better data collection during the quiet examination. Crying is beneficial in (1) ductal closure and transition from fetal to neonatal cardiorespiratory status, (2) improving pulmonary capacity, (3) maintaining homeostasis, (4) facilitating vocal tract development, and (5) cueing and care-eliciting behavior. Negative effects include (1) changes in cardiovascular (e.g., tachycardia, hypoxia, changes in cerebral blood flow, increased risk for brain injury and cardiac dysfunction)[117] and endocrine systems; (2) stress production and energy drainage;[117] and (3) strong, sometimes negative feelings in care providers.

Although uniquely individual, types of cries that reflect the infant's state and contextual basis have been identified as birth, distress call, hunger, pain, spontaneous, and pleasure.[52] At birth, the term neonate has a loud, lusty cry (a signal of robustness and wellness), whereas the preterm's cry may be weak or absent. Observe the infant's ability to quiet himself or herself when crying. High responsivity of the newborn to sustained handling, undressing, and being put down is associated with more infant crying.

A high-pitched cry suggests CNS irritation from increased intracranial pressure, injury, infection, or abnormality. *Weak crying,* no crying, or constant, irritable crying may indicate brain injury, infection, or abnormality. *Hoarse cries* or crowing inspirations result from laryngeal inflammation, injury, vocal cord dysfunction (e.g., paresis/paralysis), or anomalies. *A weak,* groaning cry or expiratory grunt is indicative of respiratory disease or systemic illness.

ANOMALIES

Obvious bodily malformations such as abdominal wall defects (omphalocele or gastroschisis), cleft lip and palate, imperforate anus, syndactyly, polydactyly, club foot (talipes equinovarus), or myelomeningocele should be observed and recorded as anomalies. Odd facies or body appearances that are often associated with specific syndromes also should be noted.

RESTING POSTURE

Resting posture should be observed while the infant is quiet and not disturbed. The infant's posture systematically develops according to GA: (1) from extension to flexion of the lower extremities, and (2) to flexion of the upper extremities. Asymmetry may result from intrauterine pressure or birth trauma. The infant may take a position of comfort assumed in utero.

RESPIRATIONS

Respirations should be evaluated while the infant is at rest and before any manipulation. The normal rate is 30 to 60 breaths/min. Count the respiratory rate and rhythm, noticing the infant's use of accessory muscles. Respiration is normally abdominal or diaphragmatic.

After the first hour of life, a respiratory rate of more than 60 breaths/min indicates tachypnea. Tachypnea is the earliest sign of many neonatal respiratory, cardiac, metabolic, and infectious illnesses. Tachypnea, apnea, dyspnea, or cyanosis may indicate cardiorespiratory distress. Labored respirations include retractions, flaring nares, and expiratory grunt. Maternal epidural analgesia with fentanyl has been shown to cause respiratory depression in neonates because fentanyl freely diffuses from the epidural space to maternal blood, equilibrating within 10 to 30 minutes and freely transporting across the placenta with slightly higher concentrations in the fetal compartment.[112] Neonatal respiratory depression secondary to fentanyl epidural analgesia is more common when mothers receive large amounts of fentanyl during labor; naloxone administration reverses the respiratory depression.[112]

If the infant is swaddled, the observation examination will not be as extensive as is possible when

the infant is unclothed in an incubator or under a radiant warmer. If the infant is swaddled, unwrap gently so that observations of the thorax, abdomen, genitalia, and extremities may also be done during this phase of the examination.

Without touching the infant, one can rule out a multitude of conditions. In fact, more than 80% of the newborn examination is made through observation.

QUIET EXAMINATION

***Quiet examination* is defined as any part of the examination in which data are best collected from the quiet, cooperative newborn. The heart, lungs, head and neck, scalp and skull, abdomen, eyes, and blood pressure are areas that should be checked during the quiet examination.** Using pacifiers, warming hands and stethoscopes, and holding and gently manipulating the infant are ways to avoid overwhelming the baby and to prevent crying.

AUSCULTATION

Heart. Auscultation of the heart, lungs, and abdomen is most effective when the infant is quiet. When the infant is quiet and at rest, auscultate the heart rate, rhythm, and regularity at the apex. The normal rate is 120 to 160 beats/min at a regular rhythm. Variations in heart rate occur with respiratory cycles and single premature beats are commonly heard and generally normal. The point of maximal intensity (PMI) of the neonatal heart is lateral to the midclavicular line at the third to fourth interspace. Note the PMI.

A rate of less than 80 beats/min is bradycardia. Full-term newborns in quiet sleep may have heart rates as low as 80 beats/min. Newborns with persistent bradycardia may have complete heart block caused by maternal systemic lupus erythematosus (see Chapter 2). A rate greater than 160 beats/min is tachycardia, which may be associated with respiratory problems, anemia, or congestive heart failure when accompanied by cardiomegaly, hepatomegaly, and generalized edema.

Murmurs are noted for loudness, quality, location, and timing. They are best auscultated at the base of the third or fourth interspace. Heart murmurs in the newborn period are common, perhaps as frequent as 10% of the population (see Chapter 24). Note dextrocardia—heart sounds audible on the right side of the chest. Pneumothorax, pneumomediastinum, dextrocardia, and diaphragmatic hernia result in muffled heart sounds or a shift in PMI. To complete the cardiac assessment, careful attention to the femoral pulses is necessary; diminished femoral pulses suggest coarctation of the aorta (see Chapter 24). Often newborns with serious congenital heart disease do not present with clinical signs and symptoms of their anomaly. Use of pulse oximetry to screen all newborns at 24 hours of age and before discharge for critical congenital heart disease is discussed in Chapter 31.

Lungs. Normally, the lungs and chest are resonant after birth, and fine rales may be present for the first few hours. Auscultation reveals bronchial breath sounds bilaterally. Air entry should be good, particularly in the midaxilla. A normal respiratory rate is 30 to 60 breaths/min.

Hyperresonance suggests pneumomediastinum, pneumothorax, or diaphragmatic hernia. *Decreased resonance* is a result of decreased aeration—atelectasis, pneumonia, or respiratory distress syndrome. Expiratory grunt suggests difficulty in aeration and oxygenation. Peristaltic sounds heard in the chest may be caused by a diaphragmatic hernia.

Abdomen. Bowel sounds are normally heard shortly after birth.

PALPATION

Palpation of the fontanels and abdomen is best accomplished before the infant begins crying, because guarded muscles and the normally tense fontanels of the crying infant give little useful data.

Scalp and Skull. Temporary deformation of the head is caused by pressures during labor and delivery. The head circumference measurements may be altered so that the occipitofrontal circumference on the first day of life may be smaller than on the second or third. *Caput succedaneum* is an edematous area over the presenting part of the scalp that extends across suture lines and resolves in 24 to 48 hours. A *cephalhematoma* is a soft mass of blood in the subperiosteal space on the surface of the skull bone. The blood mass does not extend across suture lines and resolves in 6 to 8 weeks.

Deviating from the normal, **skull fractures may be linear or depressed, palpable or nonpalpable.**

Skull fractures are more common with forceps delivery. *Craniotabes,* softening of the skull bones, is caused by maternal vitamin D deficiency.[206]

The *anterior fontanel,* a diamond-shaped space normally measuring from 1 to 4 cm, may be gently palpated at the junction of the sagittal suture and coronal suture and between the two parietal bones. Normally the anterior fontanel softly pulsates with the infant's pulse, becomes slightly depressed when the infant sits upright and is quiet, and may bulge when the infant cries. Within 24 to 48 hours after birth, the initial molding of the head and overlap of the sutures resolve, resulting in a larger fontanel and in suture lines that should be palpated as depressions.

The *posterior fontanel,* formed at the juncture of the sagittal suture and the lambdoidal suture, is palpated between the occipital and parietal bones. Normally it is triangular shaped and barely admits a fingertip.

A *bulging, tense, or full fontanel* **may be associated with increased intracranial pressure caused by birth injury, bleeding, infection, or hydrocephalus.** A *depressed fontanel,* a very late sign in the newborn, may indicate dehydration. A *third fontanel,* located along the sagittal suture between the anterior and posterior fontanels, may be a sign of congenital infection or Down syndrome or may be a normal variant.

Sutures are palpable ridges between skull bones. The coronal suture is located between the frontal and two parietal bones. The sagittal suture intersects the two parietal bones, and the lambdoidal suture lies between the occipital and the two parietal bones. With increasing GA, the suture edges become firmer and with gentle palpation are felt as hard ridges. Sutures may be open to a varying degree or may be overlapped because of molding. Lack of normal expansion may indicate microcephaly or craniosynostosis. Abnormally rapid expansion indicates hydrocephalus or increased intracranial pressure.

Abdomen. The abdomen will appear slightly scaphoid at birth but will become distended as the bowel fills with air. The technique of palpating the abdomen with one hand beneath the back as the other hand defines organs and masses is quite useful. Gentle palpation of the abdomen for organs or masses reveals that the spleen tip can be felt from the infant's left side and is sometimes 2 to 3 cm below the left costal margin. The liver is palpable 1 to 2 cm below the right costal margin. Superficial veins over the abdominal wall may be prominent.

A markedly scaphoid abdomen coupled with respiratory difficulty may indicate a diaphragmatic hernia. Abdominal distention and lack of bowel sounds may occur because of intestinal obstruction, paralytic ileus, ascites, imperforate anus, meconium plug, peritonitis, omphalocele, Hirschsprung's disease, or necrotizing enterocolitis. The abdominal wall should be inspected for defects, such as umbilical hernia, omphalocele (a herniation into the base of the umbilical cord), and gastroschisis (a defect of the abdominal wall).

The umbilical cord may also be observed and inspected while the abdomen is being palpated. The diameter of the cord varies, depending on the amount of Wharton's jelly present. **Two arteries and one vein are normally present in the umbilical cord.** The umbilical cord begins to dry soon after birth, becomes loose from the skin by 4 to 5 days, and falls off by 7 to 10 days. Redness/umbilical erythema, foul odor, or wetness/oozing of the cord may indicate omphalitis. Persistent drainage may indicate a patent urachus, umbilical fistula, or cysts.

INSPECTION

Head and Neck. The head and neck of a newborn make up 25% of the total body surface. The head is usually 2 cm larger than a newborn's chest. Normal head circumference ranges between 32 and 38 cm for a FT-AGA infant. Note the size, shape, symmetry, and general appearance.

Microcephaly is characterized by a small head size in proportion to body size. *Craniosynostosis* is a small head size caused by early closure of sutures. *Hydrocephalus* is a condition in which an increase in cerebrospinal fluid creates an abnormally large and growing head.

Eyes. Inspection of an infant's eyes is best accomplished when the infant is found in the quiet alert state or when the infant has been aroused to wakefulness during the examination. The eyes cannot be observed while the baby is crying. Tipping the baby backward and raising him or her slowly or shading the infant's eyes from bright light often causes the eyes to open.

The newborn's eyes open spontaneously, look toward a light source, fix, focus, and follow. Uncoordinated eye movements are common. Subconjunctival or scleral hemorrhages are a

common result of the pressures of labor and birth. The size, shape, and structure of the eye should be noted.

The pupils of the normal newborn respond to light by constricting. *Red reflex* is normally present and indicates an intact lens and unobstructed visual path to the retina. Tears are not normally produced until 2 months of age. The iris is usually dark blue until 3 to 6 months of age. Doll's eye maneuvers are normally associated with eyes that follow movement of the head, often with a lag and/or nystagmus.

Discharge from the eyes may represent irritation or infection. A lateral upward slope of the eyes with an epicanthal fold may indicate syndromes of mental, physical, or chromosomal aberrations. The **absence of red reflex** may indicate tumors or congenital cataracts accompanying rubella, galactosemia, or disorders of calcium metabolism. Chorioretinitis is often found in congenital viral diseases such as cytomegalovirus and toxoplasmosis. White speckles on the iris known as *Brushfield's spots* are associated with Down syndrome and developmental delay or are a normal variant. **Scleral blueness is associated with osteogenesis imperfecta and scleral yellowness with jaundice.** Brain injury may be indicated by a constricted pupil, unilaterally dilated fixed pupil, nystagmus, or strabismus.

Blood Pressure. **Blood pressure (BP) with noninvasive Doppler devices is best determined (1) by using the appropriate-size cuff for upper and lower extremities (e.g., using the same size cuff for the leg pressure that was used for the arm pressure results in a falsely elevated leg pressure), (2) by obtaining the measurement when the infant is asleep or before the infant is upset, and (3) by using the mean BP to monitor changes.**[61] **BP increases in the first 24 hours of life,** is higher in more mature infants (e.g., BW and GA) and in newborns whose mothers smoke,[82] and increases with increasing postnatal age.[59]

The BP should be checked in all four extremities to screen for coarctation of the aorta. Because the BP proximal to the area of obstruction is higher than the BP distal to the area of obstruction, BP in the upper extremities is higher (more than 15 mm Hg higher) than in the lower extremities (Figs. 5.13 and 5.14).

The only study to evaluate the efficacy of upper and lower extremity BP variations was conducted on 40 healthy neonates.[61] This study showed that with the current Doppler devices, normal neonates may have a wide variation in BPs between limbs. The researchers concluded that a difference of 20 mm Hg is more likely caused by random variability than coarctation and recommended that if weak/absent pulses are present and coarctation is suspected, an echocardiogram is necessary.[61]

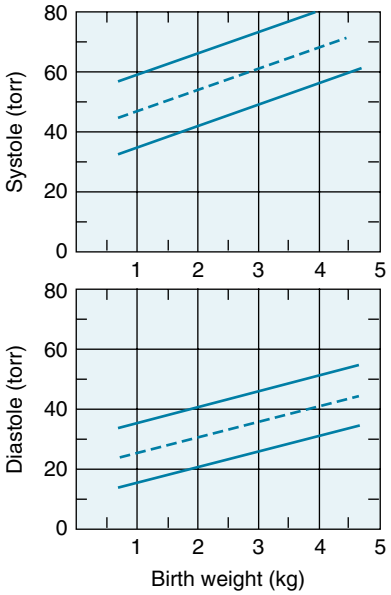

FIGURE 5.13 Aortic blood pressure during first 12 hours after birth. Linear regression *(broken lines)* and 95% confidence limits *(solid lines)* of systolic and diastolic blood pressures on birth weight in healthy newborn infants. (From Versmold HT, Kitterman JA, Phibbs RH, et al. Aortic blood pressure during the first 12 hours of life in infants with birth weight 610 to 4220 grams. *Pediatrics.* 1981;67:607.)

Head-to-Toe Examination. **The infant's crying will not affect the data to be gathered in the head-to-toe examination.**

Skin. **As each body part is examined, the skin is also inspected.** *Vernix,* a white, cheeselike material that contains quantities of α-tocopherol and surfactant proteins that provide significant protection from infection, normally covers the body of the fetus and decreases with increased GA. Discoloration of the vernix occurs with intrauterine distress, postmaturity, hemolytic disease, and breech presentations.

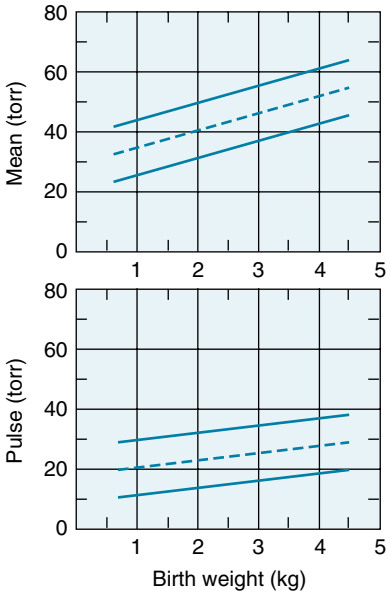

FIGURE 5.14 Mean aortic and pulse pressures during the first 12 hours after birth. Linear regression *(broken lines)* and 95% confidence limits *(solid lines)* on birth weight in healthy newborn infants. (From Versmold HT, Kitterman JA, Phibbs RH, et al. Aortic blood pressure during the first 12 hours of life in infants with birth weight 610 to 4220 grams. *Pediatrics.* 1981;67:607.)

The color of the skin is normally pink. *Mongolian spots* caused by the presence of pigmented cells may cover the sacral-gluteal areas of infants of color (e.g., black, Hispanic, Asian). The degree of generalized pigmentation varies and is less intense in the newborn period than later in life. *Nevus flammeus* may be present at the nape of the neck or on the eyelids.

Note the size, shape, color, and degree of ecchymosis, erythema, petechiae, or hemangiomas. Meconium staining, which occurs in 10% to 20% of newborns, is indicative of prior fetal distress. *Erythema toxicum* appears as a generalized red rash in the first 3 days of life. *Milia* caused by retained sebum are pinpoint white spots on the cheeks, chin, and bridge of the nose.

The normal texture of a neonate's skin is soft. A preterm infant's skin is more translucent than a term infant's skin. Slight desquamation **may occur as skin becomes dry.** Moderate to severe desquamation **occurs in postterm infants with IUGR.** Puffy, shiny skin is symptomatic of edema. Localized *edema* of a presenting part is caused by trauma and is only temporary. Edema should be distinguished from increased subcutaneous fat. *Lanugo* coverage decreases with increasing GA.

Tissue turgor is the sensation of fullness derived from the presence of hydrated subcutaneous tissue and intrauterine nutrition. Test the elasticity of the skin by grasping a fold of skin between the thumb and forefinger. When released, the skin should promptly spring back to the surface of the body. **A loss of normal skin turgor resulting in peaking of the skin is a late sign of dehydration.** A generalized hardness of the skin is a sign of *sclerema* that occurs in debilitated, stressed infants.

Ears. Cartilage development and ear form progress according to GA. Observe the external ears for size, shape, and position. **The angle of placement** of the ears is almost vertical. If the angle of placement is greater than 10 degrees from vertical, it is abnormal. The level of placement is determined by drawing an imaginary line from the outer canthus of the eye to the occiput. If the ear intersects the line, it is placed normally. Slapping hands or other sharp noises will normally elicit a twitching in the eyelid or a complete Moro reflex.

Malformed or malpositioned (low-set or rotated) ears are often associated with renal and chromosomal abnormalities and other congenital anomalies. **Abnormalities such as skin tags or sinuses may be associated with renal tract abnormalities or hearing loss.** Forceps or difficult deliveries may injure the outer ear. Congenital deafness is suspected if the infant does not respond to noise. It is confirmed by standardized hearing screening tests and follow-up.

Nose. Note the shape and size of the nose. Deformities caused by intrauterine pressure may be temporary. **Neonates are obligatory nasal breathers and must have patent nasal passages. Check the patency of the alae nasi by (1) obstructing one nostril, closing the mouth, and observing breathing from the open nostril; (2) placing a stethoscope under the nostrils that will "fog" the diaphragm and auscultate breathing; or (3) passing a soft catheter (if necessary).**

Abnormal configuration may be associated with congenital syndromes. Obstructions can be caused by drugs, infections, tumors, nasal discharge, nasal

cysts, and mucus. *Choanal atresia,* a membranous or bony obstruction in the nasal passage, may be unilateral or bilateral. **Choanal atresia is characterized by the noisy breathing, cyanosis, and apnea of the quiet infant (mouth closed) as opposed to the pink color of the same crying infant (mouth open).**

Mouth. The mouth may be examined here or at the end of the examination when the infant is crying loudly with a wide-open mouth. **At birth, a normal infant can suck and swallow (this ability develops at 32 to 34 weeks of gestation) and root and gag (this ability develops at 36 weeks of gestation). Elicit each.**

Lips and mucous membranes are normally pink. Observe the lips and mucous membranes for pallor and cyanosis. If the infant is well hydrated, the membranes should be moist. Open the mouth to look for anomalies. **Palpate the hard and soft palates for a membranous cleft or submucous cleft.** *Epithelial pearls* are common along the gum margins and the palate.

Natal teeth may be present and may require removal to prevent aspiration. A large tongue (macroglossia), cleft lip or palate (including submucous cleft), or high-arched palate may be associated with abnormal facies or be an isolated finding. If copious secretions or distress in feeding is present, it is often the result of esophageal atresia or tracheoesophageal fistula.

Thorax. Conformation of the newborn chest is cylindric with an anteroposterior ratio of 1:1. Note the shape, symmetry, position, and development of the thorax. *Asymmetry of the chest* may be caused by diaphragmatic hernia, paralysis of the diaphragm, pneumothorax, emphysema, pulmonary agenesis, or pneumonia. **Fullness of the thorax** caused by increased anteroposterior diameter occurs with an overexpansion of the lung. **Retractions, an inward pull of the soft parts of the chest while inhaling,** indicate air-entry interference or pulmonary disease.

Breasts. Breast tissue systematically develops according to GA. Enlargement of breasts because of maternal hormones occurs in either sex on the second or third day. Milky secretions may be present. Unilateral redness or firmness indicates infection.

Clavicles. Observe and palpate the area above each clavicle. A fracture of the clavicle is evidenced by a palpable mass, crepitation, tenderness at the fracture site, and limited arm movements on the affected side.

Genitalia. Male and female genitalia systematically develop according to GA. *Ambiguous genitalia* result from incomplete or altered differentiation and require urology consultation.

Male Genitalia. Inspect the genitalia for the presence and position of the urethral opening. Palpate the testes either in the inguinal canal or scrotum. The scrotum appears large and pendulous with the presence of descended testes. A tight prepuce may be found. In dark-skinned races, darker pigmentation of the genitalia is normal. *Hypospadias* exists if the urethral opening is on the ventral surface of the penis. *Epispadias* exists if the opening is on the dorsal surface. **Inguinal or scrotal swelling, discoloration, palpable masses, and pain/tenderness with palpation may indicate an inguinal hernia, testicular torsion, trauma, tumor, or *hydrocele*—**a collection of fluid in the scrotal sac.

Female Genitalia. Inspect the genitalia for the presence and position of the urethral opening. The introitus is posterior to the clitoris. A vaginal skin tag is a visible hymenal ring.

Edema of the genitalia in both sexes is common in breech presentation. Note the presence of a hydrocele or hernia. Fecal urethral discharge may indicate **rectourethral fistulas.**

Rectum. Visualize and check the patency of the anal opening by waiting for meconium passage. DO NOT use rigid objects such as glass rectal thermometers. Observe the anatomy, and feel the muscle tone. Meconium is normally present during the first days of life.

Imperforate anus, irritation, or fissures may be present. Meconium passage before birth suggests fetal intrauterine distress. Failure to pass meconium within 48 hours suggests obstruction. *Meconium ileus* is associated with cystic fibrosis.

Back. Place the infant in the prone position, and observe for a flat and straight vertebral column. Separate the buttocks to observe the coccygeal area. To check incurving reflex, stroke one side of the vertebral column. The baby will turn the buttocks toward the side stroked.

Deviations from normal include curvature of the vertebral column, pilonidal dimple, pilonidal sinus, spina bifida, or myelomeningocele. A study of spinal congenital dermal sinuses found an increased incidence (greater than 50%) of neurologic deficit, intradural tumors, or tethered cords; recommendations included a prompt radiologic evaluation and neurosurgical consultation so that timely intervention could preserve or improve neurologic function.[3]

Extremities

Upper Extremities. **Note the size, shape, and symmetry of the arms and hands.** Observe and feel for fractures, paralysis, and dislocations. Count and inspect the fingers. The hands are normally clenched into fists. The infant is capable of adduction, flexion, internal rotation, extension, and symmetry of movement. Note the tone of the muscles. Flexion develops with increasing GA.

Single transverse palmar creases may indicate chromosomal abnormalities that are frequent causes of deformity. *Polydactyly and syndactyly* of the fingers may be found. *Osteogenesis imperfecta* is characterized by multiple fractures and deformities. *Palsies* caused by fractures, dislocations, or injury to the brachial plexus are recognized by limited movement of the extremity. *Fractures* may also be present with edema, palpable crepitus, or the "palpable spongy mass sign" over the clavicle.

Lower Extremities. **Note the size, shape, and symmetry of the feet and legs.** Note the normal position of flexion (develops according to GA) and abduction. Note symmetry of movement, thigh folds, and gluteal folds. A full range of motion is possible, including the "frog position"—a rotation of the thighs with the knees flexed. Observe and feel for fractures, paralysis, and dislocations. Palpate femoral pulses.

Polydactyly and syndactyly of the toes may exist. *Osteogenesis imperfecta,* a rare genetic defect of collagen production that results in brittle bones, manifests as multiple fractures and deformities. Paralysis of both legs is caused by severe trauma or congenital anomaly of the spinal cord. **Unilateral or bilateral developmental dysplasia of the hip (e.g., congenital dislocated hip),[97] which is more common in females and breech presentations, causes a hip clunk when the baby's legs are abducted into the frog position.** Although soft clicks are common, a sharp click indicates dislocation. **Fractures may be present and are characterized by limited movement and edematous, crepitant areas.** Chromosomal abnormalities are frequent causes of deformity.

Recoil is a test of flexion development and muscle tone. Recoil appears systematically as flexion first develops in the lower extremities and then in the upper extremities. Extend the legs and then release. Both legs should return promptly to the flexed position in accordance with the GA of the infant. Then extend the arms alongside the body. On release, prompt flexion should occur at the elbows.

NEUROLOGIC EXAMINATION[6,7,66]

The neurologic examination of the newborn is an integral part of the evaluation of the newborn infant. This evaluation often receives little attention, and in too many instances the infant is dismissed from the nursery as "normal" when, in fact, little effort was expended to determine the baby's neurologic status. **The evaluation and documentation of the development of the nervous system in the normal newborn should be of paramount interest to all the health care clinicians caring for the newborn. Some portions of the neurologic examination are carried out as a component of the general physical examination of the newborn** *(activity, resting posture, symmetry, head size and morphology, rooting reflex, muscle tone, primitive reflexes, tremors and twitching, cry, recoil).* Performing a complete and thorough physical examination of the newly born is paramount.

Clinical, anatomic, and encephalographic studies of full-term and premature neonates have confirmed that the CNS of the human fetus matures in a consistent pattern.[66] However, there are recognized limitations and challenges in performing an accurate neurologic evaluation. First, because a newborn is recovering from the stress of birth, the neurologic examination is not reliable until after the infant has successfully completed the transition to extrauterine life. **Therefore, the neurologic examination should be performed after the first 12 to 24 hours of life.** Second, if the infant was born by cesarean section, or is ill and requiring NICU care, the neurologic examination may not be accurate, even after 24 hours. Third, newborns are born at different stages of brain development. Fourth, there are few tests that reflect the status of the cerebrum in the newborn.

Nevertheless, in spite of these limitations, it is still possible, with a systematic and detailed neurologic examination, to obtain enough information to gain a basic understanding of many neurologic problems in the newborn (see Chapter 26).

Assessment of Gestational Age

It is important to remember that **neurologic maturity and appropriate developmental milestones correlate with GA rather than BW.** As previously discussed, for an accurate estimation of GA, most clinicians favor systems that combine neurologic and physical signs of maturation. **Each portion of the neurologic examination is objective and easy to perform, relying on muscle tone, posture, reflex movements, and degree of extremity flexion.** The most commonly used neurologic signs for GA are posture, square window (wrist), arm/leg recoil, popliteal angle, scarf sign, heel-to-ear maneuver, head lag, ankle dorsiflexion, and ventral suspension.

Assessment of Neurologic Normality and Abnormality

The neurologic examination is most helpful if carried out systematically on an infant during quiet wakefulness between feedings, generally 1 hour before the next meal. **The examiner should be especially observant of the general alertness, spontaneous activity, symmetry of posture and spontaneous movements, muscle tone and strength, head control, developmental reflexes, and responses to manipulation and handling.**

- *State of alertness:* **Alteration in level of consciousness is an extremely important sign in determination of the neurologic status of the newborn.** A normal term infant shows a semiflexed posture and smooth spontaneous movements of all extremities. The hyperalert neonate has the appearance of increased vigilance with eyes wide open, often decreased blinking, overreaction to minimal stimulation, and reduced sleeping. Decreased state of alertness could be lethargy, stupor, and coma.
- *Posture:* **Observation of posture is one of the first steps in the neurologic examination.** Much can be predicted from the position of the limbs at rest. **Term infants should have a preponderance of flexor tone** during wakefulness and sleep with the normal semiflexed posture of the elbows and ankles. The **hand position typically shows a partially closed fist. A tight cortical thumb can be normal, but when it is persistent and obligatory, it suggests a corticospinal abnormality.** In prone position, the pelvis is elevated by hip and knee flexion. Alterations of expected patterns of posture suggest neurologic abnormalities, which can be focal or generalized.
- *Tone:* **Muscle tone is evaluated by resistance to passive movement. Pronounced hypotonia characterizes the premature infant below 29 weeks of gestation,** and tone increases in a caudal-rostral direction over the ensuing weeks. There is an orderly progression from a limp "rag doll" at 28 weeks to the flexed "frog legs" posture at 34 weeks and the fully flexed supine posture at term. **When evaluating tone in the newborn, the head should be in the midline position to avoid eliciting a tonic neck response, and a comparison should be made between the two sides of the body and between the upper and lower extremities.**
- *Neonatal hypotonia:* **Term infants with decreased tone will show less flexor posture, less resistance to passive movements, and more head lag.** The infant becomes limp and floppy, with little control. **The most frequent etiology for hypotonia is generalized depression of the CNS.** Other causes include neuromuscular disorders, CNS dysfunction, sepsis, and congenital and genetic disorders.
- *Neonatal hypertonia:* Although decreased tone in the newborn is obvious, at times the determination of increased tone can be more of a problem. **Infants with increased tone will show extensor posturing of extremities in supine and prone positions. Extensor posturing of the legs with arms held tightly fisted against the midline points to hypertonicity.** The most severe degrees of hypertonia lead to *opisthotonos.* Pronounced hypertonia is usually caused by many of the same conditions that can lead to hypotonia, but usually tends to point to more chronic or subacute conditions. Common etiologies include hypoxic-ischemic encephalopathy (HIE), sepsis and meningitis, congenital structural malformations of the brain, and intraventricular hemorrhage.
- *Developmental reflexes:* The developmental reflexes used to evaluate the newborn are best described as "primitive," because they do not require

functional brain above the diencephalon and probably not above the mesencephalon. Many such reflexes have been described; however, it is unlikely that all can be elicited in an infant at any given time. It is **better to use six to eight usually present in all newborns and to evaluate them consistently:** *Moro's reflex, tonic neck reflex, stepping reflex, Galant reflex (truncal incurvation), palm and plantar grasp reflex,* and *Babinski's reflex*.

Reflexes are complex responses to specific stimulation, probably representing integration of the brainstem and spinal cord level. **Asymmetries are always abnormal;** these reflexes should never be mandatory or persistent, and a reduction or absence of all developmental reflexes may represent generalized depression of all cerebral activity from any cause such as infection, medications, hypoxemia, or metabolic diseases.

Because the responses vary with the state of alertness of the infant, and the newborn's tolerance for prolonged examination is limited, eliciting a perfect response to each maneuver should not be expected. When the examination is not fully reassuring, repeating selected parts of the examination at a later time may be more helpful in clarifying findings than attempting an extended examination at one time.

Assessment of Neurobehavioral Development

In addition to neurologic examination, **the assessment of neurobehavioral development is an important step in the evaluation of the newborn infant.** All newborns requiring intensive care, particularly preterm infants, are going to continue their development in extrauterine settings at a time when their brains are growing more rapidly than ever in their life span. Understanding the potential role of illnesses, therapeutic interventions, and NICU environment on their neurobehavioral development is paramount for the provision of quality newborn care during this highly vulnerable phase of brain development.

Caregivers need to become knowledgeable of the tools available for the assessment of the neurobehavioral development and the potential interventions. There are numerous tools for the assessment of neurobehavioral development.[9,31] Chapter 13 offers a detailed and comprehensive review of this subject.

THE BRAZELTON SCALE

The Neonatal Behavioral Assessment Scale (NBAS) is a comprehensive behavioral assessment of the newborn.[31] The NBAS psychological scale enables assessment of the infant's individual capabilities for social relationships. Clinical application of the Brazelton scale includes neonatal research and clinical evaluation of newborn infants after illness, prematurity, or maternal medications.

The NBAS focuses on an interactive approach and highly individualized parameters of newborn functioning. Later editions of the NBAS have added supplemental items, which further qualify the behavior of the newborn, particularly of preterm infants.

A modified version of the Brazelton examination is useful in teaching parents about their individual infant's patterns of behavior, temperament, and states. By understanding the uniqueness of their infant, parents may more intelligently assess and interpret their baby's cues for interaction and distance. If the parents know their infant's individual strengths and weaknesses, they will react more realistically to him or her. It is important for the provider to elicit the parents' assessment of their infant's behavior and responsiveness. Unrealistic expectations or incorrect parental perceptions may exist. This is an excellent opportunity for parent teaching, and possibly referral. The NBAS is distinguished from other programs in its use as an intervention with parents and medical staff. Employed in this manner, it is **intended to improve and enhance the caregiver's attitude to and interaction with the infant.**

The Brazelton examination is usually performed at 2 to 3 days of life, at discharge, or on the follow-up visit at 1 to 2 weeks. This examination assesses the infant's best performance in response to stimulation and handling by the examiner. For research purposes, scoring by a certified examiner is sufficient. For clinical use, knowledge of the specific techniques and interpretations of results is all that is required. Knowledge of the infant's state is necessary (see Chapter 13, Table 13.3). **Performing the examination with the parents present provides the opportunity for teaching, parental participation, and observation of their infant's response.**

Maternal use of antidepressants, opioids and smoking have been shown to alter the newborn's neurobehavioral examination (see

Chapter 11). Neonates exposed to selective serotonin reuptake inhibitors late in pregnancy exhibit the following mild and spontaneously resolving behaviors: tremors/tremulousness, restlessness/irritability, abnormal crying, rigidity, fewer state changes, and more active sleep with startles and arousal.[75]

CARE OF THE WELL NEWBORN INFANT

Mother-Infant Bonding and Interventions

FREQUENCY OF ASSESSMENTS

During the transitional period, vital signs should be recorded frequently enough to monitor the infant's condition and provide appropriate care:

- If the **infant is distressed** (elevated heart rate or respiratory rate, retracting and/or nasal flaring), **vital signs may be required every 30 minutes.**
- If the baby's **vital signs are normal on admission** (heart rate 120 to 160 beats/min, respiratory rate 30 to 60 breaths/min, and temperature 36° to 36.5°C), **vital signs may be required every 30 to 45 minutes until the infant's condition has remained stable for 2 to 4 hours.**
- **Vital signs should be recorded at least once every 8 hours.**
- Measuring the temperature rectally is *contraindicated* in newborns because of the risk for rectal perforation (see Chapter 6).

Weight, length, and head circumference should be graphed on the appropriate intrauterine growth chart to determine at which percentile the baby falls. **Determination of the weight/length ratio (see Fig. 5.3) normally increases with fetal age because the fetus becomes heavier for length as term approaches.** In IUGR, the weight/length ratio decreases because the rate of growth in weight is affected more than length. Severe and prolonged intrauterine malnutrition may affect head, weight, and length ratios.

PREVENTIVE PRACTICES

Assessment of the infant's GA provides a reference point for individualizing care. Whether the infant is term and admitted to the normal newborn nursery or preterm and admitted to the intensive care nursery, attention to care practices that support development and neurologic integrity is essential in preventing iatrogenic disruptions or injury.

In utero, the fetus depends on the mother's physiologic systems to automatically regulate its own. At birth, the neonate's basic physiologic needs are met in new and different ways. Emerging from physiologic dependence into a physiologically independent neonatal state introduces new variables for both mother and baby in the development of their extrauterine relationship. **For both term and preterm newborns, the primary developmental task is to reestablish biorhythmic balance by (1) establishing homeostasis through self-regulation of states (e.g., arousal and sleep/wake cycles); (2) processing, storing, and organizing internal and external stimuli; and (3) establishing a reciprocal relationship with primary care providers and the environment.**

Although biorhythmic balance is internally determined, caregiving interaction between newborn and parent or caregiver either facilitates or disturbs this transition. **After birth, balance is facilitated by contact with familiar surroundings (the mother's body).**[74,148,181] The mother's sensorimotor (auditory, tactile, visual), thermal, and nutrient stimuli provide regulatory effects on the infant's behavior (activity level, sucking, sleep and wake cycles, stress management, and circadian rhythms) and physiology (endocrine secretion, oxygen consumption, and cardiovascular status).[74,148] **Full-term newborns placed on the mother's chest immediately after delivery (within 5 minutes) and longer (more than 60 minutes) display the following stereotypic innate sequence of prefeeding behavior**[181,201]**:**

- Significantly lower salivary cortisol levels and more stable cardiopulmonary function
- No sucking activity in the first 15 minutes
- Rooting and sucking activity begins and reaches maximum intensity at 45 minutes
- First hand-to-mouth movement at 35 minutes
- Spontaneous and unassisted finding of nipple and initiation of breastfeeding at about 55 minutes of age

Within the first 90 minutes after birth, neonates cared for in close body contact with the mother are quiet. However, infants separated from their mothers during this period and cared for in a crib cry and exhibit a *separation distress call* (also seen in several other mammalian species) that ceases at reunion.[52]

AVOIDANCE OF CERTAIN CARE PRACTICES

Certain care practices (e.g., separation of the mother and infant, gastric suction, noise levels in the newborn nursery) have become "routine" in some maternal/child care settings. **These practices are based on few scientific foundations, disrupt maternal and infant regulation and establishment of innate behaviors, may have hidden consequences that surpass human adaptability, and may contribute to behavioral changes that result from violations of an innate agenda.**[81] For example, gastric suction after birth evokes aversive reflexes (e.g., retching, combative movements, alterations in arterial blood pressure and heart rate, including bradycardia), disrupts development of early feeding behaviors, is unpleasant, and has no advantages in a healthy term infant following a normal pregnancy and normal vaginal delivery.[11,81] Use of maternal analgesia may interfere with the newborn's spontaneous breast-seeking and breastfeeding behavior.

During transition of a term neonate, prone position has been shown to improve oxygenation, decrease heart and respiratory rates, and encourage more favorable behavioral states.[159] In the newborn nursery, the lack of diurnal rhythm in noise levels and care-providing activities disrupts reestablishment of biorhythmic balance. **Significant differences in nighttime sleep and wake patterns exist between newborns cared for in the nursery (exposed to more light, noise, crying, and noncontingent care) and newborns rooming with the mother (more quiet sleep and less crying).**[102] Term infants exposed to soothing music in the newborn nursery spent less time in high arousal states (i.e., nonalert waking and crying) and had fewer behavioral state changes.[101]

MINIMIZING PROCEDURAL PAIN IN NEWBORN CARE

Placing full-term and preterm infants skin-to-skin in whole-body contact with their mothers or breastfeeding during heelstick procedures reduces heart rate, crying (by 91%), and grimacing (by 84%)[1,43,83,100] (see Chapter 12). When possible, breastfeeding throughout the procedure, rather than offering pumped breast milk, offers more comfort because of the synergism between skin-to-skin contact with the mother, sucking, and reception of breast milk by the infant.[3] Either breastfeeding/breastmilk or glucose/sucrose should be used to alleviate a newborn's procedural pain rather than positioning alone or no intervention.[162,165] The proximity and caregiving of the mother provide term and preterm infants with a barrier against outside stimulation and an ability to increase their threshold to noxious stimuli.[74]

One barrier to using skin-to-skin care and breastfeeding to relieve neonatal pain during invasive procedures such as heelstick and injections is the uncomfortable position of the professional performing the procedure. An ergonomically sound protocol using an adjustable-height stool has been developed and tested in the clinical setting. This approach has resulted in a more comfortable position for the professional and greater use of skin-to-skin care and breastfeeding for neonatal pain relief during procedures.[57]

NURSERY CARE PRACTICES AND ADAPTATION TO EXTRAUTERINE LIFE

Adaptation of full-term neonates is influenced either positively or negatively by nursery care practices (early care and handling). **The influence of these practices in the adaptation of preterm or sick neonates may be even greater.** Stress-reduction techniques to prevent fluctuations in BP, vital signs, and oxygenation often are not initiated until after the preterm infant has been admitted and stabilized in the NICU. **Individualized developmental care (e.g., dimmed lights, decreased noise, gentle handling, contingent stimuli) (see Chapter 13) may be delayed in the presence of urgent expeditious assessment, diagnosis, and life-supporting interventions in the delivery room and on admission to the nursery.** Consequently, the physiologic, anatomic, and psychological transition to extrauterine life makes at-risk neonates extremely vulnerable to the stress of resuscitation and initial nursery care.

MINIMIZING STRESS DURING RESPIRATORY AND CIRCULATORY SUPPORT

Minimizing stress and conserving energy should accompany establishing and maintaining an airway, adequate oxygenation and ventilation, and circulatory support. An immature preterm infant (less than 32 weeks of gestation) (see Chapter 13) who is physiologically unstable may deteriorate if not handled gently and protected from overstimulation. **Rapid fluctuations in oxygenation and blood pressure, overwhelming stimuli, too-rapid volume expansion, suction, unrelieved pain, and hypothermia contribute to the incidence of intraventricular hemorrhage that occurs most commonly**

in the first 24 hours after birth (see Chapters 4, 6, 12, 23, and 26). In preterm infants, "routine" procedures such as bathing[19,190] result in increased heart rate and BP, motor stress behaviors, changes in stability and reorganizational behavior, hypoxia, and increased intracranial pressure (see Chapter 13). Overwhelmed by external stimuli, a neonate's global response to stress may be apnea and bradycardia.

Based on the infant's ability to tolerate an intervention and the benefits of early assessment and intervention, the admission process should be prioritized to (1) provide life-supportive care, (2) conserve energy, and (3) collect data and complete the health care record. Table 5.8 outlines developmental interventions for neonatal admissions and care after birth that decrease stress, reduce energy consumption, improve oxygenation and respiratory and heart rates, and prevent iatrogenic stress and injury. **Developmentally supportive care should begin immediately after birth.**

SURVEILLANCE FOR POTENTIAL COMPLICATIONS

Complications of common morbidities (see Fig. 5.12) are prevented by classification, assessment, and screening of all newborns at birth. These morbidities and their complications are thoroughly discussed in the appropriate chapters. Close monitoring and surveillance of these groups of infants, and long-term follow-up studies, would allow us

TABLE 5.8 DEVELOPMENTAL INTERVENTIONS DURING ADMISSION AND INITIAL NURSERY CARE

Oxygenation	Apply noninvasive monitor (see Chapter 7) Titrate Fio2 to maintain saturation at 92%–94% (see Chapters 7 and 8) Handle gently, minimally (see Chapters 13 and 23) Skin-to-skin care improves gaseous exchange, especially in preterm infants <1000 g (see Chapter 13) Position prone to maximize oxygenation (see Chapter 13 and below) Delay or defer bathing[35,55,118] (see Chapters 6 and 19)
Thermoregulation	Maintain temperature axillary (36.5°C–37.5°C in term infants); skin (36°C–36.5°C in preterm infants) (see Chapter 6) Skin-to-skin contact (kangaroo care) provided by mothers or fathers to preterm/term newborns warms better than incubator care[26] Prewarm linen, scales, radiant warmer; incubator (see Chapter 6) Decrease heat loss with position (i.e., prone, flexion) (see Chapters 6 and 13) Use warm water on skin before applying probe, electrodes (see Chapter 19) Thermoregulation is the primary consideration in the timing and location of the first bath:† • Healthy term infants with axillary temperature >36.8°C can be bathed after 1 hour of age when appropriate care is taken to support thermal stability.[20,190] However, two newer studies show that: (a) bathing at 1 hour of age increases the incidence of hypothermia even when skin-to-skin care is used after the bath,[25] and (b) routine newborn care, including bathing delays thermoregulation[169] • First bath delayed till 2–4 hours of age, after vital signs and temperature are stable.[14] • First bath delayed till the next day for full-term baby[203] • Delay first bath and use swaddled, immersion bathing by parents instead of sponge bath[35,42] (see Chapters 6, 13, and 19) • Sponge bathing of healthy neonates (≥37 weeks of gestation) by an RN in mother's room at 3, 6, or 9 hours of age resulted in an initial reduction of skin and axillary temperatures that recovered after the bath.[103] Offer parents the opportunity to bathe[20,35,125] (see Chapters 6 and 13)
Nutrition	Screen at-risk and symptomatic infants for hypoglycemia (see Chapter 15) Provide fluids and/or calories (orally or intravenously) (see Chapters 14 to 17) Decrease energy expenditures by decreasing internal stressors (e.g., hypothermia, hypoxia) and external stressors (e.g., noise, light) (see Chapters 13 and 15)
Pain	Minimize painful stimuli (see Chapters 12 and 13) Use venipuncture rather than heelstick (see Chapter 12) Relieve pain with nonpharmacologic interventions: • Provide comfort measures (e.g., pacifier, containment, grasping) (see Chapters 12 and 13) • Use sucrose, skin-to-skin care, and/or breastfeeding during painful procedures.‡ Relieve pain with pharmacologic interventions (see Chapter 12)

Continued

TABLE 5.8 DEVELOPMENTAL INTERVENTIONS DURING ADMISSION AND INITIAL NURSERY CARE—CONT'D

Environmental stimuli	*Tactile* (see Chapter 13): Handle gently and minimally Support and contain in flexion Provide rest periods between procedures, handling Early (within 5 minutes of birth) and longer (>60 minutes) skin-to-skin care stabilizes cardiopulmonary systems and reduces newborn stress after birth[181] *Visual* (see Chapter 13): Shield from bright, direct light Dim lights as soon as possible Cover oxygen hood, face with washcloth Cover incubator with blanket or cover *Auditory* (see Chapter 13): Talk quietly Respond quickly to alarms Parents talk softly to infant Keep ill neonates away from crying babies[102]
Position	Promote flexion in side-lying position with blankets, rolls (see Chapter 13) Prone (oxygenation better; less apnea; quiet, more restful sleep; decreased caloric expenditure; decreased reflux) (see Chapter 13) Swaddle (see Chapter 13) Avoid supine if newborn is hypoxic and has an oxygen requirement; otherwise, always position all well term newborns supine (see Chapter 13)
Assess and interpret newborn cries	Assess avoidance and approach behaviors so that care is individualized (see Chapter 13) Support infant strengths and adaptive and coping behaviors (see Chapter 13) Modulate environmental and caregiver stimuli based on infant cues (contingent on cues rather than noncontingent stimuli and interaction) (see Chapter 13) Teach parents infant cues (see Chapter 13)

*References 43, 83, 100, 161, 164.
†References 35, 55, 93, 111, 118, 125.
‡References 73, 93, 108, 175, 185, 197, 210.

to establish patterns of potential outcomes for each specific subgroup. For example: Preterm SGA/IUGR infants are at increased risk for mortality, more gross motor and neurologic dysfunction, more cognitive disorders needing special education, but less cerebral palsy compared with AGA infants.

PARENT TEACHING

Transitional care, neonatal assessment, and initial care do not necessarily take place in a nursery in which the newborn and family are isolated from each other. Alternative settings for initial care include birthing rooms, recovery rooms in which family and baby are kept together, the mother's postpartum room, or at a home visit. **In fact, keeping the family together not only facilitates bonding but also provides an excellent opportunity for teaching parents about the individuality of their newborn.**[125]

The assessments of GA and physical condition are best performed with the mother and father in attendance so that deviations from normal such as caput, cleft lip, cleft palate, or clubfoot can be explained. Eliciting parental cooperation is important. For example, when the major concern is "Will the procedure hurt?" a response such as "It is routine" will not comfort and reassure well-informed, noninterventionist consumers. Rather, a more physiologically oriented explanation about the condition being screened, why their particular infant is at increased risk, and what interventions are available encourages parental cooperation.

Professional care providers are only temporary caregivers. It is our responsibility to help parents become confident, primary caregivers of their own infants. **Actively involving parents in the care and treatment of their newborn further solidifies their position as primary caregivers.**[125] Encouraging active parental involvement enhances the parents' self-esteem and confidence in their abilities; thus our actions must tell and reassure the parents, "You are able to care for this baby." An RCT comparing the ability of parents to perform the baby's first bath in the mother's room versus a nurse bathing the baby in the admission nursery found no difference in temperature changes irrespective of who bathed the baby or where the bath was given.[125] The newborn heat loss experienced with bathing was significant and returned to normal in 1 hour. **Parents in the study wanted the opportunity to bathe their infants and gained confidence in their parenting skill/ability.** With the supervision of the nurse, ensuring an environment to reduce heat loss (e.g., warm, draft-free room, temperature assessment, warm water, use of kangaroo care after the bath) and using the bath as a teaching opportunity, parents can bathe their own infants.

At discharge, performing the physical examination in the room with the parents offers a final opportunity to teach, counsel, and advise them before they take their new baby home. Information about feeding, cord care, bathing, elimination patterns, safety, signs of illness, medications, and the importance of follow-up care is essential for parents of a full-term, healthy newborn (Box 5.5). It is also essential for parents taking home an

BOX 5.5 PARENT/CAREGIVER TEACHING[69,168]

- Every encounter with the parents is a teaching opportunity, so that by the time of discharge, parents are totally competent to care for their infant. Assess each individual family's ability to care for their infant and readiness for discharge.
- Teach parents how to care for the newborn's skin, umbilicus, and circumcision site and the appropriate urination/stooling patterns for newborns.
- Teach parents about the nutritional needs of their newborn, how to breast/bottle feed, and how to burp their baby. Develop a feeding plan with the parents for the late-preterm infant, and teach parents how and why to adhere to the plan for a late-preterm infant.
- Teach parents how to take an axillary temperature on their newborn and maintain the axillary temperature between 36.5° and 37.4°C (97.7° and 99.3°F) with clothes, blankets, and an appropriate environmental temperature.
- The presence and clinical significance of jaundice are determined before discharge (see Chapter 21), appropriate follow-up care has been determined, and the importance is stressed to parents. Parents are taught how to assess jaundice at home.
- Teach parents the importance of follow-up care, either at a clinic, physician's office, or home visit: (a) within 24 to 48 hours after discharge for late-preterm infants,[69] (b) within 48 hours (if discharged at ≤48 hours of age),[23] or (c) within 3 to 5 days after discharge.[87]
- Give parents the newborn immunization record with documentation of what immunizations their infant has received and the importance of follow-up for childhood immunizations.
- Teach parents appropriate safety precautions:
- Verbal and written information about recognizing signs and symptoms of a "sick"/"ill" infant, how the infant acts, and whom to notify.
- Proper use of car seats including positioning with supports, facing the rear in the backseat, middle of rear seat, preferably with an adult seated next to the preterm to enable ongoing observation of the infant during travel.
- Proper positioning supine for safe sleep: "Back to Sleep." Model "Back to Sleep" by placing babies who are in cribs only on their backs to sleep. *All* care providers (e.g., parents, grandparents, day care providers, babysitters) should sleep babies supine (see Chapter 13).
- Use of skin-to-skin care for full term infant is soothing, calming, and recommended.[54] A 50-minute session of skin-to-skin care at 5 to 7 weeks of age has been shown to decrease an infant's salivary cortisol level prior to a bath.[21] Skin-to-skin contact must be done safely—position infant prone on adult chest with head turned to one side, face visible with nose and mouth uncovered; neck is straight, not bent, and head is in the "sniffing" position; legs are flexed, and the baby is covered with a blanket. Adults do not sleep while the baby is in skin-to-skin contact.[73]
- Importance of a smoke-free environment because secondhand smoke is associated with an increased risk for developing health problems.
- *NEVER* shake the baby! Babies are shaken by frustrated caregivers when the infant continues to cry. Dangers of shaking infants include blindness, brain damage, developmental delays, seizures, paralysis, and death. (See Resource Materials for Parents at the end of this chapter.) Education of parents about normal sleep and crying patterns, techniques for soothing infants, possible medical causes for crying, and parent self-care advice lowers parental depression and enhances parent confidence in caregiving.
- Information, in writing, about all medications for their infant including name, action, dose, route, side effects, and schedule (see Chapter 10).
- Proper swaddling technique: Safe swaddling includes positioning the baby's extremities in slight flexion and abduction; baby should be able to freely move lower extremities. Placing an infant's hips and knees in an extended position with swaddling increases the risk of hip dysplasia and dislocation.[97]
- Teach parents the importance of their own self-care: need for adequate sleep/rest, nutrition/hydration, privacy, stress management, recreation, and sex.

infant after prolonged hospitalization. In addition, a modified version of the Brazelton examination on all neonates enables parents to become familiar with a newborn's competencies for reacting to and shaping his or her environment and with strategies for parental intervention. Developing written materials for parents about normal newborn care and documenting teaching sessions and return demonstrations ensure that no important information is forgotten (see Chapter 31 for discharge planning and teaching strategies).

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6 HEAT BALANCE

SANDRA L. GARDNER AND BETSY H. CAMMACK

Adaptation to extrauterine life involves the newborn infant in a series of biologic adjustments to a totally new set of environmental conditions. Prime among these is the accommodation to a **new thermal environment that represents a distinct "cold challenge."** Failure to adjust to this cold stress has historically been recognized, particularly in premature and low-birth-weight (LBW) infants, with the development of variable degrees of hypothermia and increased morbidity and mortality rates. At birth, the body temperature of the newborn infant will approximate or slightly exceed that of the mother. Within minutes of birth, however, core temperature begins to fall precipitously, particularly in infants with birth weights less than 1500 g. **These infants have a diminished capacity for metabolic heat production, a high surface area to volume ratio, and immature epidermal barrier leading to extraordinarily high evaporative heat losses.** Consequently, they are highly vulnerable to the development of hypothermia. **Thermal management has become a cornerstone in neonatal intensive care.** Earlier studies conducted in term and preterm infants worldwide concluded that **maintenance of body temperature through control of the thermal environment is paramount for the reduction of morbidity and mortality risks in LBW infants.**[102,105,114]

Over the past several decades, researchers and clinicians have gained insight into the physiology of thermoregulation and developed the technology to maintain thermal neutrality in the tiniest and sickest neonates.[65,89,93,132,135] Although the staff of modern neonatal intensive care units (NICUs) have the expertise and equipment to avoid or minimize the consequences of inadequate thermoregulation, determining the **most appropriate ways of getting the best temperature balance (normothermia)** is the subject of ongoing investigation. This chapter discusses the current knowledge of the physiology and pathophysiology of neonatal thermoregulation and techniques used not only to prevent heat loss but also to manage heat balance.

HISTORICAL MILESTONES[23,90,97]

The *first incubator for neonates* was introduced in the early 1830s. Dr. Stephane Tarnier, Chairman of Obstetrics of the University of Paris, first applied the principle of graded incubation (commonly used in chick embryos) in developing a covered incubator chamber that has been widely recognized as the first attempt to systematically provide a warmed environment for premature infants. In 1835 in St. Petersburg, Russia, Von Ruehl introduced an incubator described as a double-walled box that circulated warmed water within the interspace.[110] Tarnier's students, Budin and Auvard, modified Tarnier's incubator by adding a thermometer and regulatory alarms to alert the infant's nurse attendant to either increase or decrease the incubator's prescribed temperature. The care of newborns was delegated to Madame Henry, Midwife-in-Chief, who oversaw the building of a pavilion specifically for the care of these weakling newborns.[128] This pavilion housed 12 incubators, in which fragile newborns were warmed over a hot-water reservoir attached to an external source of heat. These were impressive first steps in attempting to control the fragile heat balance of weak preterm infants. Over the next 60 years, in Tarnier's and Budin's clinic, refinements of incubation techniques resulted in an increased survival from 38% to 66% in infants weighing between 1200 and 2000 g. Dr. Tarnier's successor, Dr. Budin, continued this important early practice of neonatology, focusing on the home care of these

BLUE type highlights content that is particularly applicable to clinical settings.

high-risk babies. Alexandre Lion improved the design of incubators and charged spectators a fee to see them in action, which led to a very popular show at the Berlin Exposition of 1896. An associate of Lion, Martin Couney, brought the incubator shows to the United States, where Dr. Joseph DeLee adopted the technology and opened an "incubator station" in 1900 at the Chicago Lying-in Hospital. Nearly all of the large expositions in America hosted "Incubator Baby Side Shows." These began in 1898 with the Trans-Mississippi Exposition and continued on to the New York World's Fair in 1939.

Dr. Couney's display of incubators at Luna Park on Coney Island and at a second park named *Dreamland* hosted premature babies from New York hospitals that lacked the facilities to care for them. These infants were lined up under heaters in incubators, and they breathed filtered air. At least 8000 babies passed through these incubators, and at least 6000 were saved. Servocontrolled radiant heat in incubators was initially reported by Agate and Silverman in 1963.[110]

Today's *radiant warmer* is an evolution from the original idea of Agate and Silverman. Radiant energy as the sole source of heat from an overhead panel was described in 1969 by Due and Oliver. Widespread use of the warmer in the delivery room was readily accepted and soon led to its use in the NICU. The factors that affect heat loss and heat production were elucidated. As intensive care became more readily available, easy accessibility to the infants became increasingly necessary and the open warmer became more readily used.[66]

Changes in the radiant warmer have included the introduction of incubators that are interchangeable with and convert to radiant warmers. The use of humidification in the incubators has also been improved to allow for varying humidification based on the infant's gestational age and weight. These new beds allow the caregiver to rotate the mattress 360 degrees for easy patient access and provide an in-bed scale. In recent years, new approaches to thermal care of the newborn preterm baby have been extensively studied,* including occlusive wrapping, placing on heated mattresses, and skin-to-skin (kangaroo) care. The role and clinical significance of these approaches will be discussed later.

*References 10, 24, 47, 57, 64, 65, 75, 89, 97

PHYSIOLOGIC CONSIDERATIONS

Animals that maintain their body temperature within a narrow range through a wide range of environmental temperatures are known as *homeotherms.* **Humans, as homeotherms, maintain a "normal" body temperature by balancing the amount of heat lost from the body with the amount of heat generated from within the body.** Our ability to cope with changing thermal environments improves physically and physiologically with age. Eventually we are physically able to move to a different place with a more suitable environment or dress more appropriately when the temperature is uncomfortable.

Babies, especially preterm or small-for-gestational-age (SGA) babies, of course cannot physically respond as older children would, and even their physiologic responses are different and limited. Adults lose some thermoregulatory control during rapid-eye-movement sleep. Although newborn infants spend much time in active sleep, their thermoregulatory control is not impaired during this period of active sleep,[71] which indicates the developmental importance of both thermoregulation and active sleep in the maturation of newborn infants.

Neutral Thermal Environment

Physiologic responses to a cold environment include metabolic reactions that consume substrate and oxygen and result in heat production. **A neutral thermal temperature is the body temperature at which an individual baby's oxygen consumption is minimized (Fig. 6.1). Thus a minimal amount of the baby's energy is expended for heat maintenance, and energy is conserved for other basic functions and for growth.** Minimal metabolic activity is possible within a narrow range of temperatures, so temperatures that are too high or too low add stress and increase metabolic rate. Extreme deviations from this range overwhelm the thermoregulatory mechanisms, leading to body temperature imbalances and potentially death.

The goal in controlling a neonate's environment is to minimize energy expended by him or her to maintain a "normal" temperature, thus eliminating thermal stress. This neutral thermal environment is the sum total of factors at which a baby with a normal body temperature has a minimal metabolic rate and therefore minimal oxygen consumption (Fig. 6.2). Both traditional indirect calorimetry and

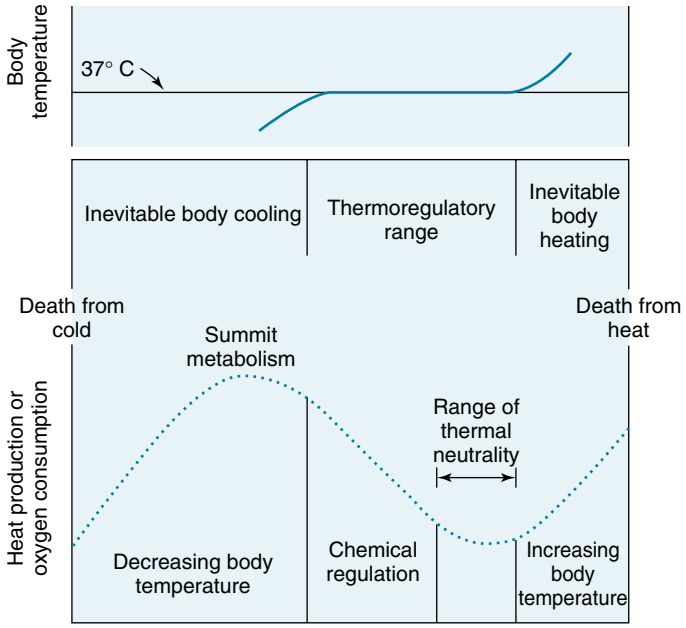

FIGURE 6.1 Temperature versus oxygen consumption. Effect of environmental oxygen consumption and body temperature. (From Klaus M, Fanaroff A. *Care of the High-Risk Neonate,* 2nd ed. Philadelphia, PA: Saunders; 1979.)

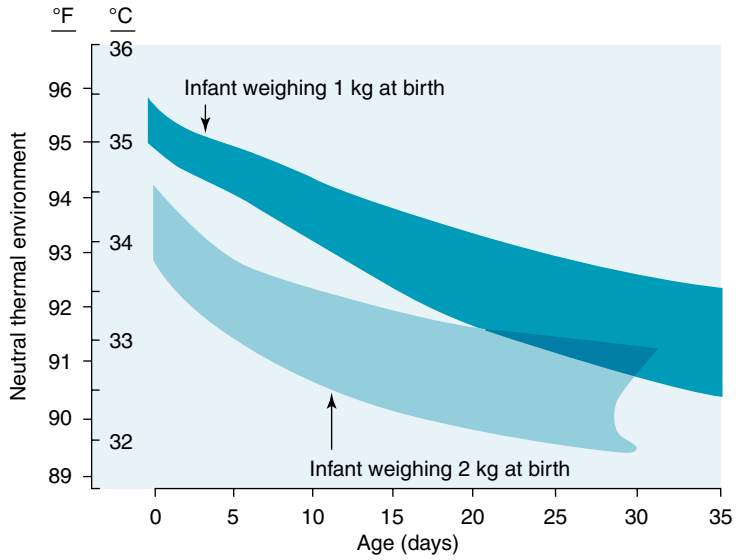

FIGURE 6.2 Neutral thermal environments. Range of temperature to provide neutral environmental conditions for infant lying naked on warm mattress in draft-free surroundings of moderate humidity (50% saturation) when the mean radiant temperature is the same as air temperature. Shaded areas show average neutral temperature range for healthy infant weighing 1 kg *(dark)* or 2 kg *(light)* at birth. Optimal temperature probably approximates to lower limit of neutral range as defined here. Approximately 1°C (1.8°F) should be added to these operative temperatures to derive appropriate neutral air temperature for single-walled incubator when room temperature is less than 27°C (80°F) and more if room temperature is much less. (From Hey EN, Katz G. The optimum thermal environment for naked babies. *Arch Dis Child.* 1970;45:328.)

the more accurate and sensitive direct calorimetry are used to study the production and expenditure of heat in newborns. Factors such as ambient air temperature, airflow velocity, relative humidity (RH), and temperature and composition of objects in direct contact with the infant or to which heat may be radiated compose the infant's thermal environment.

Maintaining Heat Balance (Heat Production vs. Losses)

When exposed to a cold environment, a neonate senses the reduced skin surface temperature (using sensors in the skin, primarily the face) and senses core body temperature (using sensors along the spinal cord and in the hypothalamus). Information from these various sensors is processed (probably in the posterior hypothalamus), including average temperature, rate of temperature change, and size of the stimulated area. **Cold stress results in the initiation of a series of reactions to increase heat production and decrease heat loss.** In adults, the most significant involuntary method of heat production is shivering. **Neonates rarely shiver and must rely on nonshivering, or chemical, thermogenesis to produce the needed heat.** This process is initiated in the hypothalamus and transmitted through the sympathetic nervous system, leading to the release of norepinephrine at the site of brown fat. ***Brown fat,* found mostly in the nape of the neck, axillae, and between the scapulae of newborns, is a specialized type of fat.** It is unique in that it contains thermogenin, which is the key enzyme regulating nonshivering thermogenesis. Norepinephrine causes the release of free fatty acids, which with thermogenesis undergo combustion in the mitochondria of brown fat cells, releasing heat. Lipoprotein lipase also provides further triglyceride substrate for heat production.

Oxygen and glucose also are consumed during nonshivering thermogenesis. Thus an infant who already has low oxygen or glucose levels may become hypoxemic or hypoglycemic if added thermal stress occurs. **Preterm babies do not possess sufficient brown fat stores to mount a significant heat production response to compensate for even minimal cold stress.[36] When servocontrol is used, the thermistor must not be placed over an area of brown fat (such as in the axilla), which may directly heat the overlying skin, causing a decrease in servocontrolled heat output.[3]**

Heat generated within the body is transferred by conduction through tissues along a gradient from warmer to cooler areas such as the skin surface. **An initial response to a cold environment is to constrict superficial blood vessels to minimize the transfer of heat from the core to the surface of the body.** Superficial vasoconstriction, which gives the skin a mottled appearance in response to cold stimulus, results in a lower skin temperature reading to the thermocontroller and consequently causes an increase in the incubator temperature. **The smaller the body size, the less effective vasoconstriction is in conserving heat.**

Compared with adults, **newborns have a very large surface area to body mass ratio and therefore have a relatively large area exposed to the environment from which heat can be lost.** More mature infants may try to minimize their surface area by changing positions to decrease exposed surface area when faced with cold stimulus, but immature infants cannot flex the trunk and extremities effectively. They also have little subcutaneous fat tissue (which acts as insulation) to help prevent heat conduction to the body's surface, where the heat would be lost.

Heat is transferred from the infant's body to the environment (i.e., everything in proximity to the baby) along a temperature gradient from warmest to coolest. **Heat losses occur by four principal mechanisms: *radiation, conduction, evaporation,* and *convection*.** Fig. 6.3 illustrates these four mechanisms and identifies interventions to minimize their effects.

Much less frequently, a newborn must call on physiologic responses to an environment that is too warm, and these responses are somewhat limited. **As skin temperature rises, superficial blood vessels dilate, increasing the transfer of core body temperature to the surface. Increasing the temperature gradient between the skin and the environment increases heat loss from the body.** When exposed to elevated environmental temperatures, preterm babies generally cannot generate sweat to eliminate heat by evaporation. Maturing babies develop this eccrine gland function first on the forehead, followed by the chest, upper arms, and more caudal areas.

Thermoregulation requires energy (caloric) expenditure:

- Basal metabolic rate: 50 kcal/kg/day
- Thermoregulation: 10 kcal/kg/day
- Thermic effects of feeding: 8 kcal/kg/day[6] (see Chapter 17)

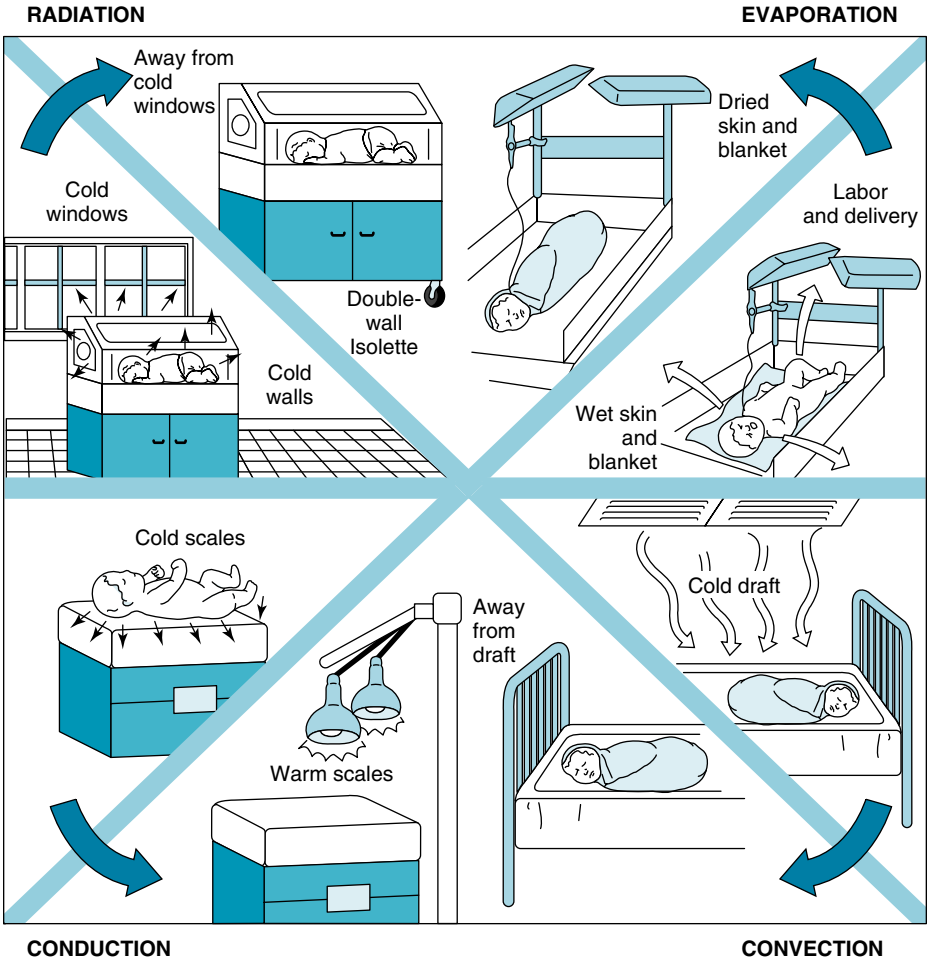

FIGURE 6.3 Radiation, or heat loss in the form of electromagnetic photons, occurs from warm skin surfaces to a cooler object not in contact with the newborn (e.g., inside the incubator wall, nursery wall, window). Radiant heat loss is independent of ambient air temperature and is the main source of heat loss because of the infant's large exposed body surface area. Conduction is the loss of heat to a cooler object in direct contact with the newborn (e.g., cold scale, unwarmed bed, stethoscope, examiner's hand). Convection is the loss of heat to moving air at the skin surface and depends on the air's velocity and temperature. Evaporation of water from the skin and mucous membranes also causes heat loss, especially in the delivery room. The thinner stratum corneum layer of skin of very-low-birth-weight infants makes evaporative heat and water loss and fluid management ongoing problems. (Courtesy Lynn Jones, RN.)

Methods of Measuring Temperature

A neonate's temperature can be determined by various methods.[123] Deep body (core) temperature may be measured in the rectum or esophagus and on the tympanic membrane. Rectal thermistors are thin, flexible probes that must be inserted at least 5 cm to obtain an accurate reading. Insertion of a rigid rectal thermometer to this depth increases the risk for perforation, because the sigmoid colon makes a right-angle turn approximately 3 cm from the anal opening. Esophageal and tympanic readings are difficult to obtain and usually impractical.

Continuous monitoring of abdominal skin temperature with the newborn lying supine is a noninvasive method that has good correlation with rectal temperatures in preterm[35] and very-low-birth-weight (VLBW) preterm infants.[131] *Only* abdominal skin

BOX 6.1 ALTERATIONS IN OXYGEN CONSUMPTION WITH CHANGES IN ABDOMINAL SKIN TEMPERATURE: RESEARCH BASIS[118,119]

- Abdominal skin temperature of 36.5°C (97.7°F) results in minimal oxygen consumption.
- Abdominal skin temperature of 35.9°C (96.6°F) results in an increase in oxygen consumption of 10%.
- Abdominal skin temperature of 37.2°C (98.9°F) results in an increase in oxygen consumption of 6%.

temperature has been shown to be an effective monitor of neutral thermal environment. Box 6.1 clearly illustrates that even a slight change (less than 1°C) in abdominal skin temperatures affects oxygen consumption and basal metabolic rates. Therefore the **range of thermal neutrality illustrated in** Fig. 6.1 **is a very narrow range—less than 1°C on either side of abdominal skin temperature of 36.5°C (97.7°F).**

Because of the risks involved, rectal temperatures should not be taken on a routine basis in neonates. Axillary temperatures require disturbing and handling, minimal exposure due to undressing (which may lower temperature), and result in crying and restlessness in some neonates.[38,74] Axillary temperatures are measured by using glass, electronic, or disposable thermometers. The tip of the thermometer should be held firmly in the midaxillary area for at least 3 minutes in preterm infants and 5 minutes in term infants. **When taken properly, axillary temperatures provide readings as accurate as rectal and core temperature methods.[45] Approximating rectal temperatures from axillary temperatures is clinically possible by adding 0.3°C (difference in axillary and rectal values in preterm neonates) to 0.4°C (difference in axillary and rectal values in term neonates) to the axillary value.[68] In term infants, axillary temperatures should be maintained at 36.5°C to 37.5°C (97.7°F to 99.5°F). For preterm infants, the normal axillary temperature ranges between 36.3°C and 36.9°C (97.3°F and 98.4°F).[110]**

A randomized study comparing temperature values from three skin probe positions with digital axillary temperature values was conducted in healthy preterm infants.[115] **There was no statistically significant difference in any of the three probe site temperature values or between the probe site values and the digital axillary temperatures.[115]** The results of this study are similar to a previous study conducted in healthy full-term infants.[126] Because of the small size of the sample and methodology followed, the results of these studies *cannot* be generalized to all preterm infants, especially those with extremely low birth weight (ELBW). **Both researchers recommend consistency in temperature measurement and evaluation of trends and patterns over time, along with evaluation of the entire clinical picture of each individual infant.[115,126]**

In search of a quicker, noninvasive, less disruptive mode of temperature taking, the accuracy of noninvasive infrared thermometers in the neonatal population has been evaluated in studies in premature[38,74] and in healthy late-preterm and term infants.[50] **These studies found the readings between the infrared midforehead and temporal artery and axillary readings to be very comparable.** A more recent study of temporal artery measurement found it no more accurate than axillary or rectal temperatures in 49 neonates.[125] For neonates in incubators the temporal artery measurement was less accurate than for neonates in cribs. As postmenstrual age (PMA) increased, the accuracy of temporal artery measurements of neonatal temperature also increased.[125] More research with various populations of neonates, in various environments (cribs, incubators, radiant warmers), and using larger numbers of study subjects is necessary.[123] During the first week of life, infrared thermal imaging has been studied to evaluate the full body temperature and perfusion differentials of extremely preterm infants in heated incubators.[67]

In critically ill infants, the skin temperature is usually routinely monitored in addition to axillary temperature readings. A skin probe is secured to the right upper quadrant of the abdomen. The temperature probe should not be placed under the axilla or any other position except as recommended by the manufacturer. **Because an infant responds to cold stress by vasoconstriction, a drop in skin temperature may be the first sign of hypothermia.** The core temperature may not fall until the infant can no longer compensate. The axillary temperature may remain normal (or even be elevated) because of proximity to brown fat stores.

ETIOLOGY OF HEAT IMBALANCES

The ambient temperature range in which a healthy full-term infant maintains a stable core temperature is narrower than the temperature range in which an adult maintains a normal temperature. When measures are taken to provide a neutral thermal

environment for the neonate, excessive heat losses or gains are avoided and heat balance is maintained. Recognition of infants at risk for heat imbalance is essential in the prevention of thermal stress.

Premature infants have a limited ability to control body temperature and are extremely susceptible to hypothermia. Factors that contribute to temperature instability include very thin skin, large surface area relative to body mass, limited substrate for heat production, decreased subcutaneous tissue, and an immature nervous system. These infants often have multiple health problems that necessitate frequent interventions by health care providers with consequent disruption of the infant's neutral thermal environment.

A premature infant's very thin skin and larger surface area to body mass ratio allow for increased evaporative heat loss. Term infants can reduce surface area by flexing their extremities onto their trunk, a skill that increases with gestational age. Unable to maintain flexion, a preterm infant lies primarily with extremities extended. **Care providers may reduce the surface area by positioning infants in flexion and supporting them with blankets and rolls.** The shortened gestation limits lipid supplies, brown fat, and the accumulation of subcutaneous tissue. The immature nervous system delays or mutes the infant's response to thermal stress.

The premature infant is likely to experience other complications (e.g., respiratory distress, sepsis, intraventricular hemorrhage, hypoglycemia) that may increase basal metabolic rate and oxygen consumption, thus interfering with the ability to maintain thermal stability. Numerous procedures and interventions (e.g., medication administration, placement of intravascular catheters, obtaining vital signs) may impede efforts to maintain a neutral thermal environment. **Care providers should routinely check the infant's temperature before initiating treatments. If the temperature is low, treatment should be delayed until a more normal temperature is obtained. If interventions are prolonged, temperature should be monitored frequently, an external heat source provided, and the intervention stopped if hypothermia occurs.**

***Late-preterm infants* are predisposed to morbidities because of their developmental immaturity (see Chapter 5).** Less adipose tissue for insulation, less brown fat for chemical thermogenesis, more heat loss, and a larger ratio of surface area to weight contribute to problems with heat balance in these infants. Morbidity associated with heat balance in the late-preterm infant is 10% compared with 0% for term infants.[41]

Low-Birth-Weight Newborns

LBW (<2500 g) infants can be divided into two groups: the VLBW infant (<1500 g) and the ELBW infant (<1000 g). Preterm infants in each of these groups have specific needs for thermoregulation. Heated incubators, radiant warmers, and skin-to-skin care are all methods for maintaining the temperature and promoting weight gain of the VLBW infant. With caregiving, VLBW infants in servocontrolled incubators decrease their abdominal skin temperature with incubator opening in proportion to the type and length of the procedure being done.[32] **Infants weighing between 1500 and 1600 g may be weaned to an open crib if all criteria are met.**[6,7,84] (see Fig. 6.5 for weaning criteria).

During the first 12 hours of life, ELBW preterms become hypothermic with procedures such as intubations, chest x-ray examinations, intravenous (IV) line placement and manipulation, suctioning, repositioning, and vital signs. Like the late-preterm and the LBW infant, ELBW infants have even less brown and subcutaneous fat for maintaining body temperature. Their thin skin also contributes to increased insensible water loss (IWL).

***SGA infants,* like preterm infants, have a large surface area relative to body mass and decreased subcutaneous tissue, brown fat, and glycogen stores, all of which contribute to heat imbalance.** Decreased placental blood flow frequently contributes to the small size. The relatively large surface area of an SGA infant increases evaporative and radiant heat loss, whereas limited brown fat stores and subcutaneous tissue contribute to a decreased ability to produce and conserve body heat. Some flexion of the extremities may be present because flexion depends on gestational age and not weight. SGA infants have a higher metabolic rate compared with infants at similar weights who are appropriate for gestational age (AGA). This is believed to be caused by the larger brain size relative to body weight. **Hypoxia in utero may depress the infant's central nervous system (CNS) and alter the ability to regulate temperature.** Increased energy requirements coupled with limited glycogen stores may result in hypoglycemia and limited ability to produce heat. SGA infants may require numerous interventions that disrupt the neutral thermal environment. **Care providers should ensure that the infant has a normal and stable temperature before initiation of treatments. If treatments are prolonged, temperature should be monitored frequently, an external**

heat source provided, and treatments stopped if hypothermia occurs.

Infants with neurologic damage or depression may experience difficulty maintaining a stable temperature. Hypoxia before, during, or after delivery, neurologic defects, and exposure to drugs such as analgesics and anesthetics may depress the infant's neurologic response to thermal stress. Hypoxia decreases the effect of norepinephrine on nonshivering thermogenesis, the main route of thermal regulation in the newborn infant. Hypoxia may also reduce the oxidative capacity of the mitochondria in brown fat and skeletal muscles, which are involved in thermogenesis. Infants who have experienced hypoxia in utero may have increased norepinephrine concentrations, which result in peripheral vasoconstriction. This may cause a delayed metabolic response to cold stress and delayed vasodilation in response to heat stress.

Neurologic defects that affect the hypothalamus also may interfere with heat balance. The hypothalamus coordinates temperature input from various sensors. Drugs such as analgesics and anesthetics cause CNS depression and reduce the infant's ability to respond to thermal stress. Neuromuscular blocking agents inhibit the infant's ability to maintain a flexed position, increasing exposed body surface and heat loss. **Care providers must be alert to the effect of drugs on the CNS and the infant's ability to regulate temperature.**

Infants with sepsis may have hypothermia or hyperthermia. In a newborn, an elevated temperature may begin as a response to cold stress, with peripheral vasoconstriction and thermogenesis. Heat production continues as the infant attempts to achieve a higher core body temperature. Exogenous and endogenous pyrogens may enhance thermogenesis.

Initially, an infant with sepsis may feel cool to the touch and may have a low body temperature. As fever progresses, temperature may rise and the infant feels warm to the touch. **Infants nursed in servocontrolled incubators may not have an elevated temperature. The lower heater output in response to increasing skin temperature (by manual or servocontrol adjustment) may mask a fever by keeping the baby's temperature within normal limits. The care provider should be alert to a sudden decreased need for incubator heat support in a previously stable infant.**

Hyperthermia may be iatrogenic, caused by inappropriate control of the neonate's environmental temperature. The most common cause is the inappropriate use of external heat sources. Dehydration may also contribute to hyperthermia. **Infants nursed with the use of external heat sources should have their temperatures monitored frequently. Phototherapy, sunlight, and the use of excessive clothing and blankets contribute to overheating.** Dehydration may be avoided by early recognition of infants at risk for increased fluid loss. Increased IWL occurs in preterm infants because of increased skin permeability and the use of phototherapy and radiant warmers. Vomiting, diarrhea, gastric suction, and ostomy drainage also increase fluid loss. These infants should receive additional fluids to replace the increased losses (see Chapter 14).

PREVENTION OF HEAT/COLD STRESS

Management of the thermal environment is paramount for newborn well-being. Heat balance is determined by the amount of heat lost to the baby's environment offset by the amount of heat generated by the body plus the amount of heat supplied from outside sources. Because a smaller, more immature, and sicker baby is less able to regulate body temperature, it is crucial that care providers understand the physical and physiologic principles of heat balance and be able to maintain a neutral thermal environment. **Two broad categories of interventions foster thermal neutrality[1]: blocking avenues of heat loss, and providing external heat and environmental support to maintain temperature within the normal range of 36.5°C to 37.5°C (97.7°F to 99.5°F).** The theoretical neutral thermal environment necessary for neonates of 1 and 2 kg at a given age is graphed in Fig. 6.2. **Newborns of less than 800 g are not adequately addressed in currently available tables but should have a starting environmental temperature setting of 36.5°C (97.7°F).**

Delivery/Birthing Room

Attention to the details of these interventions begins in the delivery/birthing room, in which the first step is to adjust the ambient delivery room temperature higher than ordinary operating rooms or patient rooms. **The air temperature in newborn care areas should be kept at 23.8°C to 26.1°C (75°F to 79°F), and humidity should be kept at 30% to 60%.[110]** Warming the room and placing the resuscitation table away from doors or drafts minimizes convective heat

loss. **Raising the delivery room temperature to 24°C to 26°C, as recommended by the World Health Organization (WHO), decreases cold stress in preterm infants less than or equal to 32 weeks of gestation.**[60] One study that increased the ambient temperature of the operating room from 20°C to 23°C reduced the rate of neonatal hypothermia on admission from 50% to 35%.[39] A retrospective cohort study found that raising the delivery room's ambient temperature from 28°C to 34°C resulted in fewer VLBW premature infants with hypothermia (<36.5°C) on admission to the NICU, and an increase in hyperthermia (>37.5°C).[61] Box 6.2 lists important components of the "warm chain" advocated by the WHO.

The newborn's skin temperature may drop by as much as 0.3°C/min, with core temperature dropping more slowly after delivery. At birth, most heat loss results from evaporation of amniotic fluid from the baby's skin surface. Drying the infant with prewarmed towels and immediately replacing used ones with dry, warm towels minimize evaporative heat loss. Dry towels conduct heat poorly when contacting the neonate's skin. However, cold examiner hands, stethoscopes, scales, and bare mattresses are good heat conductors and can add significant cold stress if not warmed before coming in contact with the newborn. Early skin-to-skin care for the first 24 hours of life decreases hypothermia for the first 48 hours of life in late preterm and term newborns.[106]

Because hypothermia on admission to the NICU is associated with higher morbidity and mortality,[30,83] prevention of hypothermia is one of four evidence-based interventions (delivery in an appropriate level of care; antenatal asteroids; surfactant within 2 hours of birth, or early nasal continuous positive airway pressure) **that improve the outcomes of very preterm infants.**[138] Recent rates of hypothermia on admission to the NICU in VLBW newborns were 12.9% to 53.4% in a large cohort in 11 European countries[133]; 36% in a Canadian study[83]; 51% in a Brazilian study[30]; and 79% in a single-center US study.[107] Another study found that the incidence of hypothermia in preterm infants between 27 to 30 weeks' gestational age was 93% in the first 3 hours after admission.[70] A cohort study in 11 European countries found that 88.2% of very preterm infants were born in units with one or more hypothermia-prevention strategy, but 50.9% of these infants were hypothermic on admission to the NICU.[134] Admission hypothermia rates were 73.2% in very preterm infants born in units without systematic hypothermia-prevention strategies. The most recent study from 18 centers in the NICHD Neonatal Research Network found that low and high admission temperatures were more common in the extremely preterm than in the moderately preterm infants[69] (see Box 6.3). The probability of being

BOX 6.2 THE WARM CHAIN[135]

1. Maintain thermal care in a draft-free delivery room (ambient temperature in delivery room at least 25°C to 28°C; prewarm all linens and surfaces that will be in contact with the infant's skin). Turn radiant warmer on 20 to 30 minutes before birth, on manual mode with 100% heater output.
2. Warm resuscitation—more preterm infants resuscitated with heated, humidified gas were normothermic on admission to the NICU than those who received cold, dry gas[94]
3. Immediate drying after birth from head-to-toe, covered with dry towel/blanket and hat placed on head.
4. Skin-to-skin contact with the mother after delivery, during transfer and in the postpartum area to prevent hypothermia and to treat cold stress.
5. Breastfeeding as soon as possible after birth, preferably within the first hour. Provides caloric intake for heat generation.
6. Postponing bathing and weighing. In a full-term newborn, bathing should be postponed until the next day. Weighing should be postponed till baby is adequately covered and making a zero correction for clothing.
7. Clothing/Bedding. Newborns should be covered in one to two layers of clothes, a hat, and hands covered. Swaddling, a custom of wrapping bands should be avoided.
8. Rooming-in between mother and baby should be encouraged and facilitated so that frequent skin-to-skin contact and breastfeeding occur.
9. Warm transportation within the institution, between institutions, or discharge home must be provided to protect thermal stability. Stable babies (including preterm and LBW infants) should be transported well-wrapped and skin-to-skin with their mothers. VLBW and/or unstable admitted babies should be transported in a prewarmed incubator. Temperature should be monitored before and after transport. In utero transport to a regional center is the preferred mode of transport.
10. Education. All neonatal care providers must be adequately educated and informed about the principles of the warm chain.

Modified from The World Health Organization Protocol. *Thermal Management of the Newborn;* 2014. https://www.who.int/maternal_child_adolescent/documents/ws42097th/en/. Accessed July 22, 2019.

BOX 6.3 ADMISSION TEMPERATURES OF EXTREMELY AND MODERATELY PRETERM NEWBORNS

Digitalizing Schedule	Extremely preterm newborns (< 29 weeks' gestation)		Moderately preterm newborns (29–33 weeks' gestation)
	(2012–2013)	(2002–2003)	(2012–2013)
< 36.5°C	40.9 %	32%	38.6%
36.5°C–37.5°C	56%	6.2%	57.3%
> 37.5°C	52.9%	2%	4.2%

Data from: Laptook AR, Bell EF, Shankaran S, et al and the Generic and Moderate Preterm Subcommittee of the NICHD Neonatal Research Network: Admission temperature and associated mortality and morbidity among moderately and extremely preterm infants. *J Pediatr.* 2018;192:53.

hypothermic on admission to the NICU increased with decreasing gestational age[69,134] and in-hospital mortality is inversely related to admission temperature.[69] Higher admission temperatures in preterm infants after delayed cord clamping (see Chapter 4) have been demonstrated in two studies.[7,43]

The benefit of using *polyethylene plastic bags* and wraps for babies born at 26 to 30 weeks of gestation to preserve body heat and prevent hypothermia at admission has been shown in numerous studies.* This type of warming is ideal for a preterm infant (at birth and the immediate hours following) awaiting transportation to a tertiary care facility or indeed a baby born in a tertiary care facility. **The baby is placed on a warm towel (but not dried) and placed under a radiant warming heating device. The baby (excluding his or her head) is placed fully in the polyethylene bag or is wrapped in the polyethylene sheet. The baby should remain under the radiant warmer, as the heat, acting through the covering on the baby's moist skin, creates a warm thermal environment. Cutting an appropriate-size hole through the covering over the area of insertion can facilitate the introduction of any catheter or cannula.** Polyethylene bags for warmth have been adopted by the Neonatal Resuscitation Program (NRP) (see Chapter 4).

*References 20, 22, 34, 47, 57, 64, 73, 76, 78, 89, 112, 113, 120, 124

NRP guidelines emphasize how hypothermia may reduce the extent of brain injury after hypoxia and that hyperthermia may worsen the extent of brain injury during reperfusion after hypoxic events. **The recommended goal is to maintain normothermia for the infant and avoid iatrogenic hyperthermia in resuscitated newborns, especially those late preterm and term neonates who meet the criteria for neonatal cooling for hypoxic-ischemic encephalopathy (HIE)** (see Chapter 26, Box 26.7).

Resuscitation should take place on a preheated radiant warmer so that the adverse consequences of hypothermia are avoided. Use of heated, humidified oxygen (rather than cold, dry oxygen) given from birth through NICU admission results in normothermia of preterm newborns on admission to the NICU.[90,94] In an attempt to maintain heat balance, the neonate increases cellular metabolism and oxygen consumption, which increases the risk for hypoxia, cardiorespiratory problems, and acidosis. **Hypoglycemia is also a risk factor, because the infant must consume more glucose for heat production.** Other complications include clotting disorders, neurologic problems, hyperbilirubinemia, and even death if the untreated hypothermia progresses.

Because a significant amount of heat is lost through the surface area of the head, with its abundant blood supply and the brain's high heat production, **covering the infant's head with some insulating material conserves heat** during transfer to the nursery or NICU and afterward. Stockinet material is relatively ineffective for this purpose and provides poor insulation. The best material is thick, maintains its shape with use, and has a high percentage of air volume trapped in the fibers. Knitted wool caps, plastic caps, or Thinsulate material may provide the best results.[88] Combining polyethylene body wraps and polyethylene caps results in better temperatures in preterm infants than use of polyethylene wraps and a cotton cap.[116]

Occlusive plastic wrap alone is not totally effective in preventing hypothermia after birth in the very preterm infant. Several recent studies using plastic wrap and self-heating gel mattresses together to prevent heat loss in preterm infants less than 31 weeks of gestation have been conducted.[58,89,112,120,122] These studies have found **significant reduction in the incidence of hypothermia with the use of gel mattresses** compared with the incidence of

hypothermia on admission in very preterm infants who were born before the use of gel mattresses (3.3% vs. 22.6%).[58] **Several of these studies have also noticed a higher incidence of hyperthermia on admission.[58,89,112] Three nursing interventions (occlusive wrap, occlusive wrap and chemical mattress, and increasing delivery room temperature)** were studied to determine if they normalized admission temperatures in ELBW (<1000 g) and LBW (<1500 g) preterms.[12,76] **Each intervention resulted in a normal admission temperature without the risk of hyperthermia.[12,76]** Several other studies using occlusive wrap have elevated the initial temperature of VLBW infants without producing hyperthermia.[34,112,113] Quality improvement programs using bundled interventions have been successful in reducing the incidence of hypothermia in VLBW preterm infants,[19,29,52,108,111,136] as well as late preterm and LBW infants in mother-baby units.[6] Monitoring admission temperatures is recommended as a resuscitation quality indicator by the Australian and New Zealand Committee on Resuscitation Guidelines.[79]

There are a variety of ways to maintain thermal neutrality. Accessibility, IWL, servocontrol versus manual control of temperature, and safety are major considerations when determining the method to use for an individual neonate.

Incubators

Incubators provide a controlled, enclosed environment that is heated convectively with warm air. **The temperature in an incubator may be *servocontrolled* to maintain a desired skin temperature or air temperature.** As the temperature varies from the desired "set point," proportional control units gradually increase or decrease heat output to maintain a constant temperature (without the wider temperature fluctuations seen with simple on-off controllers). **Incubators controlled by abdominal skin servocontrol have been found to reduce neonatal death rates in LBW, and especially in VLBW, neonates.[121] In setting the servocontrolled incubator to the desired skin temperature, the sensor should be attached to the right upper quadrant of the abdomen with insulated temperature patches. The sensor should not be placed over areas of brown fat deposits, because the higher-than-expected temperature information to the controlling unit will result in a lower-than-desired heat output.[3]**

Inadvertent cooling may take place if the sensor is covered with clothes or a blanket or if the baby lies on it. Lying prone on the abdominal skin probe results in warmer temperatures than those recorded from probes not entrapped between the skin and mattress, resulting in a cooler incubator than intended.[14] If the sensor becomes disconnected from the skin, unwanted heating may occur because an erroneously low temperature reading causes an unwanted increase in heat output.[101] One must also consider that when an insulated patch is used to cover the thermistor, skin temperature is sensed as being higher than if tape covers the thermistor, resulting in decreased heat output by the warming device. **The desired skin temperature used for skin servocontrol is generally 36.0°C to 36.5°C (96.8°F to 97.7°F).[85]** Modern incubators also can be servocontrolled to a desired air temperature. This mode has been shown to provide a more stable thermal environment and less temperature variation compared with skin servocontrol.

Air servocontrol maintains a constant ambient air temperature when other factors such as phototherapy, external radiant heat, unstable room temperature, or direct sunlight are not confounding variables. **Infants who were managed with skin servocontrol had more variable but higher air temperatures and spent more time in a neutral thermal environment. Babies managed with air servocontrol had less variability in air temperatures but more variability in infant body temperature. A review of published trials concluded that VLBW babies whose skin servocontrol is set at 36°C had a lower mortality rate than those managed with air servocontrol at 31.8°C.[121]** A newer study of air temperature control versus skin servocontrol in preterm neonates less than 32 weeks gestational age found that a body temperature of 37°C was associated with lower energy costs and greater weight gain in the first 11 days of life.[31] The question of air versus skin servocontrol or manual control is still debatable for any given situation, and probably neither is the perfect solution for all babies. Fig. 6.4 depicts a research-based algorithm for weaning from servocontrol to air control in an incubator.

Radiant heat loss to cooler incubator walls, especially in single-walled incubators, is a significant source of heat loss. **The use of *double-walled incubators*** (with the inner wall warmed to the ambient air temperature inside the incubator) **results in less radiant heat loss from the baby.** With a skin-set servocontrol temperature, the decreased radiant heat loss (because of warmer incubator walls) is offset by

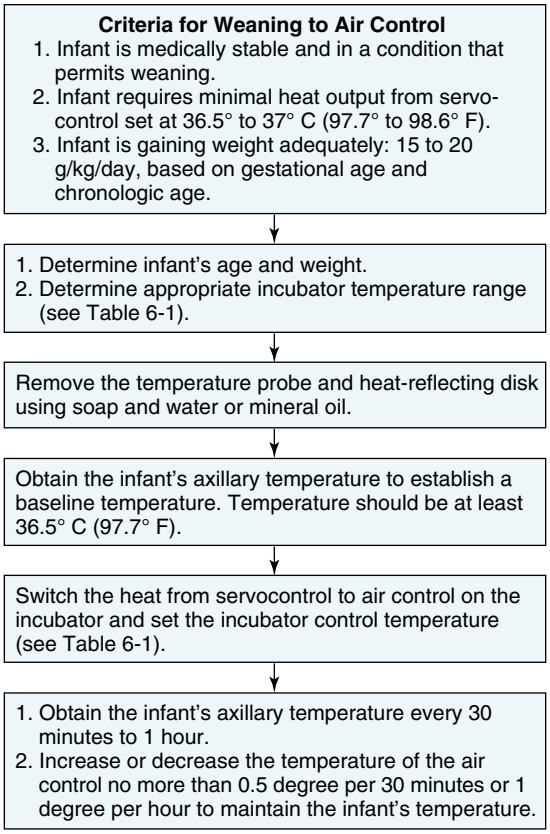

FIGURE 6.4 Research-based algorithm for weaning from servocontrol to air control mode in an incubator. (Courtesy Vivian Brown, RN.)

increased convective heat loss (because the ambient air temperature necessary for the desired skin temperature is lower). Consequently, there is no net change in the mean environmental temperature. **Double-walled incubators provide less temperature fluctuation when doors are open, thus providing a more stable caregiving environment.** Evaporative heat loss is not appreciably different with single- and double-walled incubators. One may increase the humidity in incubators to decrease the infant's metabolic rate only if a neutral thermal environment cannot be achieved by increasing the ambient temperature.

In one study, addition of a double-walled roof to a single-walled incubator resulted in less radiant heat loss but more convective and evaporative skin heat loss that was off-set by increasing the incubator's ambient temperature by 0.15 to 0.20°C.[33]

The tiniest neonate has a large evaporative heat loss, and maximum air temperature is limited by the incubator controls, thus making it difficult to reach an air temperature high enough for thermal support. **In such cases, hypothermia can be avoided by increasing the ambient humidity within the incubator by using the water reservoir or supplying warmed humidified air into the incubator with respiratory humidifiers. Humidification has been shown to decrease fluid requirements and decrease the incidence of electrolyte imbalances in babies weighing less than 1000 g.**[46] Careful attention should be given to preventing bacterial growth in the humidification system (see Chapter 23). Incubator temperatures may also be manually controlled by estimating the appropriate temperature for the baby's age and weight and setting the incubator to that temperature (see Table 6.1).

Regardless of whether one is using skin or air servocontrol or manual temperature adjustments, the baby's temperature and the air temperature must be monitored and recorded regularly. The incubator should be kept away from air conditioning ducts, direct sunlight, and cool windows that may cool or warm the incubator. **Room temperature should be kept at 23.8°C to 26.1°C (75°F to 79°F), and humidity should be maintained at 30% to 60%.**[4] Seasonal mapping of one NICU showed seasonal variation in humidity level and evaporative temperature, both influences on thermal environment.[127] The researchers recommend periodic assessment of air, evaporative, and radiant temperatures, as well as humidity, in multiroom NICUs.[127] **Alarms for both high and low temperature levels always should be turned on.**

The principal disadvantage of maintaining sick newborns in incubators is the limited access to them when extensive procedures are necessary. Incubators also may be perceived by mothers as a barrier between them and their infants and prolong feelings of fear and insecurity, compared with heating methods that provide easier access to the baby. **Holding the baby in skin-to-skin contact (kangaroo care) helps promote bonding and relieves some of maternal and paternal fears** (see later). Stable preterm infants dressed in a diaper, shirt, and cap and wrapped in two blankets can also maintain a normal temperature when held close to their parent's body. **Keeping the skin probe attached to the infant and plugged into the incubator allows frequent monitoring of the infant's temperature.** We also now have an increasing awareness of and concern about the high noise levels within incubators. Such noise poses a potential deleterious effect on the

TABLE 6.1 NEUTRAL THERMAL ENVIRONMENTAL TEMPERATURES

AGE AND WEIGHT	STARTING TEMPERATURE (°C)	RANGE OF TEMPERATURE (°C)
0–6 h		
Under 1200 g	35.0	34.0–35.4
1200–1500 g	34.1	33.9–34.4
1501–2500 g	33.4	32.8–33.8
Over 2500 g (and >36 wk)	33.9	32.0–33.8
>6–12 h		
Under 1200 g	35.0	34.0–35.4
1200–1500 g	34.0	33.5–34.4
1501–2500 g	33.1	32.2–33.8
Over 2500 g (and >36 wk)	32.8	31.4–33.8
>12–24 h		
Under 1200 g	34.0	34.0–35.4
1200–1500 g	33.8	33.3–34.3
1501–2500 g	32.8	31.8–33.8
Over 2500 g (and >36 wk)	32.4	31.0–33.7
>24–36 h		
Under 1200 g	34.0	34.0–35.0
1200–1500 g	33.6	33.1–34.2
1501–2500 g	32.6	31.6–33.6
Over 2500 g (and >36 wk)	32.1	30.7–33.5
>36–48 h		
Under 1200 g	34.0	34.0–35.0
1200–1500 g	33.5	33.0–34.1
1501–2500 g	32.5	31.4–33.5
Over 2500 g (and >36 wk)	31.9	30.5–33.3
>48–72 h		
Under 1200 g	34.0	34.0–35.0
1200–1500 g	33.5	33.0–34.0
1501–2500 g	32.3	31.2–33.4
Over 2500 g (and >36 wk)	31.7	30.1–33.2
>72–96 h		
Under 1200 g	34.0	34.0–35.0
1200–1500 g	33.5	33.0–34.0
1501–2500 g	32.2	31.1–33.2
Over 2500 g (and >36 wk)	31.3	29.8–32.8
>4–12 days		
Under 1500 g	33.5	33.0–34.0
1501–2500 g	32.1	31.0–33.2
Over 2500 g (and >36 wk)	31.0	29.5–32.6
4–5 days	30.9	29.4–32.3
5–6 days	30.6	29.0–32.2
6–8 days	30.3	29.0–31.8
8–10 days	30.1	29.0–31.4
10–12 days		

Continued

TABLE 6.1 NEUTRAL THERMAL ENVIRONMENTAL TEMPERATURES—CONT'D

AGE AND WEIGHT	STARTING TEMPERATURE (°C)	RANGE OF TEMPERATURE (°C)
>12–14 days		
Under 1500 g	33.5	32.6–34.0
1501–2500 g	32.1	31.0–33.2
>2–3 wk		
Under 1500 g	33.1	32.2–34.0
1501–2500 g	31.7	30.5–33.0
>3–4 wk		
Under 1500 g	32.6	31.6–33.6
1501–2500 g	31.4	30.0–32.7
>4–5 wk		
Under 1500 g	32.0	31.2–33.0
1501–2500 g	30.9	29.5–32.2
>5–6 wk		
Under 1500 g	31.4	30.6–32.3
1501–2500 g	30.4	29.0–31.8

Note: For their table, Scopes and Ahmed had the walls of the incubator 1° to 2°C warmer than the ambient air temperature. Generally, the smaller infants in each weight group require a temperature in the higher portion of the temperature range. Within each time range, the younger the infant, the higher the temperature required.

From American Academy of Pediatrics and American College of Obstetricians and Gynecologists: Guidelines for perinatal care, 2nd ed, Evanston, IL: American Academy of Pediatrics and American College of Obstetricians and Gynecologists; 1988. Data from Scopes JW, Ahmed I. Minimal rates of oxygen consumption in sick and premature infants. Arch Dis Child 1966;41:407; Scopes JW, Ahmed I. Range of critical temperatures in sick and premature newborn babies. Arch Dis Child 1966;41:417.

hearing development of preterm infants (see Chapter 13). Improved alarm technology minimizes the risk for inappropriate heating, but malfunctions still occur occasionally. When experienced nurses provide care, infants can be appropriately managed in incubators using any of the three modes of temperature control. Box 6.4 outlines "dos and don'ts" when using an incubator to provide heat and humidity.

Weaning an infant from an incubator to an open crib is an important step in preparing for discharge but may result in an increase in the resting metabolic rate for LBW infants.[36] **Indicators that an infant may be successfully weaned include weight of 1600 g or more,[8,103,104,137] 5 days of consistent weight gain, an absence of medical complications, and tolerance of enteral feeds. Earlier weaning at lower body weight does not affect weight gain or temperature stability and may result in earlier discharge.[8,103,137] Weaning may occur over several days and involves dressing the infant in a shirt, hat, and diaper and swaddling with a blanket.** The incubator temperature is manually lowered while monitoring the infant's temperature.

Abdominal skin temperature should be 36°C to 37°C (96.8°F to 98.6°F). Figs 6.5 and 6.6 are research-based algorithms for weaning infants to open cribs. After weaning has been successful, the crib should be placed in a draft-free environment. **If an infant cannot maintain his or her temperature in an open crib, he or she is returned to the incubator. An attempt at weaning should be considered again by 48 hours after the initial weaning if all criteria for weaning have been met.** The temperature in the neonatal unit should be evaluated, as well as the location of the crib in relation to air conditioner vents or drafts. There may also be other medical reasons (e.g., infection) that the infant cannot maintain his or her temperature in the open crib if all other conditions have been ruled out.[1]

Humidification and Topical Ointments

Many studies and clinical trials have demonstrated the clinical application of the uses of both humidity and topical ointment therapy (see Chapter 19) in preterm

BOX 6.4 USE OF AN INCUBATOR DOS AND DON'TS

Dos

1. Place temperature probes according to manufacturer recommendations.
2. Work through the portholes rather than opening the canopy to improve temperature control.[15]
3. Change the incubator once a month.
4. Use sterile water for humidification.
5. Keep the incubator clean and free of spills.
6. Adequately humidify the incubator according to birth weight and gestational age of the infant.
7. Keep walls locked in place to prevent falls and provide a safe environment for the infant.
8. Clean incubators after each use and between patients with recommended cleaner, by trained staff.
9. Use servocontrol when first placing neonates in an incubator.
10. Follow weaning guidelines when changing from servocontrol to air control, using the weight and age chart (see Table 6.1).
11. Change the temperature probe site as directed by the manufacturer and hospital procedure.
12. Frequently monitor and record the infant's temperature, and observe for changes in clinical condition.

Don'ts

1. *Don't* place the temperature probe in the infant's axilla.[3]
2. *Avoid* pinching lines/tubes when opening/closing portholes and sides.
3. *Avoid* placing noisy equipment inside or on top of the incubator.
4. *Avoid* tapping, hitting, or knocking the incubator when the infant is in the bed.
5. *Avoid* keeping portholes open except for care and handling.
6. *Avoid* epidermal stripping (see Chapter 19) when applying/changing temperature probe sites.
7. *Avoid* pulling out lines or extubating the infant when moving/taking him or her out of the incubator.
8. *Don't* wean the servocontrol temperature less than 36.5°C (97.7°F).
9. *Don't* wean the temperature on the air control any faster than 0.5° per 30 minutes or 1° per hour.
10. Avoid cleaning the incubator with alcohol or acetone.
11. Do not keep the incubator in an unlocked position when in use. Do not position the incubator next to an air conditioner duct or in direct sunlight from a window.

Courtesy Vivian Brown, RN.

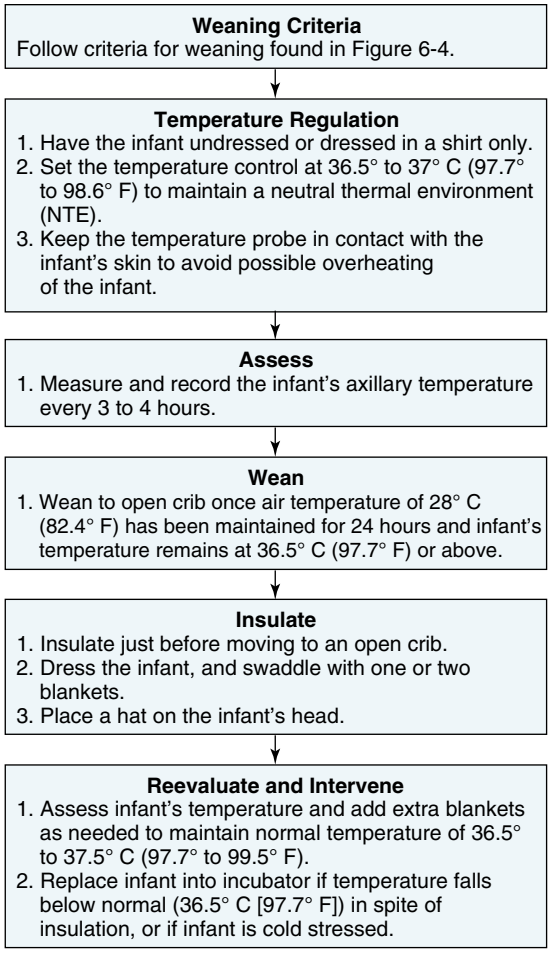

FIGURE 6.5 Research-based algorithm for servocontrolled weaning from an incubator to an open crib. (Courtesy Vivian Brown, RN.)

infants. **The optimal humidity level for the neonate is 50% RH.** This is achieved by a variety of methods such as relative humidity (RH) closed humidified incubators and humidity "tents." **In the first 2 weeks of life, extremely premature infants may require up to 85% RH.** Box 6.5 describes the advantages and disadvantages of using heated, humidified air for ELBW infants while in an incubator.

Radiant Warmers

Radiant warmers provide infrared energy to heat the baby's skin while he or she lies naked on an open bed. The radiant warmer must generate enough energy to offset the tremendous amount of radiant heat lost to

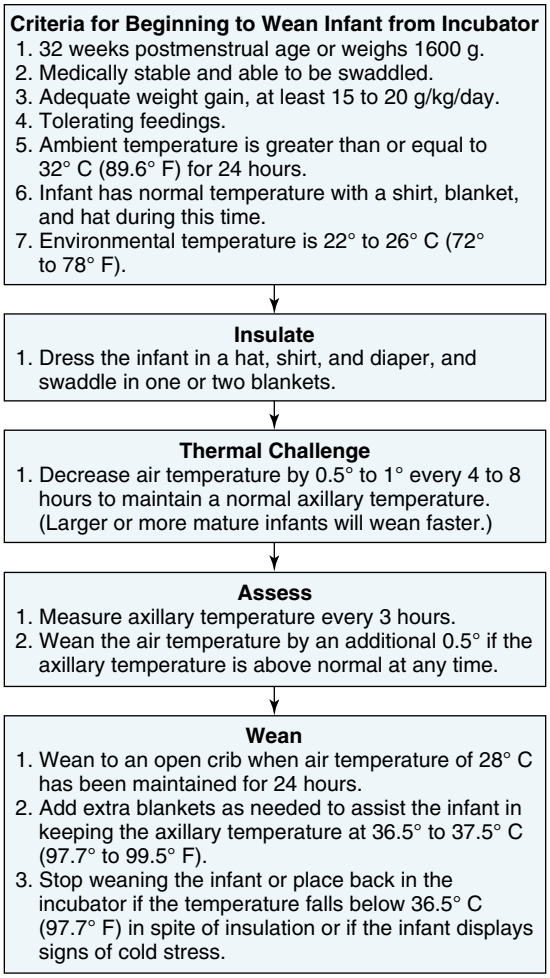

FIGURE 6.6 Research-based algorithm for air mode/manual weaning from an incubator. (Courtesy Vivian Brown, RN.)

the room by a naked baby lying in an open environment. Heat output can be servocontrolled or manually controlled. Because with manual control no feedback from the infant is used, this poses a greater risk for overheating or overcooling. **Therefore manual control should not be used routinely, except for short periods (e.g., while initiating resuscitation).** The servocontrol sensor measuring skin temperature must be protected from the infrared heat source, or the probe will sense a temperature higher than the skin temperature and decrease radiant heat output, leading to cold stress. Conversely, insulating the sensor with an aluminum reflective patch protects the underlying skin from the radiant heat and keeps the protected skin cooler than the surrounding skin. When the skin under the patch is warmed to the desired temperature, the rest of the skin may be overheated. Vasodilation then may increase convective heat loss, resulting in an effective, although precarious, heat balance. **Caregivers must use caution to ensure that the sensor does not become detached from the skin; otherwise the baby could be exposed to excess heat and become hyperthermic.**

Insensible water loss (IWL) for babies cared for under radiant warmers is increased by 40% to 50% compared with losses in incubators. Directly related to the amount of heat necessary from the warmer, this loss also is influenced by other factors (e.g., low RH and convective air currents) on an open bed. Even though transepidermal water loss is increased under radiant warmers, there is evidence that the hydration

BOX 6.5 RESEARCH-BASED ADVANTAGES AND DISADVANTAGES OF HEATED HUMIDITY IN THE INCUBATOR OF ELBW INFANTS

Advantages

1. Decreased transepidermal water loss (e.g., insensible water loss [IWL], evaporative water loss, and epidermal heat loss) from the skin of infants less than 31 weeks of gestation. IWL is inversely proportional to the gestational age of the infant.
2. Increased ability to maintain the infant's temperature.
3. Improved maintenance of fluid and electrolyte balance.
4. Improved energy balance—fewer calories expended in temperature maintenance.
5. Improved skin integrity.
6. Possible reduction in the incidence of (1) PDA, (2) IVH (grades III/IV), and (3) BPD because of improved fluid and electrolyte balance.

Disadvantages

1. Increased risk for infection associated with contamination of the humidifier reservoir with bacteria.
2. Moist environment impairs adhesion of equipment (e.g., electrodes, ETT, dressings).
3. Unstable temperatures when procedures are performed and the incubator door is open. In modern incubators, loss of humidity is not significant during clinical procedures that last less than 5 minutes. Based on the number of open portals and an open incubator door, these incubators are able to restore humidity within 1 to 15 minutes of a procedure lasting longer than 5 minutes.[86]
4. Delayed maturation of skin barrier.[2]

BPD, Bronchopulmonary dysplasia; *ELBW,* extremely low birth weight; *ETT,* endotracheal tube; *IVH,* intraventricular hemorrhage; *PDA,* patent ductus arteriosus.

of the stratum corneum is not affected; therefore the barrier function of the skin remains the same.[85] **With very premature infants, severe dehydration may occur if water intake is not increased to replace the inordinate IWL** (see Chapter 14). Plexiglas heat shields and polyethylene blankets (plastic wrap) have been used in an attempt to prevent large IWLs. Using plastic covers over preterm infants (28 to 30 weeks gestational age) in the first few days of life has been shown to result in higher mean body temperatures, even when the warmer was set on low temperature.[130] The microenvironment created by these blankets undergoes drastic change every time the blanket is removed for procedures or routine nursing care. Even without such blankets, the baby may experience wide swings in heat balance when the infrared heat is blocked from reaching him or her by hands, heads, or drapes during a procedure. These blankets should not be used while the infant is in an incubator, because the purpose is to have the humidity and heat reach the infant.

Both incubators and radiant warmers are effective in maintaining an appropriate thermal balance in sick and preterm infants. Evidence is insufficient to show a clear advantage of one method over the other with the caveat that IWL is significantly higher under radiant warmers.[44] The method chosen should be individualized to the infant and to the situation. Experience, skill, and nurse preference often influence the choice of heating methods. These factors also influence the extent to which incubators are perceived to interfere with the performance of care providers' tasks. Basic principles of care (e.g., keeping bed linens dry to prevent evaporative heat loss) apply to use of both heating methods. Box 6.6 lists advantages and disadvantages of open radiant warmers and incubators for temperature management in premature infants.[85]

Radiant warmers provide easy access for performing procedures—a definite advantage over incubators, in which procedures must be done through portholes. Performing invasive procedures on a radiant warmer protects premature infants from hypothermia better than performing invasive procedures in the incubator.[51] Advances in equipment technology now make it possible to convert a single unit from radiant mode to convection mode without moving the baby from one platform to another. This is an efficient way to provide the improved access needed when a baby's condition changes while maintaining appropriate warming without the potential risks of moving the baby.[37] These hybrid devices improve care of ELBW infants by enhancing growth velocity, improving electrolyte balance, decreasing fluid intake, and maintaining stable body temperature.[63] Fluid management is easier for infants in incubators because humidity is easily added to the enclosed environment, and there are fewer losses from radiation and convection. The large flux of heat exchange among the radiant heat source, the baby, and the environment

BOX 6.6 ADVANTAGES AND DISADVANTAGES OF OPEN RADIANT WARMER VS. INCUBATOR USE FOR PREMATURE INFANTS

Advantages: Open Radiant Warmer

1. Easy access to the infant and larger surface on which to work
2. Useful for initial admission procedures (e.g., intubation, line placement, x-ray examination)
3. Decreased risk for infection without the use of humidity
4. Decreased risk for unplanned extubation and lines being pulled out
5. Better access by parents and staff

Disadvantages: Open Radiant Warmer

1. Increased insensible water loss[44,51] (without humidification or plastic blanket)
2. Active induction of acute bouts of heat imbalance resulting in fluctuations in skin and rectal temperatures. Transient bouts of heat storage do not exacerbate physiologic strain (increased heart and respiratory rates and mean arterial pressure), but could occur in longer bouts of heat imbalance.[96]
3. Increased stimulation from external noise and light
4. Decreased growth and weight gain patterns
5. Decreased ability to wean the infant slowly from the heat source
6. Better access by parents and staff

Advantages: Incubator

1. Less insensible water loss with use of humidity
2. Acts as a barrier with more difficult access that decreases tactile contact; easier to use minimal stimulation
3. Increased weight gain
4. Heat provided by two methods: convection and conduction
5. Ability to wean temperature control from servocontrol to air control, and from air control to an open crib
6. Ability to cover the incubator to decrease exposure to light

Disadvantages: Incubator

1. Decreased access for treatments, line placements, intubations, and laboratory draws
2. Increased chance of infection with humidity
3. Increased risk for extubation or accidental clamping of lines

makes wide fluctuations in heat balance more likely when compared with the more easily controlled temperature within an incubator. Many variables influence oxygen consumption using these two heating methods. The metabolic rate and oxygen consumption of infants under radiant warmers are slightly higher than in incubators; however, the clinical significance of this finding is uncertain. Infection rates are comparable between the two methods.[92] **Regardless of the type of heat supplied, care must be taken to minimize thermal instability during nursing interventions. Radiant warmers may be able to rewarm a baby faster than an incubator with convective heating after a procedure.**[101] Organizing interventions (i.e., clustering care) so their frequency and duration limit as much as possible the exposure to a thermally unstable environment can minimize thermal instability. In the first 10 days of life, opening the incubator for nursing procedures negatively affects weight gain in healthy, moderately preterm (32 to 34 weeks of gestation) infants.[77] Box 6.7 outlines dos and don'ts when using a radiant warmer for providing heat.

Other Methods

In the tiniest preterm infants, a conductive heat source (e.g., a heating pad) may also be needed to raise and maintain body temperature. Heated water mattresses provide a neutral thermal environment for less critically ill babies lying in open cribs (making access easier than in closed incubators). This may also provide a feasible and effective means of rewarming hypothermic infants. Heated, water-filled mattresses are most useful in the newborn units of developing countries.

Electric warming mattresses filled with water provide additional moist heat when caring for the infant in surgery, to use for rewarming techniques, or when caring for the LBW or ELBW infant. In a randomized controlled trial, the use of a thermal blanket for VLBW premature infants (<1500 g) reduced the incidence of hypothermia, and hypotension without causing hyperthermia.[54] Manufacturer's recommendations should be followed, and the **temperature is usually set at 100°F (37.8°C). Heat is provided by conduction; therefore a linen layer should be placed between the mattress and the infant to avoid skin burns.** The temperature of these mattresses should be weaned before weaning any temperature of the open warmer or incubator.

BOX 6.7 USE OF OPEN RADIANT WARMER DOS AND DON'TS

Dos

1. Use the automatic mode (skin probe/servocontrol) for continuous thermal support.
2. Use the manual mode for short-term warming *only;* check the infant's condition and temperature at least every 15 minutes.
3. Place the sensor on the skin surface exposed to the warmer and never beneath the infant. (Follow manufacturer's recommendations.)
4. Check sensor attachments frequently. Poor skin contact causes poor temperature control.
5. Change temperature probe sites according to unit policy and manufacturer's recommendations.
6. Be familiar with the radiant warmer in use as the effectiveness varies among commercial devices.[129]
7. Adjust fluid replacement to compensate for increased insensible water loss.

Don'ts

1. *Don't* forget to switch from manual to servocontrol after weighing the infant. When removing the infant from the radiant warmer, keep the bed on servocontrol and silence the alarm until the infant is returned to the radiant warmer.
2. *Never* use a rectal temperature probe for warmer control. Before normal core temperature is reached, the infant's skin may be burned.
3. *Don't* place anything flammable on top of or under the radiant warmer.
4. *Never* just reset alarms; instead, determine the cause of any alarms.
5. *Never* use your hand to estimate the amount of heat reaching the infant. Set the temperature control point at 36.5°C.
6. *Avoid* use of thermal blankets (e.g., bubble wrap); may cause incorrect skin temperature sensing and overheating.

Some **portable, disposable, warming mattresses** containing a gel that is chemically activated by squeezing may be used for initial stabilization of the infant and for transport. **Because heat is provided by conduction, a linen layer is placed between the infant and the mattress surface. The usual temperature for these mattresses is 100°F.**

Heel warmers, which are pads that are chemically activated by squeezing, are used to warm the heels of infants before obtaining blood and are especially necessary when obtaining capillary blood gases. **The temperature should never exceed 104°F.**

Swaddling materials include various types of infant wrappings (e.g., blanket, clothing, foil, or bubble wrap). The use of swaddling materials makes

observation of the infant more difficult and blocks heat from overhead radiant warmers. **Before one wraps the infant in insulating materials, the infant must be warm, because these merely retain body warmth and do not generate heat.**

Oxygen and air delivered to the neonate should be warmed and humidified to minimize convective and evaporative heat loss (see Chapter 23). More premature infants (i.e., less than 28 weeks gestational age) who received heated, humidified gas for resuscitation were more normothermic on admission to the NICU than those who received cold, dry gas. In this study, only 2% of the preterm infants receiving heated, humidified gas were hypothermic compared to 12% who received cold, dry gas.[94]

Skin-to-skin (kangaroo) care provides a safe and effective alternative method of caring for premature infants. Both AGA and SGA infants experience a beneficial warming effect and a stable skin and core temperature when held skin-to-skin.[82] In LBW preterm infants, skin-to-skin care is also associated with less hypothermia.[27] **Mothers exhibit thermal synchrony with the infants so that their body temperature increases or decreases to maintain the infant's thermal neutrality.[12,81]** Regardless of the care provider (e.g., father, adoptive parent, grandparent) during skin-to-skin care, heat loss does not occur and temperature rises and can be maintained within acceptable parameters (see Chapter 5). In one study, each mother's skin temperature met the neutral thermal environmental zone of her particular infant. **Mothers also preferred this method for holding their infant, compared with the traditional method of wrapping the infant in a blanket and the infant being cradled in the parent's arms.** Heat loss may occur during the transfer process from bed to parent. Having a protocol in place that uses one or more staff to help with the transfer and covering the infant with a blanket will reduce the transfer time and subsequent heat loss[82] (see Chapter 13).

Skin-to-skin contact between mother and infant reduces conductive and radiant heat loss and is an excellent way to maintain a neutral thermal condition for the healthy newborn.[13,100] If the infant remains with the parents for an extended time, temperature should be monitored. In the case of a preterm infant in stable condition, the use of an additional heat source (e.g., a radiant warmer) enables parents to spend more time with their infant before transfer to the NICU. Thermal stability of 26 extremely preterm infants (22 to 26 weeks; 2 to 9 days of age) in early skin-to-skin care has been studied. **During skin-to-skin care, extremely preterm infants were able to both maintain and increase their body temperature after the drop that occurred during transfer from the incubator.[62]** Another study of skin-to-skin care of 22 extremely preterm infants (mean gestational age of 25⅐ weeks and mean weight of 702 g) found that these infants maintained adequate skin temperature and physical stability.[84]

Analyzing 70 skin-to-skin sessions in another study found lower variation in body temperature in 25- to 28-week gestational age preterms compared with the 29- to 32-week gestational age group at 33 to 36 weeks postmenstrual age (PMA). These very preterm infants exhibited an advanced maturation of thermoregulation compared with the higher gestational age group.[109]

Bathing removes blood and body fluids from the newborn's skin, prevents the transmission of infections, and promotes bonding when performed by parents. **Sponge bathing is traditionally done in the NICU and newborn nursery and can result in significant heat loss. Immersing the stable, swaddled infant in a tub of water reduces evaporative heat loss and helps maintain a normal temperature.*** Even late preterm infants, who are prone to hypothermia, have better thermal stability (i.e., higher temperatures and less temperature variability) when immersion bathing was compared with sponge baths.[80] Because preterm infants have limited ability to compensate for heat loss, they are more prone to the morbidities of cold stress (see Box 6.8) and the vicious cycle resulting from cooling (see Fig. 6.7) and should not be bathed (see Chapters 5 and 19).

Transport

The same principles of heat balance that apply to infants in NICUs apply to infants during transport. Infants should have a normal and stable temperature before transport. The infant should be transferred from nursery to transport incubator rapidly to prevent prolonged exposure to an uncontrolled thermal environment. Transport incubators that can provide thermal stability inside the transport vehicle must be used. Oxygen provided during transport also should be warmed and humidified. The infant's temperature should be monitored continuously or at least every 30

*References 5, 16, 17, 18, 25, 41, 44, 53, 56

BOX 6.8 MORBIDITIES OF COLD STRESS[26,91]

- Hypothermia
- Hypoglycemia
- Respiratory distress
- Increased basal metabolic rate
- Increased caloric use to maintain thermal stability
- Increased oxygen consumption/need
- Respiratory and cardiac alterations (see Fig. 6.7) with decreased cardiac output (hypotension), shock, and renal failure
- Alteration in cerebral blood flow, the final common pathway to intraventricular hemorrhage (IVH)

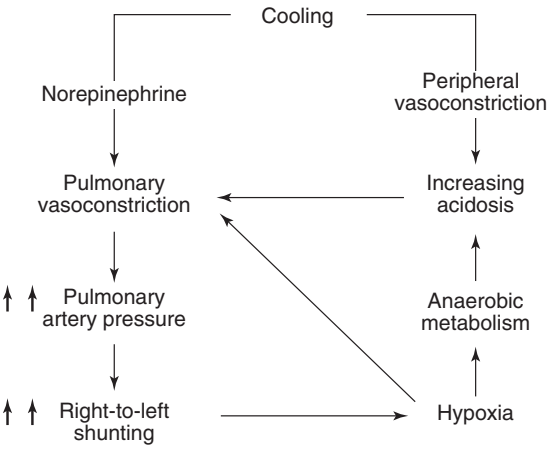

FIGURE 6.7 The vicious cycle resulting from cooling in the neonate. (From Fanaroff AA, Klaus MH. The physical environment. In: *Klaus and Fanaroff's Care of the High-Risk Neonate,* MI, USA: Elsevier Inc 66th ed; 2013:137.)

minutes. Thin plastic wrap may be useful in decreasing IWL and convective and radiant heat loss. Chemically heated mattresses can also be used to provide a short-term heat source.

Polyethylene bags that prevent hypothermia at birth also are effective in reducing the rate of hypothermia of VLBW infants during transport.[55]

After Cesarean Delivery

Most cesarean (C-section) deliveries are performed using an epidural or spinal anesthesia so the mother is awake and able to hear her infant as soon as he or she is born. **Once the baby is assessed after birth, he or she is then placed skin-to-skin on the mother's chest, and both are wrapped with a warm blanket.** After operative delivery, term newborns placed skin-to-skin with their mothers had: (1) no temperature change (21%), (2) increase in temperature (35%), and (3) a decrease in temperature (44%).[13] When the infant recovers in the same room as the mother, skin-to-skin contact and bonding are facilitated.[92] If the mother and baby do not recover together in the same room and the mother must return from the operating room, skin-to-skin care is still possible. **The father may provide skin-to-skin care and keep the baby warm after C-section until the mother returns to her postpartum room.** In a study of elective C-sections, 34 pairs of mothers and their newborns were randomized to skin-to-skin or routine nursery care within the 2 hours after the mother returned from the operating room.[48] Mean temperatures in both groups were equivalent, but the skin-to-skin care babies attached to the breast earlier, were exclusively or prevalently breastfed at discharge and 3 months, and mothers were highly satisfied with skin-to-skin contact with their babies[48] (see Chapter 5).

Providing Thermoregulation for the Surgical Patient

The chilled environment of the surgical suite poses extra challenges to the newborn for thermoregulation.

A case-control study of 108 infants in the NICU receiving operative procedures either in the operating room (OR) or the NICU found that hypothermia developed in 40% of the infants during the perioperative period.[99] When neonates were treated in the OR there was a higher rate of perioperative hypothermia (65% vs. 13% in NICU) as well as during and after the operation. Sequelae from hypothermia included respiratory distress and interventions to treat, need for thermal interventions, and need for cardiac support interventions.[99] A more recent study found that 90% of neonates were normothermic leaving the NICU, but only 24% were still normothermic at the beginning of surgery and 52% were normothermic on returning from the OR.[37] Quality improvement interventions reduce the rate of perioperative hypothermia in vulnerable neonates.[42] Heat losses occur by (1) evaporation during surgery, (2) conduction when placed on cold surfaces, (3) convection with cold drafts around the infant,[121] and (4) radiation of heat from opened body cavities. Coordination between neonatal and surgical staff will be necessary to prevent heat imbalance, as follows:

- Prewarm transport incubator.
- Use portable, disposable mattresses in the incubators and on the operating table.
- Use radiant heat in the operating suite.
- Wrap the infant's extremities in warmed soft cotton material.
- Prewarm all surfaces, as well as all fluids for cleansing and irrigation of body cavities.
- IV fluids should be at room temperature and prewarmed if stored in refrigeration.
- Temperatures should be monitored/documented before, during, and after surgery.

THERMAL IMBALANCE: CLINICAL DISORDERS

Data Collection

Anticipation and early recognition of the infant at risk for temperature instability are important in the management and prevention of complications associated with both hypothermia and hyperthermia. The perinatal history and ongoing neonatal evaluation identify events and early risk factors of temperature instability.

History

Events during pregnancy and the early neonatal period may increase an infant's risk for thermal instability. Review of the maternal history should include estimated date of confinement because preterm infants at delivery are at increased risk for hypothermia. Exposure to viral agents (e.g., herpes), as well as vaginal and cervical colonization, increases the risk for acquiring an infection before or during delivery (see Chapter 22). Intrapartal use of analgesics and anesthetics may depress the infant's CNS and mute the thermoregulatory ability.

Fetal stress manifested as fetal decelerations, meconium-stained fluid, or low Apgar scores may suggest an impaired thermoregulatory response. Neonatal interventions that may depress the CNS and thermal response include resuscitation and administration of analgesics, anesthetics, or neuromuscular blocking agents. Invasive procedures (e.g., endotracheal intubations, umbilical catheterization) increase the infant's risk for infection and need for prolonged use of antibiotics. Poor handwashing by care providers also may contribute to infectious nursery outbreaks, such as outbreaks of necrotizing enterocolitis (see Chapters 22 and 28).

Physical Examination: Signs and Symptoms

Physical assessment of the infant should include not only gestational age but also appropriateness of size. Evaluation of the infant's neurologic status (e.g., tone, activity, alertness) may give the caregiver an indication of the extent of neurologic impairment. Hypotonia results in decreased flexion, with an increased exposed surface area and resultant heat loss.

TEMPERATURE DETERMINATIONS

Temperature determinations may need to be made as often as every 30 minutes until thermostability is achieved. After that, temperatures should be recorded every 1 to 3 hours in LBW and preterm infants and every 4 hours in the healthy term infant. Critically ill infants should have continuous monitoring of skin temperature, with axillary determinations every 1 to 2 hours.[4] Documentation should include environmental temperature (e.g., air temperature in the incubator or radiant warmer settings). Measuring the skin and core temperatures simultaneously may help differentiate fever as a result of disease versus environmental overheating. Noting that the baby's servocontrolled skin temperature is relatively stable but that the environmental temperature has dropped also may be indicative of fever as the incubator responds to the high probe reading by cooling the infant's environment.

Laboratory Data

The following may be used to evaluate metabolic derangements associated with thermal instability:

- Arterial blood gases (to assess for hypoxemia and metabolic acidosis)
- Complete blood count (to assess for sepsis)
- Blood glucose level (to assess for hypoglycemia)
- Electrolytes, blood urea nitrogen (BUN), and serum and urine osmolality (to assess hydration, acid-base balance, and renal function)

HYPOTHERMIA

As the infant attempts to conserve heat by vasoconstriction, he or she may be pale, appear mottled, and feel cool to touch, particularly on the extremities. Acrocyanosis and respiratory distress may occur as the infant increases oxygen consumption in an attempt to increase heat

production. If hypothermia continues, apnea, bradycardia, and central cyanosis may occur. The hypothermic infant initially may be irritable but may become lethargic as cold stress continues. Other changes that may occur include hypotonia, weak cry, weak suck, increased gastric residuals, abdominal distention, and emesis. Infants generally do not shiver in response to cold stress, but shivering may occur in more mature babies in the presence of severe hypothermia. Chronic hypothermia may result in poor weight gain (Box 6.8).

Treatment and Intervention

To avoid the complications of hypothermia, rewarming of cold infants should begin immediately by providing external heat. However, rewarming too rapidly may further compromise the already cold-stressed infant and result in apnea. Oxygen consumption is minimal when the difference between the skin and the ambient air temperature is less than 1.5°C (2.7°F). Avenues of heat loss should be blocked, temperatures should be monitored, and iatrogenic or pathologic causes should be investigated.

If hypothermia is mild, slow rewarming is preferred. External heat sources should be slightly warmer than the skin temperature and gradually increased until the neutral thermal environmental temperature range is attained. Efforts to block heat loss by convection, radiation, evaporation, and conduction should be initiated. Skin, axillary, and environmental temperatures should be measured and recorded every 30 minutes during the rewarming period. For more extreme hypothermia (i.e., core temperatures <35°C [95°F]), more rapid rewarming with a radiant heater (servo-control 37°C [98.6°F]) or heated water mattress prevents prolonged metabolic acidosis or hypoglycemia and decreases mortality. A faster rewarming rate (>0.5°C/hour) of hypothermic ELBW preterm infants on admission resulted in a reduced incidence of respiratory distress syndrome (RDS), but no other differences between the rapid and slower rewarming groups.[98]

BOX 6.9 CRITICAL FINDINGS HYPOTHERMIA

Critical assessment findings for hypothermia are as follows:

- Pale, mottled skin that is cool to touch
- Acrocyanosis
- Respiratory distress
- Apnea, bradycardia, central cyanosis
- Irritability initially
- Lethargy developing as hypothermia worsens
- Hypotonia
- Weak cry and suck
- Gastric residuals, abdominal distention, emesis
- Shivering in more mature babies
- Metabolic acidosis
- Hypoglycemia

Complications

Hypothermia on admission to the NICU is strongly associated with increased mortality within the first week of life as well as during the first month of life.[23,30,71,83,95,133] Neonatal morbidities associated with admission hypothermia include: (1) increase in late-onset sepsis with every degree C decrease in admission,[71] (2) increase in intraventricular hemorrhage (IVH),[95] (3) increase in RDS,[23] and (4) severe neurologic damage, retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), and nosocomial infections.[83] However, a study of hypothermia in premature infants less than 32 weeks gestational age admitted to a Danish NICU found no association between admission hypothermia and RDS or death and BPD or death after adjusting for confounders (i.e., early-onset sepsis, gestational age, Apgar score, sex, treatment year, and birth weight).[59] A recent study of the outcomes of hypothermic preterm infants treated with oxygen or CPAP for RDS in a low-resource setting found: (1) none of the infants with a temperature below 35.8°C survived to discharge regardless of the type of respiratory support, (2) 100% of preterm infants with temperatures above 35.8°C treated with CPAP survived, and (3) if more than 50% of measured temperatures were hypothermic only 5.6% survived who were treated with CPAP.[21]

Acute cold stress results in the release of norepinephrine, which causes vasoconstriction to reduce heat loss and initiate thermogenesis, which increases metabolic rate. As glycogen stores are depleted and oxygen consumption increases, the infant uses anaerobic metabolism to increase heat production, resulting in lactic acid production (metabolic acidosis).

Pulmonary vasoconstriction, accentuated by metabolic acidosis, is associated with hypoxia, decreased surfactant production, and further acidosis (see Chapter 23). Blood flow to vital organs is diminished, and pulmonary hemorrhage and death may occur if hypothermia continues.

Hyperbilirubinemia and kernicterus may occur as nonesterified free fatty acids from brown fat metabolism compete with bilirubin for albumin-binding sites. Acidosis not only decreases the affinity of albumin for bilirubin but also increases the permeability of the blood-brain barrier, allowing bilirubin to enter brain tissue. If hypothermia continues, carbohydrate, protein, and fat supplies will be used for heat production instead of growth.

Close monitoring of the hypothermic infant is essential for early identification and prevention of complications. Evaluation of vital signs, arterial blood gases, and oxygen saturation may give early indication of hypoxia and metabolic acidosis. The infant's skin may be dusky or bright red because failure of dissociation of oxyhemoglobin occurs at low body temperatures. Respirations may be rapid, shallow, and grunting and accompanied by bradycardia. Oxygen and ventilation should be initiated as needed to reduce hypoxia. Sodium bicarbonate may be needed to correct documented metabolic acidosis. Seizures may occur as a result of hypoxia, requiring the administration of anticonvulsants.

Intravenous glucose may be necessary to prevent or correct hypoglycemia. **Blood glucose levels should be monitored hourly until stable** (see Chapter 15). **Blood pressure and urine output should be measured** to evaluate hydration and kidney function. An elevated BUN and hyperkalemia may be indicators of decreased renal perfusion and impaired renal function. As fluid is retained, edema of the extremities and face may occur.

Bilirubin should be monitored on a regular basis, and phototherapy may be initiated at a lower-than-usual level to prevent kernicterus. Adequate nutrition to promote growth should be given either intravenously or enterally. While the infant is hypothermic, nipple feedings should be avoided to conserve calories and energy for heat production and growth and to avoid aspiration. Hypothermic infants feed poorly and fail to gain weight because calories are used to generate heat for warmth instead of for growth.

During the rewarming process, the hypothermic infant should be observed for hypotension as vasodilation occurs. Volume expanders may be needed to maintain an adequate blood pressure. Apnea and seizures may occur as a result of hypoxia or decreased cerebral blood flow after vasodilation. Hypothermia as a strategy to minimize adverse outcomes from hypoxic-ischemic encephalopathy continues to be the focus of considerable research to determine safety and efficacy (see Chapter 26).

HYPERTHERMIA

The hyperthermic infant may feel warm to touch, and skin color may be ruddy as the infant attempts to increase heat loss by vasodilation. Sweating may occur in a term infant but generally is not present in infants of less than 36 weeks gestational age. Sweating may first appear on the forehead, followed by the chest, upper arms, and lower body. Hyperthermia is manifested by irritability, lethargy, hypotonia, apnea, a weak or absent cry, or poor feeding. Tachypnea or tachycardia may be seen as the infant attempts to increase heat loss.

Infants with thermal instability should be closely watched for changes in behavior, feeding patterns, and respiratory status. Temperatures should be monitored frequently in any infant exhibiting these symptoms or who feels cool or warm to touch. Early recognition of thermal instability may prevent further consequences and possibly permanent injury or death (Box 6.10).

Treatment and Intervention

The usual approach to treating the hyperthermic infant is to cool by removing external heat sources

BOX 6.10 CRITICAL FINDINGS HYPERTHERMIA

Critical assessment findings for hyperthermia are as follows:

- Reddened skin that is warm to touch
- Tachypnea
- Tachycardia
- Irritability, lethargy, hypotonia, weak cry
- Poor feeding
- Apnea
- Sweating in more mature babies
- Dehydration

and by removing anything that blocks heat loss. The most common causes of hyperthermia in intensive care nurseries are iatrogenic. Check the heating controls for proper function and thermistors for proper position. Consider other sources of heat (e.g., direct sunlight, heaters, lights) as possible causes of hyperthermia. Excessive bundling with blankets and a hat and elevated environmental temperature can cause a newborn's body temperature to rise into the febrile range. When evaluating the treatment options in the hyperthermic infant, one should consider removing extra blankets or swaddling materials. Nonenvironmental causes of hyperthermia (e.g., infection, dehydration, CNS disorders) should be considered. During the cooling process, skin, axillary, and environmental temperatures should be monitored and recorded every 30 minutes.

Complications

Recognizing late preterm and term neonates who meet the criteria for neonatal cooling for HIE (see Chapter 26, Box 26.7) and preventing hyperthermia is critical to decreasing morbidity and mortality. Outcomes of asphyxiated newborn infants who did not receive cooling in the NICHD Neonatal Research Network whole body cooling trial were studied at 18 to 22 months[72] and at 6 to 7 years.[70] Within the first 72 hours of life, asphyxiated newborns without cooling exhibited elevated temperatures that were associated with a four-fold increase in death or moderate disability.[72] Follow-up of this cohort to ages 6.7 years found that the association between their elevated temperatures and death or IQ less than 70 persisted.[70]

Vasodilation to increase heat loss may cause hypotension and dehydration as a result of increased IWL. **Seizures and apnea may also occur as a result of high core temperature.** Fluid status should be monitored by assessing intake, output, electrolytes, serum and urine osmolality, skin turgor, and mucous membranes. Fluids should be adjusted to account for IWL. **Blood pressure should be assessed to detect hypotension,** and volume expanders should be administered as needed.

Cardiorespiratory monitoring to detect apnea should be used. Ventilation may be needed if apnea persists or is unresponsive to stimulation. Subtle signs of seizures may include facial grimacing, nystagmus, tremors, apnea, opisthotonos posturing, tongue thrusting, or staring (see Chapter 26).

PARENT/CAREGIVER TEACHING

While the neonate is in the NICU, parents should be taught the importance of maintaining the newborn's normal body temperature. Temperature should be taken before parents touch the infant through the portholes of the incubator or hold their infant. **While the infant is outside the incubator, monitor the skin temperature continuously with a telethermometer.** Unwrapping the infant to check the temperature exposes him or her to cold stress. Additional heat sources (e.g., radiant warmer, hat, extra blankets) may be needed while parents hold the infant. Teach parents to monitor their infant's temperature and to notify the nurse if it rises or falls (Box 6.11).

Before discharge, teach parents to take an accurate axillary temperature and to notify their physician if it drops below 36°C (96.8°F) or rises above 37.8°C (100°F).[4] A parent should not routinely take a rectal temperature. The temperature should be taken whenever the infant feels cool or warm to the touch. The nurse should observe the parents taking the infant's axillary temperature before discharge.

The home environment should be kept at a temperature that prevents heat and cold stress. A room temperature that is comfortable for the parent usually is suitable for the infant. The infant should be in clothing appropriate for the room temperature. For example, if the parent requires a sweater to

BOX 6.11 PARENT/CAREGIVER TEACHING TEMPERATURE REGULATION

- Teach parents how to take an axillary temperature on their newborn and maintain the axillary temperature between 36.5°C and 37.4°C (97.7°F and 99.3°F).[5]
- Teach parents how to dress their infant with clothes and blankets and use an appropriate environmental temperature to maintain the baby's temperature in the above range.
- Teach parents appropriate safety precautions, which include verbal and written information about recognizing signs and symptoms of a sick/ill infant, as well as how the infant acts, including temperatures either higher than or, more commonly, lower than the range of 36.5°C to 37.4°C (97.7°F to 99.3°F).
- Teach parents to notify their infant's primary health care provider immediately or to take the infant to the nearest emergency department for temperatures out of the above range, especially if the baby's feeding pattern changes.

be comfortable, the infant probably also requires a sweater. Parents often overdress the infant or overheat the home, and this may cause hyperthermia. Parents should be given written instructions before discharge on how and when to take an axillary temperature, when to call the physician, and how to maintain a comfortable environment for their infant.

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7 PHYSIOLOGIC MONITORING

KRISTI COE, WANDA T. BRADSHAW, AND DAVID T. TANAKA

Significant advances in the management of the ill preterm infants have been made in the past 70 years. The clinical usefulness of the umbilical vein was first demonstrated by Diamond in 1947 to perform an exchange transfusion to prevent kernicterus. Later, James used the umbilical artery for acid-base determination. In most neonatal intensive care units (NICU), use of these catheters has become the standard of care to assess blood gases, measure arterial and central venous pressures, administer medications and fluids, and obtain laboratory samples. The development of small, indwelling, peripherally inserted central catheters provides a route for administering the aforementioned items and may be used for laboratory sample withdrawal if no other method of obtaining blood is available. The frequency and clinical significance of complications and alternatives to these intravascular routes have been vigorously sought. The development of noninvasive physiologic monitoring devices has been a major step toward this goal. In addition, the use of point-of-care testing for various laboratory values is evolving in neonatal care. This chapter reviews the procedures and advances in physiologic monitoring.

PHYSIOLOGY

Pulmonary Physiology

Gas exchange takes place in the alveoli of the lung. Ventilation is the movement of air into and out of these airspaces. Diffusion is the movement of oxygen (O_2) from the alveolar space into the pulmonary capillary and the movement of carbon dioxide (CO_2) from the pulmonary capillary into the alveolar space for eventual exhalation. Pulmonary perfusion is the flow of blood through the pulmonary capillaries that surround the alveolar spaces. **Once oxygen diffuses through the cells lining the alveoli and into the capillaries, it is predominately bound to hemoglobin within the red blood cell.** Oxygen content in the arterial blood is the sum of the amount of oxygen dissolved in the plasma and the amount bound to hemoglobin. **Approximately 3% of the oxygen content is dissolved in the plasma, with the remaining 97% bound to hemoglobin.** PaO_2 is the partial pressure of the oxygen dissolved in arterial plasma. ***Fetal hemoglobin* has a higher affinity for oxygen than does adult hemoglobin; therefore, at any given PaO_2, more oxygen is bound to fetal hemoglobin** (Fig. 7.1). **Each hemoglobin molecule can carry four oxygen molecules. *Oxygen saturation* (SaO_2) is the percentage of oxygen bound to hemoglobin.**

Carbon dioxide content in arterial blood is the sum of the amount of carbon dioxide in the plasma plus the amount bound to hemoglobin. As hemoglobin gives up oxygen to the tissues, it is able to pick up carbon dioxide. **Each reduced hemoglobin molecule can carry four carbon dioxide molecules, thus lowering the free hydrogen ion (H^+) concentration.** Approximately 10% of the carbon dioxide content is gas dissolved in the plasma (CO_2), 60% is carbonic acid (H_2CO_3), and the remaining 30% is attached to proteins, predominantly hemoglobin. **$PaCO_2$ is the partial pressure of carbon dioxide dissolved in arterial blood.** It is a measured value that denotes the partial pressure of arterial carbon dioxide. **Carbon dioxide values fluctuate as needed to maintain the hydrogen ion concentration, or pH, within a normal range.** Carbon dioxide combines reversibly with water to yield hydrogen (H^+) and bicarbonate (HCO_3^-) ions. The formula is $CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$.

BLUE type highlights content that is particularly applicable to clinical settings.

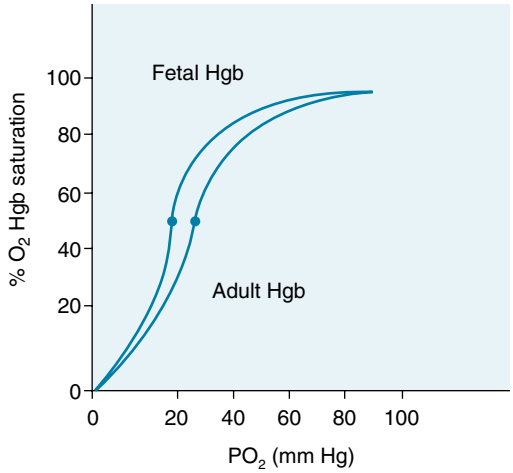

FIGURE 7.1 Oxygen dissociation curves for fetal hemoglobin (Hgb) (*left*) and adult hemoglobin (*right*).

NONINVASIVE MONITORING

Use of noninvasive technologies to monitor *all* neonates in the NICU is the standard of care. Many neonates also require invasive monitoring devices.

Oxygen and Carbon Dioxide

OXYGEN

Noninvasive monitoring of oxygenation can be accomplished by using three monitoring technologies, *pulse oximetry, transcutaneous oxygen monitoring, and near-infrared spectroscopy.* ***Oxygen saturation monitoring* is the most common and widely used method for assessing oxygenation status.** Transmission technology relies on a pulsating arterial vascular bed between a dual light source and a photoreceptor. As blood passes between the light source and the photoreceptor, different amounts of red and infrared light are absorbed, depending on the amount of oxyhemoglobin and reduced hemoglobin. With reflectance oximetry, the emitter and receptor are located beside each other. Emitted light is reflected back to the photoreceptor. This method uses the core body to obtain oxygen saturation and is useful when the patient's peripheral blood flow is diminished. **With this method, the difference in light absorption is electronically processed and displayed by the monitor as the percentage of arterial hemoglobin oxygen saturation expressed as SpO_2. Pulse oximetry probes are easy to apply and require no warm-up period, calibration, or application of heat.**

The second method of noninvasive monitoring of oxygenation is *transcutaneous oxygen tension,* **which relies on the principle of oxygen diffusing from the skin capillaries through the dermis to the surface of the skin.** To measure oxygen diffusion, it is necessary to have adequate perfusion of the site, to intermittently calibrate the sensor, and to heat the skin, which then dilates the local capillaries and arterializes the capillary bed, as well as promotes faster diffusion of the oxygen from the skin.[36]

Near-infrared spectroscopy (NIRS) is a newer method of noninvasive oxygenation measurement in the NICU. NIRS was launched in 1977 to assess cerebral oxygenation and perfusion during cardiac and neurosurgery, but its use has been expanded into neonates, initially used peri- and postoperatively for cardiac surgery.[46] This technology is based on tissue transparency to light in the 700- to 1000-nm wavelength, referred to as the *near-infrared spectrum.* Through a light-emitting diode (LED), NIRS releases two wavelengths of near-infrared light signals to maximize separation of the absorbed spectra among oxyhemoglobin and deoxyhemoglobin. The NIRS probe also contains two optodes to receive the scattered light, one from peripheral tissue and another from peripheral and deep tissues. After the peripheral value is subtracted from the other value, a tissue-specific regional oxygen saturation (RSO_2) value from a 1- to 2-cm depth is attained. In comparison with earlier technology, **NIRS signifies tissue oxygen supply and utilization, while oxygen saturation monitoring suggests (arterial) oxygen supply to tissues.** While NIRS was initially used to assess cerebral oxygenation and demand by placing the adhesive probe horizontally across the forehead, use has been expanded to deeper organs including the kidneys and intestines because of a superficial location in this age group.[46]

CARBON DIOXIDE

Carbon dioxide also can be assessed using two different devices, *transcutaneous carbon dioxide* and *end-tidal carbon dioxide* monitors. ***Transcutaneous carbon dioxide ($PtcCO_2$) monitoring works under similar principles as for transcutaneous oxygen monitoring.***[34] The probe is a glass pH electrode

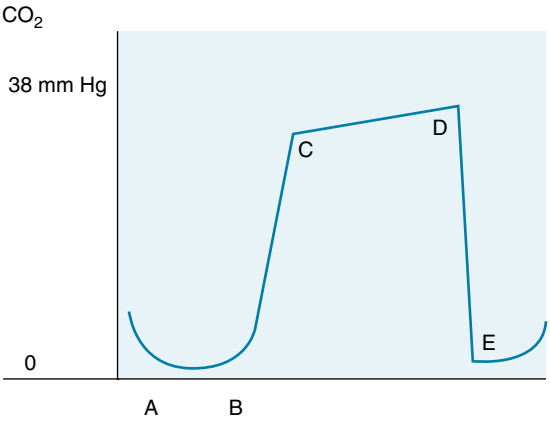

FIGURE 7.2 Variations in the content of carbon dioxide during phases of the respiratory cycle. **A,** End of inspiration. **B,** Beginning of exhalation. **C,** End of mixed gases washout (dead space and alveolar gases). **D,** End of expiration of alveolar gases. **E,** Inspiration.

that detects changes in pH caused by CO_2. Heating of the probe enhances CO_2 diffusion, providing a better correlation between the probe value and the $PaCO_2$ value. The second method used to measure the content of the carbon dioxide in the respiratory gases during the respiratory cycle is *end-tidal carbon dioxide ($PetCO_2$)* monitoring, also called *capnometry.* **With capnometry, an infrared light absorption determines the amount of CO_2 present in the sample. Capnography provides a visual graphic curve of $PetCO_2$.** The carbon dioxide content varies widely with the phase of the respiratory cycle. During inspiration, there are minimal amounts of carbon dioxide, whereas at the end of expiration, the carbon dioxide values are at their maximum level (Fig. 7.2). Until recently, the relatively fast respiratory rate of newborns, combined with the small tidal volumes, resulted in inaccurate values when measured by end-tidal carbon dioxide monitors. Advances in technology have improved the reliability of this monitoring technique for newborn infants.

COMBINED OXYGEN–CARBON DIOXIDE MONITORING

$SpO_2/PtcCO_2$ sensors combining pulse oximetry and transcutaneous carbon dioxide monitoring have been developed. The heated sensor is attached to the patient's ear. It provides rapid SpO_2 values followed by carbon dioxide information within minutes as the site is warmed and arterialized. A single probe, designed to withstand motion artifact and low perfusion states, leads from the patient to the monitor. The probe is attached to the ear, thus its removal for chest radiographs or prone positioning is not necessary. Studies on normal adults, infants, and very-low-birth-weight (VLBW) infants have shown acceptable correlation with both invasive and noninvasive monitoring techniques for oxygen. Carbon dioxide values were less reliable but allowed trending of ventilation status.[38]

Amplitude Integrated Electroencephalography

Although the gold standard for monitoring cerebral activity in neonates is continuous electroencephalography (cEEG), a tool that is complementary, amplitude-integrated electroencephalography (aEEG), is now used in many NICUs. **Infants appropriate for use of aEEG may include those with clinically evident seizure activity or those with seizure activity who have experienced a perinatal hypoxic event.**[38] Feasibility is likely improved with aEEG because this technology requires only four electrodes compared with many more channels needed for cEEG. Like other complementary tools, aEEG provides trends over time that allow clinicians to view and assess for abnormal cerebral activity allowing for prompt treatment.[38]

Cardiorespiratory Monitoring

The electrical activity of an infant's heart is picked up by chest leads (usually three) placed on the infant and recorded by a cardiorespiratory monitor. The recording is displayed on a visual screen as the infant's electrocardiographic pattern. The infant's respiratory pattern also is recorded, because the chest leads electronically detect movement of the chest with each respiration.

Blood Pressure Monitoring

***Systolic blood pressure,* measured in millimeters of mercury (mm Hg), is the pressure at the height of the arterial pulse and coincides with left ventricular systole. *Diastolic blood pressure,* also measured in mm Hg, is the lowest point of the arterial pulse and coincides with left ventricular diastole. *Pulse pressure* is the difference between**

the systolic and diastolic blood pressure. *Mean arterial pressure* is the diastolic pressure plus one-third of the pulse pressure. *Central venous pressure* is the pressure in the right atrium and may be approximated by the blood pressure (volume) in any of the large central veins.

Point-of-Care Testing

Point-of-care testing (POCT) involves testing performed at or near the patient rather than in a laboratory. This process has steadily evolved from crude blood glucose determinations to numerous types of monitoring. Currently, whole-blood glucose values, transcutaneous bilirubin, fecal occult blood, gastric pH, urine dipstick, activated clotting time, hematocrit, some electrolyte values, and arterial blood gases are part of POCT for the neonatal population.

DATA COLLECTION

The indications for using the various techniques for physiologic data collection depend on the infant's clinical situation.

Noninvasive Oxygen and Carbon Dioxide Monitoring

Oxygen monitoring is indicated in infants receiving oxygen for any reason (see Chapter 23). Acute monitoring is used as a part of the management of acute respiratory disorders. Long-term monitoring is used to wean infants with chronic lung disease from oxygen therapy. Noninvasive oxygen monitoring is useful during transport, in emergency situations, and during procedures. However, this method provides no information on hemoglobin level, adequacy of ventilation, and oxygen delivery to the tissues and should be used as one part of total oxygenation and ventilation assessment. Despite how oxygen saturation monitoring is used more, less variability in oxygen tension has been demonstrated when transcutaneous oxygen monitoring has been employed.[36]

Carbon dioxide monitoring is useful for verifying that the endotracheal tube is in the trachea (end-tidal CO_2 monitoring) and for the infant with a respiratory disease in whom retention of carbon dioxide may become clinically significant (end-tidal CO_2 and transcutaneous CO_2 monitoring).

Cardiorespiratory Monitoring

Cardiorespiratory monitoring should be used in *all* infants who require intensive or intermediate care, as well as in *all* infants at risk for apnea or rhythm disturbances.

Blood Pressure Monitoring

Blood pressure monitoring should be used in the infant requiring surgery, in the acutely ill infant with cardiorespiratory distress, and in any other illness in which hypotension may be a significant contributor to the pathologic state. Central venous pressure should be monitored in infants who may experience an excess or loss of blood volume.

Umbilical Artery Catheters

An umbilical artery catheter (UAC) is placed in those infants requiring frequent arterial blood gas determinations, continuous monitoring of arterial blood pressure, and infusion of parenteral fluids. The practice of medication administration through a UAC varies, although there are no published data in the past decade regarding this practice.[31,45] Infants who are candidates for indwelling catheters include critically ill neonates and those with congenital heart disease or disorders that cause respiratory insufficiency (e.g., surfactant deficiency, meconium aspiration syndrome, persistent pulmonary hypertension, diaphragmatic hernia). **Although use of an indwelling UAC allows arterial pressure monitoring and accessibility for parenteral infusions, it is generally not used for these indications alone.**

Umbilical Vein Catheters

Umbilical vein catheters (UVCs) are useful for exchange transfusions, central venous pressure monitoring, emergency administration of fluids or chemicals in delivery room resuscitation, and administration of parenteral fluids and medications in the NICU, as well as obtaining blood for laboratory analysis. UVCs are used with increasing frequency for initial management

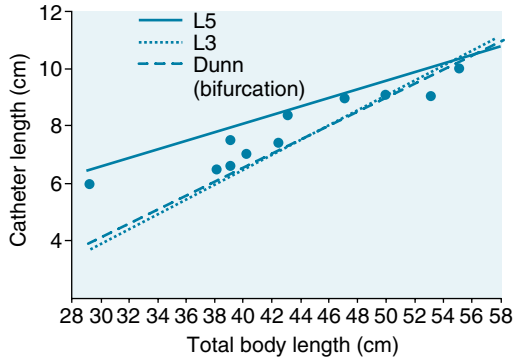

FIGURE 7.3 Graph for distance of catheter insertion from umbilical ring for low placement. (From Rosenfeld W, Biagtan J, Schaeffer H, et al. A new graph for insertion of umbilical artery catheters. *J Pediatr.* 1980;96(4):735.)

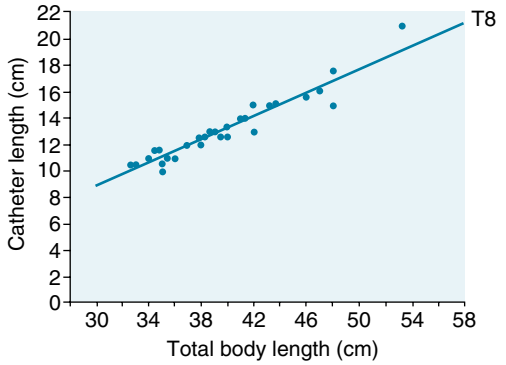

FIGURE 7.4 Graph for distance of catheter insertion from umbilical ring for high placement (T8). (From Rosenfeld W, Estrada R, Jhaveri R, et al. Evaluation of graphs for insertion of umbilical artery catheters below the diaphragm. *J Pediatr.* 1981;98(4):627.)

of extremely low-birth-weight (ELBW) infants. Catheters used to cannulate the umbilical vein are available as both single-lumen and double-lumen items. Double-lumen catheters permit the simultaneous administration of infusates and medications. Use of a UVC reduces the need for peripheral devices when multilumen UVCs are used.

INTERVENTIONS

Invasive Monitoring

Placement of UACs or UVCs and placement of a peripherally inserted central catheter (PICC) are invasive monitoring techniques.

Umbilical Artery Catheter Placement

PROCEDURE

Determine the size and length of the catheter to be inserted. **For infants weighing more than 1250 g, use a 5-Fr catheter, and for infants weighing less than 1250 g, use a 3.5-Fr catheter.** Figs. 7.3 and 7.4 correlate total body length with the length of the catheter to be inserted. Whereas these charts have worked reasonably well in larger preterm and term infants, the Wright formula (4 × birth weight in kilograms + 7) resulted in significantly better placement in VLBW infants.[22,29] A comparison of formulas for the length of UAC placement found superior correct placement of the tip of the catheter with use of the Wright formula.[29]

Place the infant in a supine position on a radiant warmer bed or in an incubator. Ensure continuous temperature monitoring. Skin temperature should remain between 36°C and 37°C (96.8°F and 98.6°F). Provide appropriate oxygenation and ventilation. Ensure cardiorespiratory and oxygen saturation monitoring. Restrain the infant's hands and feet to prevent him or her from contaminating the sterile field and interfering with the placement procedure. Don cap and mask. Open the catheterization tray; most units now use commercially available disposable trays. Catheterization tray contents are shown in Fig. 7.5. Wash hands and dry with sterile towel before the procedure. Put on sterile gown and gloves.

Connect the catheter to the stopcock, and flush and fill the entire system, including the catheter, with flush solution. Turn off the stopcock to the catheter to prevent fluid from draining out of the catheter during insertion and securing of the catheter. Cleanse the cord and base of the umbilicus with either povidone-iodine or chlorhexidine with alcohol three times and allow the site to air-dry.[33] Remove the povidone-iodine with alcohol. For infants weighing less than 1000 g, utilize sterile water. **Avoid using an excess of skin disinfectant so the infant is not lying in the solution during the procedure. Any residual skin disinfectant should be washed off the infant carefully after the procedure is completed.**

FIGURE 7.5 Argyle umbilical vessel catheter insertion tray. (Courtesy Tyco/Healthcare Kendall-LTP.)

Drape the infant by placing an eye sheet over the umbilicus. An alternative method is to use sterile drapes, as follows:

1. Hold the diagonal corners of one drape, and allow the top half to fold over the bottom half. The result is a *V* shape.
2. Place the tips of the *V* on either side of the umbilicus.
3. Repeat with another drape, and place on the other side of the umbilicus. The umbilical stump is now visible yet surrounded by drapes.

After the UAC is inserted, the drapes can be removed easily without the need to pass the stopcock and catheter through an eyehole of a drape or cut or tear the eyehole drape. **Ensure that the infant's head and feet remain visible during the procedure to assess color.** A small eye drape with adhesive backing (such as a Steri-Drape) has the advantage of being transparent, so that the infant's color can be seen, and temperature can be maintained. Towel drapes may interfere with a radiant heat source used for temperature regulation.

Place an umbilical cord tie (e.g., umbilical cord tape) around the base of the cord to control bleeding. A single overhand knot is preferred because it allows tightening as needed. Using tissue forceps, pick up the cord and cut it with a scalpel about 1 to 1.5 cm above the base. Arterial spasm allows only minimal bleeding. Identify the vessels. **There are usually two arteries and one vein. The arteries are small, thick walled, and constricted. The vein is larger, thin walled, and usually gaping open.** If the vein is at the 12-o'clock position, the arteries are usually at the 4- and 8-o'clock positions (Fig. 7.6).

Stabilize the umbilical stump by grasping the cord between the thumb and index finger or grasping the edge of the stump with a mosquito hemostat. Ensure that the hemostat does not crush the umbilical vessels. With iris forceps, dilate one of the arteries by placing the tips of the forceps in the artery and gently allowing them to spring open. This procedure may need to be repeated several times. In ELBW infants, the artery may be so small that it may be necessary to initially insert one forcep tip and then both to dilate the artery. While grasping one side of the wall of the dilated artery with small forceps, gently insert the catheter. An alternative method is to insert the catheter between the open prongs of the forceps used to dilate the artery. Instructional aids such as Baby Umb (Medical Plastics Laboratory, Inc., Gatesville,

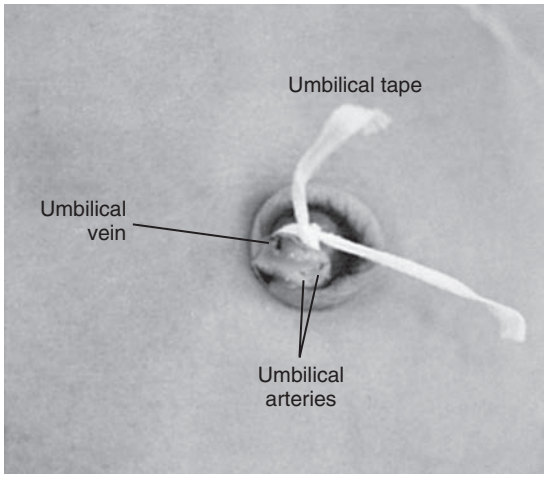

FIGURE 7.6 Umbilical tape and position of umbilical vessels.

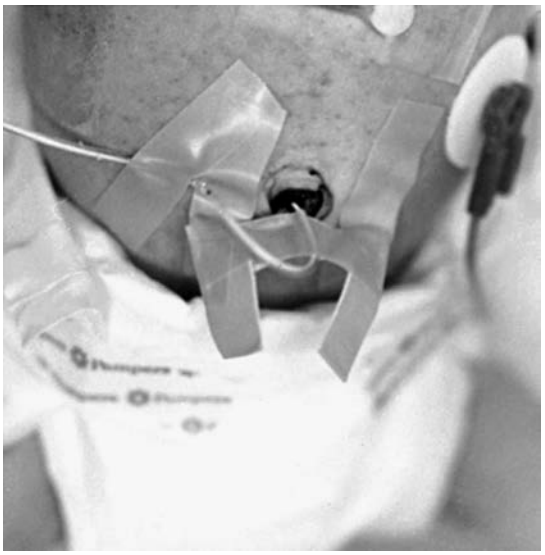

FIGURE 7.7 Umbilical artery catheter secured in "goalpost" design.

TX) and the Umbilical Artery Catheterization Slide-Tape Neonatal Educational Program (Charles R. Drew Postgraduate Medical School, Los Angeles, CA) are helpful. As the catheter passes into the artery, resistance may be encountered at several points, as follows:

- At the umbilical cord tie (tape): The tie (tape) may be tied too tightly. Loosen slightly.
- At the point at which the umbilical artery turns downward (caudal) into the abdomen: Steady, gentle pressure is important because forceful pressure may cause the catheter to perforate the artery wall and create a false channel.
- At the point at which the umbilical artery joins the external iliac artery: Once again, steady, gentle pressure is important.

Insert the catheter to the predetermined length. Aspiration on the syringe should provide immediate blood return. Lack of blood return may indicate the following:

- The catheter is not inserted far enough. Insert farther.
- The vessel wall has been perforated, or a false channel has been created. If the catheter has pierced the vessel wall, repeat the procedure using the other artery.
- The catheter is kinked. Pull back slightly and then advance.
- The stopcock is turned off. Correct the stopcock position. Return aspirated blood to the infant; then clear the catheter with flush solution.

There are several methods to secure the catheter, including suturing to the umbilical stump, use of an adhesive-type tape after using skin prep to protect the skin, use of a "goalpost" (Fig. 7.7), and use of sterile transparent dressing. The literature denotes these methods, but there is no evidence to delineate the most beneficial method. Advantages and disadvantages of each method including skin issues, cost, and ease of use need to be researched.[14]

Connect the stopcock to the intravenous (IV) solution, and set the prescribed infusion rate on the infusion pump. Ensure that no air is in the tubing, stopcock, or catheter. All connections must be secure. Automatic infusion pumps must be used for UACs because arterial pressure must be overcome to permit IV fluid infusion. Determine catheter placement by a radiologic examination (abdominal, chest, "babygram," or ultrasound depending on placement of the catheter). Fig. 7.8 shows how the UAC appears on a lateral x-ray film.

Note that the catheter enters the umbilicus and travels inferiorly before turning superiorly. This "leg loop" is characteristic of an arterial catheter. A UAC follows the aorta and is positioned slightly to the left of the patient's vertebral column. **Optimal placement is below the renal arteries and above the aortic bifurcation (L3 to L4) for a *low catheter* and below the left subclavian artery and above the diaphragm (T7 to T9) for a *high catheter*.[24] High catheter placement has fewer complications.[3]** Fig. 7.9 shows high catheter placement, and Fig. 7.10 shows low catheter placement.

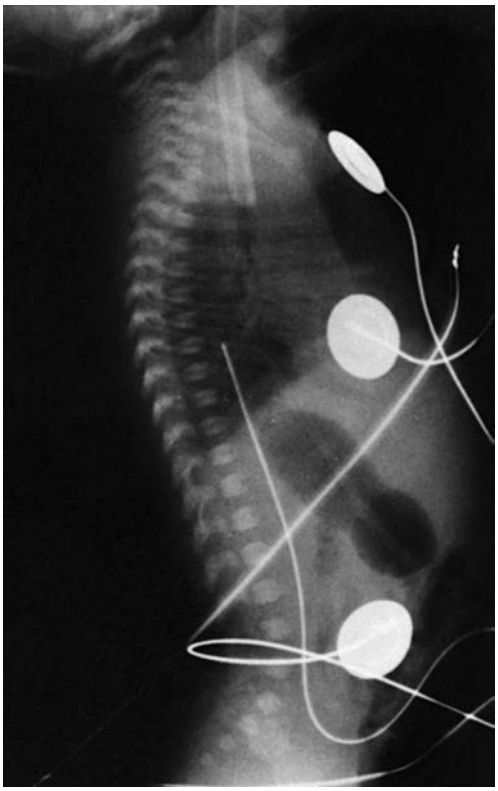

FIGURE 7.8 High catheter demonstrating "leg loop."

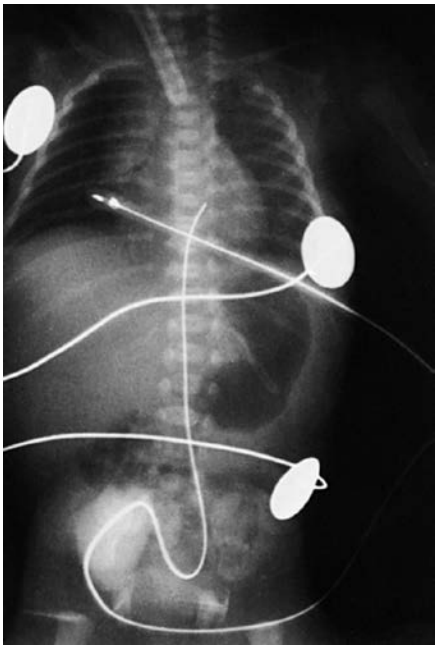

FIGURE 7.9 Umbilical artery catheter in high position (T8).

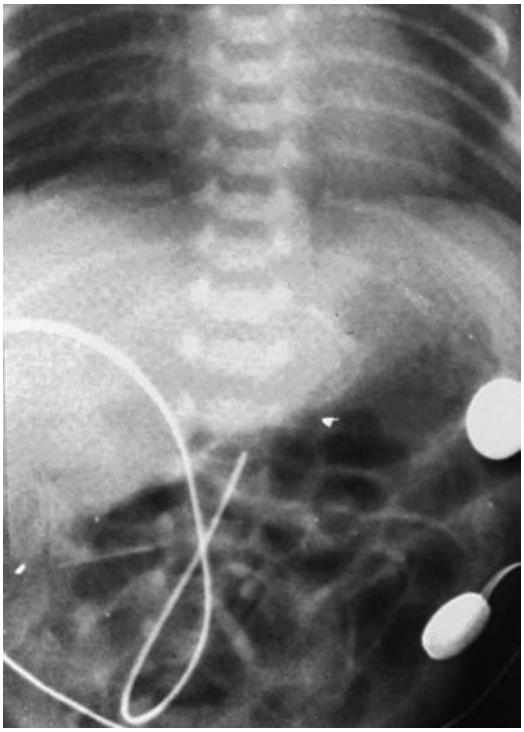

FIGURE 7.10 Umbilical artery catheter in low position (L3).

If the catheter is too high, measure on the x-ray film the distance from the tip of the catheter to the desired level, and pull the catheter back the appropriate distance. Some clinicians multiply this length by 0.8 to account for the magnifying effect of the x-ray film. **If the catheter is placed too low, the catheter cannot be advanced but must be removed and replaced because the external portion of the original catheter is no longer sterile.** Remove the umbilical cord tie (tape), or maintain the tie very loosely so as not to obstruct blood flow to the umbilical area.

As a teaching model, the umbilical cord can be used for teaching the procedure of both arterial and venous catheterization. Many of the steps can be effectively carried out using a fresh placenta. **Special UACs and monitors are available for continuous PaO_2 or oxygen saturation monitoring.**

NURSING CARE AND USE OF UMBILICAL ARTERY CATHETERS

Infants can be positioned on their sides or their backs. The abdominal position may be avoided because accidental slipping, kinking, and removal

of the catheter may occur without being immediately apparent. If the abdominal position is used, the catheter should be monitored continuously; ensure that pressure alarms are on with parameter settings that would rapidly detect pressure changes. **Care needs to be taken so that the infant is positioned to prevent dislodgement of the catheter.** Diapers are effective for preventing the feet and toes from becoming entangled in the catheter. **The diaper is folded below the umbilicus.** If the infant is receiving phototherapy and thus is not diapered, leg restraints or positioning aids may be indicated. A mitten or positioning aids are useful to prevent hands and fingers from contacting the catheter. Positioning the catheter away from the extremities lessens the chance of accidental dislodgement. **Unless using a transparent dressing to secure the UAC, a dressing over the umbilicus is unnecessary. Nontransparent dressings inhibit inspection of the umbilicus and evaluation of the catheter.** The IV tubing, connecting tubing, and stopcock should be changed daily. Clots form in the stopcock, so changing it daily prevents the likelihood of thrombus formation. Blood backing into the catheter can be caused by the following:

- Increased intraabdominal pressure, commonly caused by vigorous infant crying
- Disconnection of tubing or a loose connection
- Stopcock turned in wrong direction
- Infusion pump malfunction
- A leak in the filter or tubing or a crack in the stopcock

PROCEDURE FOR OBTAINING AN ARTERIAL BLOOD GAS SAMPLE

Drawing blood samples from an umbilical catheter is a sterile procedure. Samples may be obtained for blood gas analysis and to obtain laboratory specimens. Necessary items include a syringe for initially aspirating IV fluid and blood from the catheter, a heparinized blood gas syringe (if a blood gas sample is to be obtained), a syringe for aspirating laboratory samples (if laboratory samples are to be obtained), and a syringe containing flush solution.

The reinfusion method of obtaining blood samples is described. This practice involves returning the "discard" blood and, in theory, minimizes patient blood loss.[6] Remove the stopcock cap and place it down so that sterility will be maintained. Attach the empty aspiration syringe to the stopcock. Turn off the stopcock to the IV solution so that the IV solution stops flowing. Aspirate 1 to 2 mL from the catheter into the dry aspiration syringe (Fig. 7.11). The IV fluid is prevented from infusing, and aspiration clears the catheter of IV fluid. Turn the stopcock to the neutral position (Fig. 7.12), remove the syringe while keeping the tip sterile, and replace it with the heparinized blood gas syringe or laboratory sample syringe. The neutral position of the stopcock prevents contaminating the sample with IV fluid and prevents blood loss from the infant.

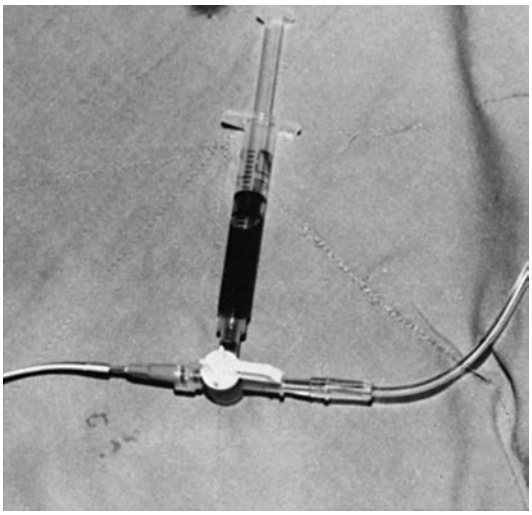

FIGURE 7.11 Stopcock off to IV solution; 1 to 2 mL aspirated into syringe.

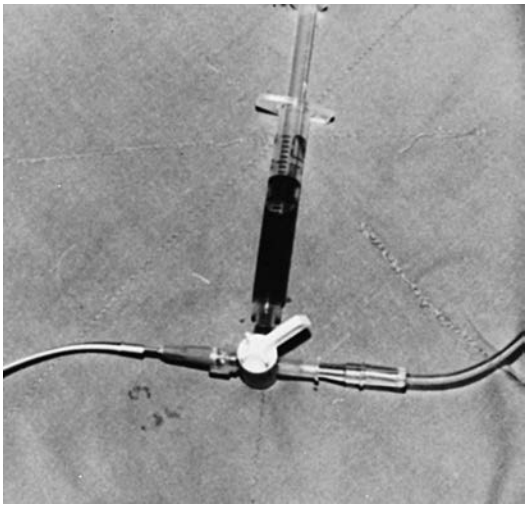

FIGURE 7.12 Stopcock in neutral position.

CAUTION: Never allow blood to drip from an open stopcock. Attach the sample syringe.

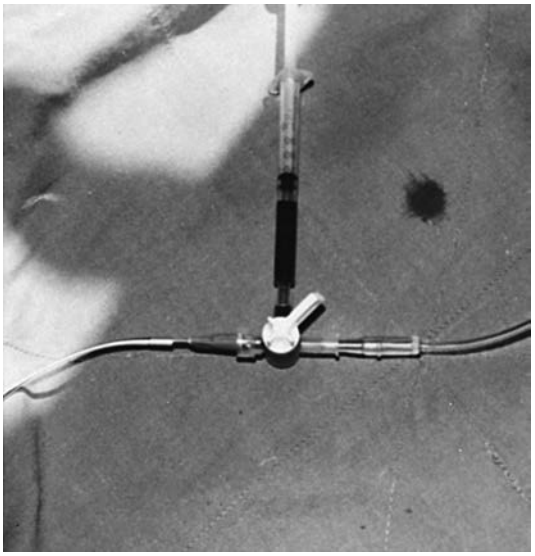

FIGURE 7.13 After blood is aspirated into heparinized 1-mL syringe, stopcock is placed in neutral position before syringe is removed.

Turn the stopcock off to the IV fluid. Using steady, even pressure, aspirate blood into the laboratory or heparinized blood gas sample syringe. Turn the stopcock to the neutral position, and remove the syringe (Fig. 7.13).

For blood gas samples, remove any air from the syringe (because air bubbles in the sample will cause an artificial rise in PaO_2 and a slight fall in $PaCO_2$), cap the end, and chill it to preserve values. Attach the aspiration syringe containing the aspirated blood and IV fluid. Slightly aspirate to remove any air in the stopcock, and then slowly infuse the aspirated blood and IV fluid. Turn the stopcock to the neutral position, and remove the aspiration syringe. Replace the now-empty aspiration syringe that had aspirated blood and IV fluid in it with the syringe filled with flush solution. Turn the stopcock off to the IV fluid. Slightly aspirate to remove any air in the stopcock, and then slowly infuse the flush solution until the catheter is clear. Return the stopcock to the off position, allowing the IV fluid to now infuse. Replace the stopcock cap. Record the amount of blood removed from the infant and the amount of flush solution used to clear the catheter. Newer methods of gradual, automatic aspiration should be considered if available to prevent abrupt changes in arterial or cerebral pressure.

To ensure the integrity of all connections, the stopcock and other connections must be visible at all times. Do not place the stopcock and other connections under linen, because this would hamper the immediate detection of an accidental disconnection that would cause severe blood loss in the infant. Immediately remove any air in the tubing or catheter because air is a potential embolus. It is best removed through the stopcock. If the air has passed the stopcock, it can be aspirated back into a syringe easily.

Obtaining an arterial blood gas specimen from a high UAC is better tolerated in premature infants when the entire procedure is done slowly. Premature and ill term infants have limited cerebral blood flow (CBF) autoregulation. Rapid drops and rises in CBF, especially in the first few days of life, can contribute to neuronal injury and intracranial bleeding. **Rapidly obtaining blood samples from a UAC has detrimental hemodynamic effects on CBF thus, sampling from the UAC should be done slowly.**[6]

Umbilical Vein Catheter Placement

PROCEDURE

Determine the size and length of the catheter to be inserted. A 5-Fr catheter is normally used in the UVC placement procedure. The ELBW infant may require a 3.5-Fr catheter. **To determine the length of the catheter to be inserted, the distance from the umbilicus to the sternal notch should be measured and multiplied by 0.6.** Complete steps for the placement procedure are found in the Umbilical Artery Catheter Placement section earlier in this chapter. The only difference is that the vein is used instead of the artery. The catheter can be advanced to the desired position easily. **The vein is usually gaping open and does not require dilation.** The catheter should lie in the inferior vena cava with the UVC above the diaphragm but below the right atrium of the heart. Catheter position must be ensured. Historically, **position confirmation was by radiologic examination**, using the anteroposterior (AP) and lateral views. **Ultrasonography is rapid and determines correct catheter tip placement** and prevention of complications such as pericardial effusion and tamponade.[18] **UVCs do not have the "leg loop" found on the lateral x-ray film of UACs.** A UVC follows the inferior vena cava and is positioned slightly to the right of the patient's vertebral column. The catheter should be secured in

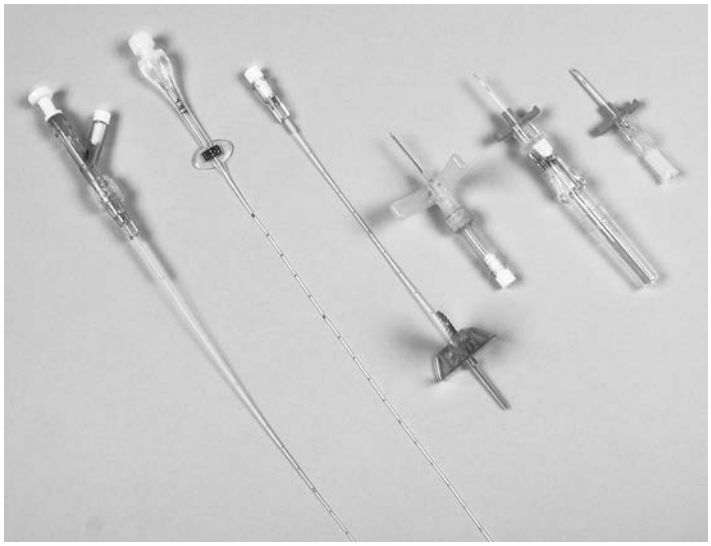

FIGURE 7.14 Peripherally inserted central catheters and introducers. (Courtesy Becton, Dickinson and Company, Franklin Lakes, NJ.)

the same manner as for a UAC. **The nursing care and procedure for drawing blood samples from a UVC are the same as those for a UAC.**

Peripherally Inserted Central Catheter Placement

PICCs are silicone or polyurethane products available in a variety of styles including single catheter and needle introducer to a complete insertion kit with instruments, skin disinfectant, and cap, mask, gown, and gloves. Some products provide a stylet and several feature breakaway (splittable) needle introducers. PICCs are available in a variety of sizes for the neonatal population from 20 gauge (3 Fr) to 28 gauge (1.2 Fr).

PICCs typically are inserted for the following reasons:

- **Infants who require IV access that is expected to be necessary for an extended period**
- **Infants with limited access**
- **As a transition from umbilical catheters for infants weighing less than 1000 g**
- **As a first-line catheter for infants weighing 1000 to 1500 g**
- **Infants with gastrointestinal anomalies, necrotizing enterocolitis, or gastrointestinal diseases that will require surgical correction**

PICCs have long been used to provide highly concentrated parenteral nutrition and hyperosmolar medications.[1,43,52] These catheters are relatively easy to insert, affordable, and low maintenance and preclude surgical placement of central venous catheters. **Due to the extensive dwell time, PICCs significantly reduce or eliminate the need for repeated painful procedures such as peripheral venipunctures, thus improving patient and parent satisfaction.**

PROCEDURE

The insertion sites for PICC lines include the brachial cephalic veins, the axilla, the scalp vessels, and the saphenous veins. This sterile procedure can be performed when the infant is on a radiant warmer or in an incubator. A video demonstrating this procedure is available.[28]

For an arm or hand insertion, measure the distance from the insertion site to the axilla and then to 1 cm above the nipple line. If the catheter is to be inserted in the scalp, measure from the insertion site to 1 cm above the nipple line, and for a leg insertion, measure from the insertion site to 1 cm above the umbilicus or to the level of the inferior vena cava.

Determine the size and length of the catheter to be inserted—PICC and introducer: 20 to 28 gauge, varying lengths 20- to 65-cm catheter (Fig. 7.14). Recommendations to trim lengthy catheters vary with manufacturer. A national survey found that 75% of respondents trim catheters. Devices supplied

by the catheter manufacturer for catheter trimming resulted in a precise cut, whereas scissors produced a ragged cut.[43]

A eutectic mixture of lidocaine and prilocaine (various manufacturers) anesthetic cream or a local anesthetic can be considered before the procedure begins, but these should be used cautiously because of variable absorption rates and the potential for cardiovascular collapse in neonates (see Chapter 12). Place the infant in the supine position on a radiant warmer bed or in an incubator. Ensure continuous temperature monitoring. Skin temperature should remain between 36°C and 37°C (96.8°F and 98.6°F). Provide appropriate oxygenation and ventilation. Ensure cardiorespiratory and oxygen saturation monitoring.

Restrain the infant's hands and feet to prevent him or her from contaminating the sterile field and interfering with the placement procedure, or swaddle the infant, with the site to be used exposed. For hand or arm insertion sites, turning the infant's head toward the insertion site will cause a slight occlusion of the jugular vein so that, as the catheter is passed into the subclavian vein, the risk for the catheter advancing upward into the jugular is diminished.[52]

Don cap and mask. Open the PICC insertion tray; most units now use commercially available disposable trays. PICC insertion tray contents are shown in Fig. 7.15. Open the PICC and introducer (if packaged separately from the PICC insertion tray). Wash hands and dry with sterile towel before the procedure. Put on a sterile gown and gloves. Connect a lipid-compatible T-connector extension tubing to a syringe of flush solution, and fill the entire apparatus.

Grasp the extremity to be used with sterile gauze so that an occlusive dressing can be applied to the distal part of the extremity, thus allowing manipulation of the extremity and precluding contamination of the insertion site by bacteria from distal sites. Cleanse the site with either povidone-iodine or chlorhexidine three times, and allow the site to air-dry. Remove the povidone-iodine with alcohol. For infants weighing less than 1000 g, use sterile water. **Avoid using an excess of skin disinfectant so the infant is not lying in the solution during the procedure. Any residual skin disinfectant should be washed off the infant carefully after the procedure is completed**. Place sterile drapes under the exposed insertion site. Reglove with new sterile gloves. Place the introducer, catheter either with or without stylet (clinician's choice), syringe, and sterile forceps on the sterile field near the planned insertion site. Insert the catheter into the introducer, being cautious if a stylet is used not to let the stylet extend beyond the tip of the introducer.

Insert the introducer tip at a flat angle to access the vein. The introducer is *not* advanced into the vein; it is used only as an introducer. At this point, there will probably be no blood return. Once the introducer is in the vein, pick up the catheter with

FIGURE 7.15 Disposable tray used for PICC insertion. (Courtesy Becton, Dickinson and Company, Franklin Lakes, NJ.)

the sterile forceps and gently advance the catheter to the premeasured length. Blood should fill the catheter. If the catheter is not advancing, pull the catheter back beyond the point of the introducer and reattempt to cannulate the vein. Once the catheter is advanced to the premeasured length, remove the stylet if used, and attach an empty sterile syringe. If a breakaway cannula is used, gently retract the cannula and slowly peel it apart to prevent premature breakage. Blood should be aspirated easily with a syringe. Flush the catheter with 0.5 to 1 mL of flush solution. Secure the catheter using sterile tape or nonfiber adhesive strips at the insertion site. Wrap extra catheter material into a coil above or below the joint to prevent occlusion. Attach the lipid-compatible T-connector extension set, and secure it to the extremity. Dress the insertion site, extra catheter loops, and PICC catheter to the T-connector area with a sterile, transparent occlusive dressing. Ensure that the dressing does not completely encircle the extremity causing a tourniquet effect. Label the dressing with the gauge and length of the catheter, the line type (PICC), and the initials of the insertion person.

Catheter position must be ensured by anteroposterior and lateral x-ray films, ultrasonography, or echocardiography.[16] **For PICC lines inserted in the upper extremities, axillae, or scalp vessels, the catheter should lie in the superior vena cava above the right atrium of the heart. Catheters placed in other vessels have a significantly higher rate of thrombus formation and infection.** An increase in PICC line infections is directly related to increased frequency of venipunctures, especially when no concurrent antibiotics are being used.[12] For **PICC lines inserted in the lower extremities, the catheter should lie in the inferior vena cava below the right atrium of the heart.** Catheter placement in the right atrium can lead to complications of dysrhythmias, pleural effusion, and perforation with cardiac tamponade.[52]

NURSING CARE OF PICCS

Infants should be positioned to prevent dislodgement or kinking of the catheter. Diapers are effective for preventing the feet and toes from becoming entangled in the IV tubing. If the infant is receiving phototherapy and thus is not diapered, leg restraints or positioning aids may be indicated. A mitten or positioning aids are useful to prevent hands and fingers from contacting the catheter dressing and IV tubing. Positioning the catheter away from the extremities lessens the chance of accidental dislodgement. The IV tubing should be changed according to the standard of care. **Observe for disconnection of tubing or a loose connection, and ensure an intact and occlusive insertion site dressing.**

The occlusive dressing should be changed only when the integrity of the dressing has been lost. A small amount of blood at the insertion site is not a reason to change the occlusive dressing. **Maintaining integrity of the occlusive dressing is instrumental in decreasing the risk for infection.**

Changing the current dressing is indicated when it is no longer occlusive. The occlusive dressing is changed under sterile conditions. The person performing the dressing change dons a cap, mask, and sterile gloves. Changing the dressing entails removing the transparent film covering the area, cleaning the insertion site with either povidone-iodine solution or chlorhexidine, allowing this to dry, and then cleaning the site with sterile water to remove the preparation agent from the skin. If the nonfiber adhesive tape or strips are no longer adhesive, they are replaced. Dress the insertion site, extra catheter loops, and PICC catheter to the T-connector area with a sterile, transparent occlusive dressing. Ensure that the dressing does not completely encircle the extremity causing a tourniquet effect. Label the dressing with the gauge and length of the catheter, the line type (PICC), and the initials of the insertion person.

Because of the small gauge, PICCs are not routinely used for blood sampling. Clotting of the catheter may rapidly occur. Because the IV tubing does not contain a stopcock, significant blood loss and introduction of air into the venous circulation can occur.

Peripherally Inserted Midline Catheter

In infants not requiring or unable to receive a central catheter (vena cava placement) yet still needing IV access for a few days such as for antibiotic therapy, a peripherally inserted midline catheter (PIMC) can be used. PIMCs are inserted to the midclavicular line. These products are similar to PICCs and are available as a single needle introducer and catheter or as a complete kit.

Removing Umbilical Artery, Vein, and Peripherally Inserted Central Catheters

When the UAC, UVC, or PICC is no longer needed, it is removed. For UAC catheter removal, make certain the cord tie is snug. Sterile gauze is needed, and a suture removal kit should be available if the catheter was sutured in place. Turn off the stopcock to the patient and the IV fluid. Withdraw the catheter to 3 cm, and leave it in place for 30 minutes before withdrawing it completely. This procedure works well for infants with respiratory or abdominal issues because it avoids the application of external pressure to the abdomen. Alternatively, withdraw the catheter slowly over several minutes, allowing for the artery to spasm. Pinch the umbilical stump with the sterile gauze for 5 minutes until hemostasis is achieved. Observe the umbilicus for active bleeding or oozing. Observe the lower extremities and buttocks for diminished perfusion secondary to a thrombus or embolus.

The procedure is similar for UVCs, with the exception that the catheter can be slowly withdrawn in one step. Pinch the umbilical stump with the sterile gauze for 5 minutes until hemostasis is achieved. Observe the umbilicus for active bleeding or oozing. Observe the patient for respiratory distress secondary to a pulmonary embolus.

For PICC removal, clamp the catheter, turn off the IV fluid infusion, and withdraw the catheter slowly and steadily. Apply pressure over the insertion site with the sterile gauze for 5 minutes until hemostasis is achieved. Observe the insertion site for active bleeding or oozing. Ensure that the entire catheter was removed.

Oxygen Saturation Monitoring by Pulse Oximetry

Oxygen saturation monitoring by *pulse oximetry* involves placing a small sensor on the infant in such a manner that his or her finger, toe, foot, or wrist comes between the light source and the photoreceptor. The light source emits wavelengths of light in the red and infrared spectrums. The difference between the absorption of the light is picked up by the receptor that is placed directly opposite the light source. **The calculation of the ratio of oxyhemoglobin and deoxyhemoglobin is displayed as the percent of oxygen saturation.** Key to accuracy of the monitor is that the light source and the receptor must be directly opposite each other over an area in which a pulse can be detected.

Oxygen saturation monitoring provides continuous and instantaneous readout of the oxygen saturation in the infant. In comparison with a blood gas analyzer, which calculates the relative oxygen saturation based on established nomograms, **the oxygen saturation monitor measures the actual saturation of the hemoglobin.** Calculated values using standard nomograms do not reflect shifts in the affinity of oxygen for hemoglobin based on changes in the patient's temperature, pH, PCO_2, or 2,3-DPG.

An inorganic phosphate produced in red cells; 2,3-DPG binds to the beta chain of reduced hemoglobin (Hb), lowering Hb's affinity for O_2 and by extension, facilitating O_2 release to tissues, causing a "right shift" of the O_2 dissociation curve. 2,3-DPG further shifts the curve to the right by lowering the red cells' pH. When transfused, red cells regain 50% of the 2,3-DPG within 3 to 8 hours and 100% within 24 hours.

The oxygen saturation monitor relies on adequate perfusion to the site and the ability to detect arterial pulsations; thus, if it is placed distal to a blood pressure cuff, the reading will be inaccurate while the cuff is inflated. Newer models of pulse oximetry reduce the artifact that results from motion and low perfusion. These newer models also are indifferent to ambient light, whereas older models were affected by light sources such as phototherapy. Newer neonatal probes have built-in external light source protectors. **Pigmentation of the patient's skin may produce artificially high readings, especially at lower oxygen levels.[37] However, a recent comparison of two commonly used pulse oximeters found no significant difference in systematic bias based on skin pigment (comparing darker to lighter pigmentation in infants with hypoxemia) with either oximeter.[16]**

Oxygen saturation is more indicative of the total oxygen content of the blood than is PaO_2 and is the most sensitive to hypoxemia when it is on the steep part of the oxygen dissociation curve (see Fig. 7.1). **Keeping the SaO_2 at 90% to 92% keeps the infant in a normoxemic state under most conditions.** Oxygen saturation monitoring by pulse oximetry generally is considered reliable and practical for use in infants over a wide range of birth

weights and postnatal ages.[2] *Pulse oximetry saturation (SpO_2)* **values vary significantly from measured arterial tension values obtained with an arterial blood gas specimen.**[37] A contributing factor may be that the calibration of pulse oximeters typically has been performed on healthy adults. A compelling argument for the use of both *pulse oximetry* and *transcutaneous oxygen monitoring* in critically ill infants can be made because each monitor has its own shortcomings.

Pulse oximetry monitoring is common in neonatal care. Many infants in NICUs require prolonged monitoring, and a long-lasting oximeter probe could offer a substantial cost savings. **No complications are associated with the use of oxygen saturation monitoring other than the potential for skin trauma caused by adhesive on the probe.** Newer probes held in position by gentle elastic pressure have no adhesive touching the infant's skin.

In the asymptomatic newly born infant, the incidence of congenital heart anomalies is approximately 1% to 2% of live births, with one-fourth of these having critical congenital heart defects (CCHDs). CCHD lesions are ductal dependent or require cardiac catheterization or surgery before 1 year of age, with most requiring intervention within the first month. If not detected early, organ hypoperfusion and hypoxemia occur as the infant continues to transition to adult circulation. **Detection of CCHDs before discharge allows medical and surgical interventions that may be lifesaving.** Multiple organizations in the United States[10,24] and globally[25,41,42] have recommended routine screening of all infants after 24 hours of life and before discharge. In 2011, the U.S. Department of Health and Human Services (USDHHS) added screening for CCHDs to the Recommended Uniform Screening Panel.[48] The American Academy of Pediatrics endorsed the USDHHS recommendation.[23] Refer to a full discussion in Chapter 31.

Noninvasive Oxygen–Carbon Dioxide Monitoring

END-TIDAL CARBON DIOXIDE MONITORING

End-tidal CO_2 monitors use either sidestream or mainstream analysis. For sidestream analysis, the endotracheal tube has a second narrow lumen that opens at the end of the endotracheal tube. Gases are analyzed from samples taken from the end of the tube. **The advantages of this system are that there is no increased dead space in the ventilator circuit and less chance of inspiratory gases contaminating the sample.** The disadvantage to this method is that secretions may pool at the tip of the endotracheal tube and occlude the sampling port. The response time to changes in carbon dioxide content is slower than when mainstream analysis is used.

Mainstream analysis of carbon dioxide samples gases in the ventilator circuit. These gases are thought to be reflective of gases at the tip of the endotracheal tube. **This method requires a separate chamber attached to the end of the endotracheal tube adapter, thus adding increased dead space and additional weight at the endotracheal tube adapter.**

A comparison of sidestream and mainstream analyses of end-tidal CO_2 found that distal values were higher than proximal values and that distal values correlated more closely with $PaCO_2$ values.[47] This discrepancy was thought to result from the mixing of end-tidal gases with fresh gases in the ventilator circuit. **In an infant with a large alveolar-arterial (A-a) gradient, $PetCO_2$ monitoring cannot be relied on for accuracy. In premature infants, it may be useful if the lung disease is mild to moderate; in infants with normal lung function, this method is reliable.**[45]

The waveform output of the end-tidal CO_2 monitor can be used clinically if the clinician understands how the waveform corresponds to the exchange of gases in the lung (see Fig. 7.2). **The waveform has a sharp rise on expiration that reflects the carbon dioxide content of various lung areas. This expiration is followed by a plateau that reflects the cessation of dead space gases and the measurement of alveolar gas. At the end of the plateau is a sharp drop that reflects the inspiration of fresh gases with minimal carbon dioxide content.** When using the monitor, the clinician should recognize that a sharp rise indicates compromised exhalation, such as in reactive airway disease. **Partially plugged and dislodged endotracheal tubes will change the angle of rise on the capnogram.** The plateau phase of the capnogram can be altered by severe hypotension or decreased cardiac output secondary to an altered minute ventilation-perfusion ($\dot{V}/\dot{Q}$) mismatch (as in pulmonary embolus, cardiac arrest,

persistent pulmonary hypertension, atelectasis). **No waveform or failure of the waveform to change indicates ineffective respiration (dislodged endotracheal tube).**

TRANSCUTANEOUS OXYGEN–CARBON DIOXIDE MONITORING

Skin oxygen tension ($TcPO_2$) and carbon dioxide tension ($TcPCO_2$) are measured by using one or two electrodes, depending on the model and brand of the monitor. The electrodes, once positioned on the skin, heat the area under the probe and cause certain physiologic changes as discussed. **Oxygen and carbon dioxide that diffuse through the heated skin are measured by the electrode, and the value is digitally displayed on the monitor. If intervals between calibration are longer than 4 hours, the readings are subject to drift.** The calibration procedures vary with the instruments used. Inherent in the calibration process is the necessity to change the position of the skin electrode on the infant. **Better correlations are found when the instrument is calibrated every 4 hours, the temperature is set correctly, and the infant is well perfused and normothermic. If the temperature of the probe cannot be maintained at 43°C to 44°C (109.4°F to 111.2°F), a lower temperature should be selected to avoid possible burns.** At a lower temperature, the $TcPO_2$ monitor can be used to monitor trends but should not be interpreted as actual PaO_2 values. The range of accuracy of $TcPO_2$ monitors is limited; hypoxia (less than 40 mm Hg) and hyperoxia (greater than 120 mm Hg) may not be accurately reflected.

In an infant with suspected significant right-to-left shunting through a patent ductus arteriosus such as in persistent pulmonary hypertension, two transcutaneous oxygen electrodes can be used: one preductally (right shoulder) and the other postductally (lower abdomen or legs). Significant right-to-left shunting through the patent ductus arteriosus is present when the preductal oxygen tension is significantly higher than the postductal oxygen tension.

The disadvantages of the use of transcutaneous monitoring are that the instrument requires frequent calibration; requires the use of a heated electrode, which may burn the skin, especially in low-birth-weight (LBW) infants; requires a 15-minute period after calibration to heat the skin to the correct temperature; and has a 15- to 20-second delay in the readings compared with the patient's real-time values. The advantages are that it is not invasive, does not require the removal of blood for analysis, and displays a continuous readout of skin oxygen–carbon dioxide tensions.

NURSING CARE OF INFANTS WITH NONINVASIVE TRANSCUTANEOUS OXYGEN AND CARBON DIOXIDE MONITORS

The electrode can be placed on any portion of the infant's body as long as good contact between the electrode and the skin is maintained. Uneven areas of skin such as over bones and joints should be avoided because of poor contact between the membrane and the skin surface. The infant should not lie on the electrode. Placing the infant on top of the electrode increases the pressure on the underlying capillaries, thus affecting the flow of blood under the probe and resulting in a drop in $TcPO_2$ values. **Because of the heat generated by the electrode (43°C to 44°C [109.4°F to 111.2°F]), small red areas resembling first-degree burns are produced on the infant's skin. To minimize trauma to the infant's skin, the electrode should be repositioned every 2 to 4 hours, depending on his or her skin sensitivity.** Grouping of nursing interventions has resulted in minimizing the time that the infant receives less-than-optimal oxygenation.

Cardiorespiratory Monitoring

The chest leads are applied in a triangular pattern on the infant's chest. Integrity of the leads must be ensured. Allowing the contact gel to dry or inadvertently dislodging the lead during procedures such as x-ray examination, echocardiography, and lumbar puncture may account for inaccurate tracings. Various components of the electrocardiogram (ECG) pattern may be diagnostically helpful. The QRS complex should be monitored for baseline height and width. **A sudden decrease in QRS complex height that is not caused by artifact may be an indication of pneumothorax.** The QT interval is helpful in diagnosing hypocalcemia in some infants. Other portions of the strip may be evaluated for electrolyte imbalance and possible cardiac ischemia. Hyperkalemia can induce arrhythmias, including heart block, ventricular tachycardia and fibrillation, and asystole. Initially the ECG will

show peaked T waves with a narrow base. As the potassium level rises, the P dampens, the PR interval increases, and the QRS widens. Further increases in the potassium value lead to absent P waves, QRS merging with the T wave to form a sine wave, followed by fibrillation, and then asystole.[27]

Humans display variability in vital signs because of the constant adjustments by the sympathetic and parasympathetic nervous systems. Vital sign variability in the healthy infant is maintained near a baseline value. When stressful events such as late-onset sepsis, intraventricular hemorrhage, or severe chronic lung disease are present, there is a corresponding change in vital signs and diminution in variability. Infants developing late-onset infection may exhibit subtle, nonspecific signs in advance of a clinical diagnosis. To aid in detecting heart rate changes that may indicate developing infection, some NICUs now use the HeRO system (Medical Predictive Sciences, Charlottesville, VA). Heart rate changes over a 5-day period are tracked allowing health care personnel to follow patient trends. **Loss of beat-to-beat variability and rising heart rate warrant investigation.** As with any instrument, use of this device requires patient assessment and judgment.[19]

Blood Pressure Monitoring

Arterial pressure monitoring may be accomplished via the UAC attached to a transducer and monitor. Central venous pressure monitoring may be carried out in the same manner using the UVC. The same type of transducer may be used for either arterial or venous pressure recording.

Some research has indicated that the predictive value of peripheral blood pressure screening for CCHD is small and that oscillator blood pressure measurements are less accurate than pulse oximetry screening to detect CCHD.[5] This failure to detect CCHD is more pronounced in aortic arch obstructive defects.

Point-of-Care Testing

The Centers for Medicare and Medicaid Services regulates POCT through the Clinical Laboratory Improvement Act (CLIA).[9] **Federal regulations require initial education about POCT procedures, as well as annual reassessment of competency.** The quality of these tests is imperative to ensure proper diagnosis and treatment, and the CLIA regulations strive to ensure quality testing.

The accuracy of whole blood glucometers compared with laboratory values may vary depending on hypoxia, hematocrit, and elevated triglyceride values. Accuracy also depends on the product that is being measured, because some glucometers measure glucose only, whereas others measure total sugars, including glucose, galactose, maltose, and xylose. In addition, the clinician must remember that an **approximately 11% difference exists between plasma glucose (laboratory sample) and whole-blood glucose (POCT device). The POCT value should be multiplied by 1.11 to determine a more approximate plasma value.**[13] A variance of accuracy also exists with bedside electrolyte assessment devices. Transcutaneous neonatal bilirubin assessments require correlation between the serum bilirubin value and each device, institution, and patient population for which it is used.[11] As neonatal care advances, rapid availability of patient information will become more and more crucial. Expect continuous expansion of POCT.

Event Monitoring

The advancement of physiologic monitors with memory capability has enhanced the ability of the practitioner to **review the physiologic status of the infant as measured by multiple physiologic parameters for the past 24 to 48 hours**. In many NICUs, the monitor output is integrated into the electronic or computerized chart. This integration allows the care provider to retrieve the data from the monitors into the chart at preselected times, either prospectively or retrospectively. **When the monitors are programmed with critical value ranges, any deviation outside these ranges is noted as an event, which can then be reviewed, tallied, or otherwise annotated.** For care providers at the bedside, the challenge is to keep iatrogenic events (e.g., lead removal, excessive activity of the infant, a stopcock turned the wrong direction) minimized such that the infant's record is as valid a reflection of actual physiologic status as possible. Any circumstances noted at the time of the event that may produce false readings should be recorded so that when the infant's record is reviewed, these events can be placed in context of the circumstances at the time.

BOX 7.1 CRITICAL FINDINGS
COMPLICATIONS OF INDWELLING CATHETERS

- Umbilical artery catheters
  - Ischemia from thrombi, emboli, or arterial spasms
  - Hemorrhage caused by catheter dislodgement or loose connections
  - Infection
  - Malposition
- Umbilical vein catheters
  - Thrombus formation leading to pulmonary embolization
  - Thrombus formation in portal vessels
  - Hepatic necrosis
  - Intestinal ischemia
  - Hemorrhage caused by catheter dislodgement or loose connections
  - Cardiac complications: dysrhythmias, myocardial perforation, pericardial effusion
  - Infection
- Peripherally inserted central catheter lines
  - Occlusion
  - Clotting
  - Infection
  - Malposition
  - Cardiac complications: dysrhythmias, myocardial perforation, pericardial effusion
  - Breakage and leaking
  - Phlebitis
  - Peripheral edema
  - Vascular erosion into the pleural space[4]

COMPLICATIONS

UACs act as foreign bodies, causing fibrin deposition and thrombus formation around the catheter. Although most catheters are associated with thrombus formation, it is of clinical significance in less than 10% of patients (Box 7.1). **A common problem associated with major complications of UACs is ischemic disease resulting from emboli or arterial spasms. In such cases, the catheter should be removed immediately and antithrombin therapy should be considered.** Although vasospasm is common, usually it does not require immediate removal of the catheter. **Blue discoloration, commonly called "catheter toes," is seen, rather than blanching.** Obviously, **a hemorrhage may occur when the catheter slips out or when any of the various connections loosen.** For reasons such as these, **UACs require constant attention.** If the **lower extremities or buttocks blanch, the catheter should be removed immediately and antithrombin therapy considered.** The benefit of antithrombin therapy must be balanced against the increased risk for intracranial hemorrhage.

To prevent bleeding once the catheter is removed, immediately pinch the subumbilical area with sterile gauze for 5 minutes until hemostasis is achieved. **Avoid downward abdominal pressure that may compromise respiratory effort.** When the color has returned to the affected area and the infant is stable, replacement of the catheter can be considered. **If vasospasm occurs in one leg or foot, apply warm wraps (diapers wetted with warm water or chemical heel warmers) to the opposite leg, or apply wraps to the upper extremities, thereby producing a reflex vasodilation to the legs. However, inherent in this action is the hazard of obscuring recognition of compromise in that extremity. The wraps should be reheated every 10 to 15 minutes until the spasm has resolved. The skin temperature of the infant must be greater than 36°C (96.8°F) for wraps to be effective.**

UVCs may cause thrombus formation. Thrombi can result in pulmonary embolisms. Clots may form in the portal vessels, resulting in portal hypertension. Hepatic necrosis, gut ischemia, and hemorrhage have been associated with UVCs. Other complications include dysrhythmias, myocardial perforation, pericardial effusion, and endocarditis.

PICCs that are placed in central veins have complication rates lower than those placed in noncentral veins.[51] Complications include occlusion, clotting, infection, sepsis, phlebitis, leakage, extravasation, peripheral edema, malposition, catheter migration, cardiac tamponade, and catheter breakage.[52] **Bacteremia, always a major concern, will require the removal of the catheter if the blood culture remains positive for more than 24 hours. To prevent central line–associated bloodstream infection (CLABSI), establishment of and strict adherence to a care bundle is beneficial.[8]** Bundle items for insertion include a procedure cart with sterile perimeter,

skin disinfection, and strict sterile technique. Maintenance items include handwashing, use of gloves, attention to PICC access and fluid tubing changes, and daily CLABSI surveillance. Refer to a full discussion in Chapter 16. Occlusion sometimes may be treated with clot-dissolving agents. Establishment of a PICC team to insert and manage these devices, catheter tip placement in the superior or inferior vena cava, and heparinized solutions have been shown to reduce complications. In an emergent situation, evaluate catheter tip placement before administering medications or fluid boluses in case of catheter malposition and cardiac tamponade.

CONTROVERSIES

Clinicians continue to disagree on the optimal placement site for UACs. However, a Cochrane review and subsequent update determined that **high UACs resulted in fewer vascular complications than did low UACs and recommended the exclusive use of high placement for UACs.**[3] Prophylactic administration of antibiotic agents is not indicated.[33] Use of the UAC for infusion of antibiotic agents, calcium, hyperalimentation solutions, or blood varies, and no definitive studies are available. Blood cultures can be drawn from the UAC for up to 6 hours after insertion. The use of heparin in the infusate has been controversial because heparin decreases catheter occlusion but not thrombosis.[34] In addition, heparin use in a flush solution alone is not beneficial in preventing catheter occlusion.

Enteral feeding with an umbilical line in place lacks definitive studies; however, this practice is more common than was previously thought. A *Cochrane* review found that trophic enteral feedings were not detrimental.[30] Select NICUs provided trophic and more substantial enteral feedings with umbilical catheters in place.[21]

Routine monitoring of all infants receiving intermediate or intensive care is the standard of care. Indwelling catheters for blood pressure monitoring have the advantage of continuous readout, but external cuffs are less invasive. There is a continued need for research into the efficacy and safety of umbilical catheters. Box 7.2 cites new research into future possibilities for neonatal physiologic monitoring.

BOX 7.2 WHAT'S NEXT IN PHYSIOLOGIC MONITORING?

1. Intelligent monitoring systems. Rather than signal when a single parameter exceeds a preset threshold, these monitors would integrate multiple data, including patient medications and laboratory results, to provide a more complete view of the patient's status.[2]
2. Telemedicine has demonstrated success in examining and diagnosing retinopathy of prematurity and genetic and neurologic abnormalities.[51] It will now evolve to allow a remote neonatal intensive care unit model where a neonatologist can simultaneously monitor multiple infants continuously—visually and by the integration of multiple data. Virtual rounds as needed, as well as care direction, can occur.[47,50]
3. Telemedicine to provide follow-up care of newborns discharged from NICU, resulting in a decreased need for hospital visits.[37]
4. Use of nasogastric tubes to monitor intraabdominal pressure of VLBW preterm infants (<1500 g) to evaluate for feeding intolerance.[7]
5. Electrode-free, noninvasive wireless vital signs monitoring systems.[32,44]
6. Artificial womb for preterm infants <26 weeks of gestation.[15,35,49]

BOX 7.3 PARENT/CAREGIVER TEACHING PHYSIOLOGIC MONITORING

Physiologic Monitoring

1. Placement of umbilical lines is invasive. Educate parents about the following:
   - Placement is painless because the umbilical cord contains no nerves.
   - The point of catheter insertion and where the tip of the catheter is located.
   - The umbilical catheter can be used for numerous functions: administering IV fluid, medications, and blood products; monitoring; and obtaining laboratory specimens.
   - Care should be taken when holding or manipulating the infant to prevent catheter dislodgement and blood loss.
   - Holding the infant out of the incubator and wrapped in blankets obscures visualization of the catheter and connections.
2. The NICU environment can be frightening. Educate parents about the following:
   - The baby is being monitored by various methods, including cardiorespiratory, blood pressure, and transcutaneous monitors.
   - The purpose and a short description of each monitor.

PARENT TEACHING

Important elements of parent teaching are listed in Box 7.3. As with the many other invasive procedures in neonatology, the clinician obtains

permission from the parents for umbilical vessel catheterization and PICC placement. This may be the clinician's first contact with the family and thus sets the atmosphere for future contacts. Although parents initially are hesitant about umbilical catheter placement, generally they are comforted to learn that it will result in a painless way of drawing blood; there are no nerves in the umbilical cord to sense pain. Parents also appreciate that PICC placement will reduce the number of peripheral IV attempts. **Before parents visit the infant, providers need to inform parents about the technology that is being used to monitor the infant** (i.e., umbilical catheter, transcutaneous monitors, cardiorespiratory monitors, blood pressure monitors), including what the technology is registering. Often parents are confused about where the catheter goes once it enters the umbilicus and the purposes of other monitoring devices.

Parents need to be instructed on how to hold their infant while an umbilical catheter or PICC is in place because manipulating the infant may accidentally dislodge the catheter and result in blood loss and potential infection. When the infant is being held out of the incubator and wrapped in blankets, the integrity of the catheter and connections is not easily evaluated. The parents' vigilance around the technology used on their infant can potentially avoid these incidents.

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8 ACID-BASE HOMEOSTASIS AND OXYGENATION

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Accurate interpretation of blood gas values and an understanding of acid-base and oxygenation physiology are essential to the proper diagnosis or management of an ill neonate.[9,33,53] The measurement of arterial blood gases allows an analysis of two interrelated but separate processes: acid-base homeostasis and oxygen-carrying capacity.[1,32,44] This chapter considers the parameters that describe these processes, their measurements, and the effects of proposed treatment on homeostasis.[1,53] Common abbreviations and their meanings are listed in Box 8.1.

Components of arterial blood gases include (1) measured values (Pao_2, $Paco_2$, and pH) and (2) calculated values (oxygen saturation, bicarbonate concentration, and base excess). Some analyzer systems also estimate hemoglobin concentration. **The pH, $Paco_2$, base excess, and bicarbonate components are used to assess acid-base homeostasis,[32,44,56] whereas Pao_2, saturation (Sao_2), and hemoglobin concentration[1,9] are used to assess the adequacy of oxygen-carrying capacity** (Table 8.1).

PHYSIOLOGY

Acid-Base Homeostasis

To review basic chemistry, an acid is a hydrogen ion donor, and a base is a hydrogen ion acceptor. The pH refers to the concentration of hydrogen ions [H^+] in a liquid and reflects the acid-base balance in liquid.[56] The quantity of hydrogen ions is minute, approximately 0.0000001 mole/L. Therefore, the negative log of the hydrogen ion concentration is used to define pH and create a positive, workable number (pH = 7) (Equation 1). **A pH of 7 represents a neutral solution, a pH of less than 7 represents acidity, and a pH of greater than 7 represents alkalinity:**

$$\begin{aligned} pH &= -\log [H^+] \\ pH &= -\log [0.0000001] \\ pH &= -[-7] \\ pH &= 7 \end{aligned} \qquad (1)$$

The Henderson-Hasselbalch equation describes pH as equal to a constant (pK) plus the logarithm of the ratio of the base-to-acid concentration (Equation 2).[10,36] Thus, if there is an increase in the concentration of hydrogen ions (reflected in the denominator), the blood pH value decreases, and acidemia results. Conversely, if there is less acid or more base, the blood pH increases, and alkalemia results.[10]

$$pH = pK + \log \left({}^{base}/_{acid} \right) \qquad (2)$$

The first step in determining acid-base homeostasis is the measurement of pH. The normal human pH is between 7.35 and 7.45. *Acidemia* and *acidosis* are often used interchangeably, but strictly speaking, a pH of less than 7.35 is acidemia, and the process that caused it is acidosis; a pH of greater than 7.45 is alkalemia, and the process that caused it is alkalosis.[33] **Arterial carbon dioxide ($Paco_2$) and bicarbonate [HCO_3^-] values represent the two main components of acid-base homeostasis: (1) the respiratory contribution ($Paco_2$) controlled by alveolar ventilation[1,17,20] and (2) the nonrespiratory or metabolic contribution controlled primarily by renal excretion, retention, or production of HCO_3^-.[1,30,50]** Other factors that affect the nonrespiratory components of acid-base

BLUE type highlights content that is particularly applicable to clinical settings.

BOX 8.1 ABBREVIATIONS

A	Alveolar
a	Arterial
D	Difference
F	Fraction
I	Inhalation, inspired
P	Partial pressure (tension, driving force)
pH	Negative log of hydrogen ion concentration

Combined Abbreviations

Pao_2	Partial pressure of arterial oxygen
Fio_2	Fraction of inspired oxygen
Pio_2	Partial pressure of inspired oxygen
P_{50}	Partial pressure at which hemoglobin is 50% saturated

balance cause a change in $[HCO_3^-]$; thus, $[HCO_3^-]$ is an indicator of the nonrespiratory component.[30,35,50]

RESPIRATORY CONTRIBUTION

Carbon dioxide is produced from cellular metabolism.[1,46] As carbon dioxide is produced, it dissolves in intracellular fluid and can be measured as the partial pressure (P) of the dissolved gas (CO_2). As the pressure of the dissolved gas increases inside the cell, carbon dioxide moves out of the cell and into the blood. Blood transports dissolved carbon dioxide (some combined with hemoglobin as carboxyhemoglobin, most as bicarbonate) to the lung, where the partial pressure in the pulmonary capillary is greater than that in the alveoli,[43] causing carbon dioxide to move into the alveoli down a concentration gradient. **Ventilation is the only method of removing carbon dioxide. The amount of carbon dioxide in the blood is the net result of the body's metabolism (production) and alveolar ventilation (clearance).** Because metabolism does not change greatly and CO_2 diffuses easily across membranes, the only clinically important limitation to CO_2 removal is at the lungs. **Thus, $Paco_2$ reflects alveolar ventilation.**[10,17,20,33]

In the red blood cell, the enzyme *carbonic anhydrase* promotes the combination of a fraction of dissolved CO_2 with water to form carbonic acid (H_2CO_3), which then dissociates into a hydrogen ion $[H^+]$ and a bicarbonate ion $[HCO_3^-]$[1,46]

$$CO_2 + H_2O = H_2CO_3 = [H^+] + [HCO_3^-] \quad (3)$$

TABLE 8.1 NORMAL (ARTERIAL) BLOOD GAS VALUES

BLOOD GASES	VALUES
pH	7.35–7.45
$Paco_2$	35-45 mm Hg
HCO_3^-	18-26 mEq/L
Base excess	(–5) to (+5)
Pao_2	60–80 mm Hg
O_2 saturation	92%–94%

Therefore, an increase in $Paco_2$ (hypoventilation) causes pH to fall. This is called *respiratory acidosis*.[17] **A decrease in $Paco_2$ (hyperventilation) results in less acid formation in the blood and causes pH to rise. This pathophysiologic process is known as *respiratory alkalosis*.**

NONRESPIRATORY (METABOLIC) CONTRIBUTION

Nonrespiratory (metabolic) derangements can also disturb acid-base homeostasis. Normal metabolism produces hydrogen ions. **Blood pH is maintained within normal limits by renal mechanisms for excreting hydrogen ions. Increased production of $[H^+]$ may occur in conditions such as shock with poor peripheral tissue perfusion or genetically determined aberrations of metabolism.**[52] The hydrogen ions produced must be eliminated to avoid a fall in blood pH. Derangements also occur when hydrogen ions are lost (e.g., in gastric fluids) or when bicarbonate is lost (e.g., in diarrheal fluid or ileostomy drainage).[53]

Authorities differ as to the best way to describe nonrespiratory derangements in acid-base status. The traditional approach relies on the measurement of pH, Pco_2, and $[HCO_3^-]$. An alternative description is of acid-base status in terms of (1) strong ions (Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-), strong because they remain dissociated at normal human blood pH, and (2) weak acids (hemoglobin, albumin, inorganic phosphate), weak because they are partially dissociated at the normal human blood pH. Blood pH in this conceptualization is a function of the difference between strong cations and strong anions, the strong ion difference (SID). As an example, the alkalosis associated

with the loss of gastric fluid would be described exclusively in terms of the loss of [Cl^-], with the loss of [H^+] making no independent contribution to the resulting alkalemia. Advocates maintain that the measurement of SID leads to a greater understanding of the causes of nonrespiratory and mixed acid-base derangements.[16,24,29,46] Others favor staying with the traditional bicarbonate-centered model.[15,34] The present discussion focuses on the traditional bicarbonate-centered approach. Readers are referred to recent reviews for comparisons of the two methods.[29,34]

A fall in blood [HCO_3^-] might indicate that bicarbonate, a base and therefore a hydrogen ion acceptor, has been used up by the addition of [H^+]. As shown in Equation 3, a change in [HCO_3^-] might also reflect a change in Pco_2. This difficulty is overcome in blood gas analyzers by correcting the Pco_2 (graphically) to 40 mm Hg, yielding a "standard bicarbonate" concentration.[46] The standard bicarbonate concentration and the buffering properties of hemoglobin are combined in the concept of base excess (BE). **BE is strictly defined as the amount of base or acid that is needed to restore blood to a pH of 7.4 at a normal Pco_2 of 40 and temperature of 37°C.[2] A positive value suggests a deficit of fixed (i.e., not volatile as with H_2CO_3) acid or an excess of base; a negative value indicates an excess of fixed acid or a deficit of base.[46] An abnormality of the standard bicarbonate concentration or BE indicates a process of nonrespiratory (metabolic) alkalosis[30] or nonrespiratory (metabolic) acidosis.[49]** Caution is needed because various blood gas analyzers do not calculate BE in a similar manner and can vary by 3 to 9 mmol/L.[2] Additionally, BE is commonly calculated using assumptions from adult physiology with a normal bicarbonate of 26, which is significantly higher than what would be considered normal for a premature neonate.[39]

In the Henderson-Hasselbalch equation (see Equation 2), the pH is equal to a constant, pK, plus the logarithm of the base:acid ratio.[1,33,46] By substituting [HCO_3^-] for the base and dissolved CO_2 for the acid[17,46] and multiplying CO_2 by its solubility coefficient (0.03 mEq/L/mm Hg), the equation becomes the following:

$$pH = pK + \log [HCO_3^- / (Pco_2 \times 0.03)] \quad (4)$$

The value of pK is 6.1; the normal [HCO_3^-] is 24 mEq/L, and the normal $Paco_2$ is 40 mm Hg.

Substituting, we obtain the following:

$$pH - 6.1 + \log (20/1.2) \quad (5)$$

or

$$pH = 6.1 + 1.3 = 7.4$$

Changes in the 20:1.2 ratio have profound effects on the pH.[1,29] The following are two examples:

1. Hypoventilation of sufficient degree that $Paco_2$ is doubled from 40 to 80 (respiratory acidosis) results in a ratio of 24:2.4, or 10. The logarithm of 10 is 1, and the pH would be 6.1 + 1, or 7.1.
2. If a metabolic acidosis reduced [HCO_3^-] from 24 to 12 mEq/L, the ratio would be 12:1.2 or 10:1, and the pH would be 7.1.

MIXED CONTRIBUTIONS

The two most common reasons for acid-base disturbance in humans are the accumulation of carbon dioxide and the production of lactic acid through anaerobic metabolism as a consequence of tissue oxygen deprivation. Thus far, these derangements (Fig. 8.1) have been discussed as if they happened in isolation, but respiratory and nonrespiratory problems often occur simultaneously depending on pathologic processes in the body. **Besides the four single acid-base derangements, there are combined acid-base derangements: (1) respiratory acidosis and metabolic acidosis, (2) respiratory acidosis and metabolic alkalosis, (3) respiratory alkalosis and metabolic acidosis, and (4) respiratory alkalosis and metabolic alkalosis.** The combined acidoses or combined alkaloses have a cumulative effect on the pH, whereas a combination of acidosis and alkalosis tends to negate the effects of each on the pH value.[32,33,44,56]

COMPENSATION

Acid-base homeostasis maintains pH near the normal range. **The body attempts to maintain equilibrium by balancing a pathologic process with a physiologic process or predictable buffering response.**[10,33,53] Thus, if either the respiratory or nonrespiratory components of the acid-base system are deranged, the other system will compensate to counterbalance the primary process. For example, any respiratory process that leads to retention of carbon dioxide (respiratory acidosis) stimulates a nonrespiratory system, in this case the renal system, to

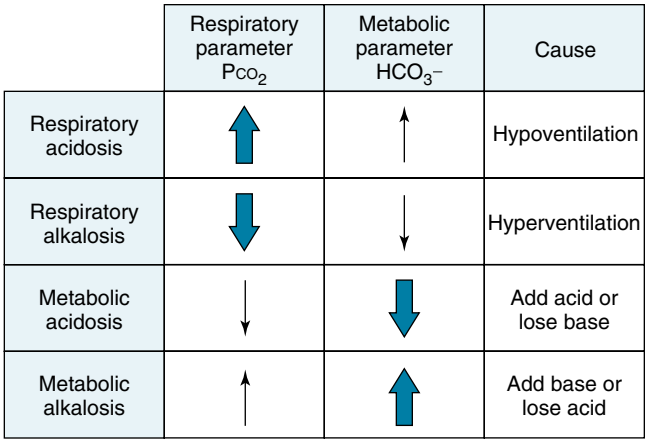

FIGURE 8.1 Acid-base derangements. *Large arrow* indicates primary process that produces change in pH. *Small arrow* indicates compensatory process.

return pH toward normal. **Retention of bicarbonate and corresponding excretion of hydrogen ions are the compensatory renal mechanisms that counterbalance respiratory acidosis.** Given sufficient time, this may increase blood bicarbonate by as much as 3 to 4 mEq/L for each increase of 10 mm Hg in carbon dioxide. Thus, a neonate with a chronically increased $Paco_2$ and a compensatory rise in bicarbonate may attain a near-normal pH.[33]

Metabolic compensations for deranged respiratory processes can go to remarkable extremes, but respiratory compensations for deranged metabolic processes are limited. Hyperventilation cannot lower the $Paco_2$ much below 10 mm Hg in compensation for metabolic acidosis. Similarly, hypoventilation is limited in compensation for metabolic alkalosis by the onset of hypoxemia.[53] Hypoxemia stimulates the respiratory drive, overriding compensatory hypoventilation and limiting the correction of alkalemia.[33]

CORRECTION

Correction of an acid-base disturbance occurs when the health care provider detects the pathophysiologic process and directs therapy at the primary pathologic process, rather than counterbalancing it with a second pathologic process.

For example, if respiratory acidosis is present, the clinician assesses the patient to discover the cause of the carbon dioxide retention and directs therapy at improving minute ventilation, the product of respiratory rate and tidal volume, rather than attempting to increase the retention of bicarbonate.

Oxygenation

The remaining components of the blood gas analysis are the Po_2, hemoglobin, and oxygen saturation.[44] Oxygenation is related to but also distinct from ventilation.[10] **The two main factors contributing to oxygenation at the tissue level are oxygen delivery and oxygen consumption.** Oxygen delivery is the product of the cardiac output and the oxygen-carrying capacity of the blood, whereas oxygen consumption is determined by the metabolic needs of the body's tissues. **Tissue hypoxia may be caused by many different factors that derange the balance between oxygen delivery and tissue needs. An inability of the lung to oxygenate the blood would decrease oxygen delivery because of arterial hypoxemia. Another cause of tissue hypoxia is interference with blood flow, as in heart failure.** The Pao_2 may be normal, but because of heart (pump) failure, oxygenated blood is not delivered in sufficient quantity. Treatment should be directed toward improving cardiac output and tissue perfusion (see Chapter 24). **A third cause of tissue hypoxia is decreased oxygen-carrying capacity of the blood, as with anemia. In this instance, the heart and lungs work adequately. Pao_2 is normal, but the quantity of hemoglobin available for oxygen transport is insufficient. Finally, tissue hypoxia may result from an abnormally high affinity of hemoglobin for oxygen, which leads to a decrease in tissue oxygen delivery. If oxyhemoglobin affinity is increased, oxygen will not dissociate from hemoglobin unless the**

venous, and therefore tissue, Po_2 falls to an unusually low level.[14]

Because Pao_2 measures only the partial pressure of oxygen in arterial blood (i.e., measures the amount of dissolved oxygen gas in the blood), it reflects lung function but not tissue oxygenation. Despite this, the measurement of Pao_2, together with the measurement of hemoglobin and a clinical assessment of tissue perfusion, is currently used as a surrogate of tissue oxygenation.[10]

Two situations merit special comment. First, in a **preterm infant whose retinal development is incomplete, high Pao_2 is associated with retinopathy of prematurity,** especially at a Pao_2 of greater than 100 mm Hg (see Chapter 23). Second, in **patients with cyanotic congenital heart disease, a right-to-left intracardiac shunt affects tissue oxygenation.** A portion of venous blood goes directly to the left side of the heart, then into the systemic circulation, bypassing the lungs. In such patients, the rise in Pao_2 with the administration of oxygen is limited. Low Pao_2 in these patients is not related to lung disease, although lung disease may complicate the picture, but results from blood bypassing gas exchange in the lungs.

Theoretically, **in a normal lung with perfectly matched ventilation and perfusion, the alveolar (Pao_2) and the arterial oxygen tension (Pao_2) should be equal.** This is not achieved. **A difference (gradient) exists between the Pao_2 and the Pao_2.** Minor mismatching of ventilation and perfusion leads to a functional intrapulmonary shunt. This creates an alveolar-arterial oxygen gradient ($D[A\text{-}a]O_2$).[10,17] However, a $D(A\text{-}a)O_2$ greater than 20 mm Hg indicates pulmonary disease.[10]

OXYHEMOGLOBIN SATURATION

Oxyhemoglobin saturation is the percentage of hemoglobin that is combined with oxygen. Oxygen binding with hemoglobin increases as the partial pressure of oxygen increases, but not linearly.[10,56] The oxygen dissociation curve is a measure of the affinity that hemoglobin has for oxygen (Fig. 8.2).

The "30-60-90 rule" is useful in remembering percent saturation and reconstructing the adult hemoglobin dissociation curve if necessary (see Fig. 8.2). At a Pao_2 of 30 mm Hg, the oxygen saturation is 60%; at a Pao_2 of 60 mm Hg, saturation is 90%; and at 90 mm Hg Pao_2, the hemoglobin is 95% saturated. At the normal venous oxygen tension of 40 mm Hg, the oxygen saturation is 75%. Factors that affect this affinity include temperature, pH, and hemoglobin structure. **Hypothermia, alkalemia, hypocapnia, and fetal hemoglobin increase the affinity of hemoglobin for oxygen (shift the curve to the left), whereas fever, acidemia, and hypercapnia decrease the affinity of hemoglobin for oxygen (shift the curve to the right).**

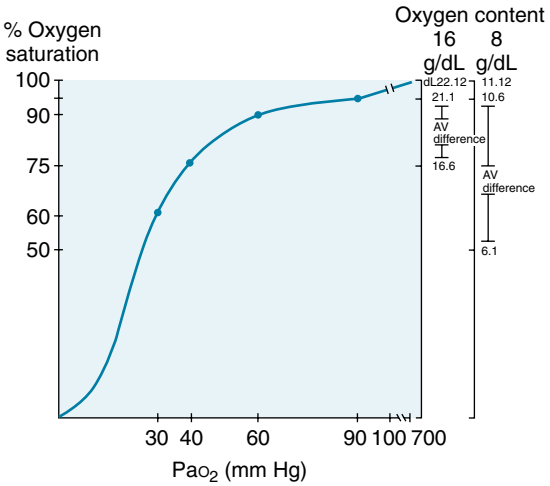

FIGURE 8.2 Oxygen-hemoglobin dissociation curve; the 30-60-90 rule is demonstrated. *Right,* The oxygen content for a hemoglobin concentration of 16 and 8 g/dL is given, demonstrating the effect of anemia on venous saturation and tissue oxygenation.

At a given tissue Po_2, an increased hemoglobin affinity for oxygen leads to less oxygen released at the tissue level, whereas a decreased affinity allows for more oxygen release to the tissues. Alternately, the Po_2 at which the oxygen-binding sites of hemoglobin are 50% saturated (the P_{50}) is low when the hemoglobin affinity is great and higher when the hemoglobin affinity is low.[10] **The affinity of fetal hemoglobin for oxygen is higher than adult hemoglobin (see Figure 7.1).** The P_{50} of fetal hemoglobin is 19 mm Hg compared with a P_{50} of 27 mm Hg for adult hemoglobin. **Approximately 70% of hemoglobin in term infants, and more in preterm infants, consists of fetal hemoglobin.**[14] As a result, hemoglobin in a term infant with a Pao_2 of 35 mm Hg will be 80% saturated, and a "pink" newborn infant may have a low Pao_2.

OXYGEN CONTENT

Oxygen content is calculated from the hemoglobin saturation and hemoglobin concentration. One gram of hemoglobin binds 1.39 mL of oxygen. The oxygen content in milliliters per deciliter is the product of the saturation percentage and the hemoglobin in grams per deciliter plus the amount of dissolved oxygen. For clinical purposes, we can neglect the amount of dissolved oxygen in the plasma because it is only 0.003 mL/dL/mm Hg.

Oxygen content becomes critical in anemia, which can decrease tissue oxygenation unless organ blood flow and cardiac output increase to maintain the delivery of oxygen.[10,55] The blood of an infant with a hemoglobin of 8 g/dL will have half the oxygen content compared to that of an infant with a hemoglobin of 16 g/dL at an equivalent oxygen saturation percentage. In Fig. 8.2, an infant with 16 g hemoglobin that is 95% saturated (Pao_2 = 90 mm Hg) carries 21.1 mL/dL oxygen, whereas the infant with 8 g hemoglobin carries 10.6 mL/dL oxygen. Tissues require approximately 4 to 5 mL/dL oxygen to maintain aerobic metabolism. With normal cardiac output, venous blood contains 4 to 5 mL of oxygen which is less than the arterial blood. The venous oxygen content in an infant with 16 g hemoglobin would be between 16 and 17 mL/dL, which corresponds to approximately 75% saturation, or a Pvo_2 of 40 mm Hg. However, unless cardiac output increases, the venous oxygen content in an infant with 8 g hemoglobin would be 6.1 mL/dL oxygen. The saturation is 55%, which corresponds to a Po_2 of less than 30.

BLOOD FLOW AND SHUNTS

The product of oxygen content and blood flow returning from the lungs determines the total amount of oxygen in arterial blood if no intra- or extracardiac shunting occurs. Total pulmonary blood flow can be divided into the amount of blood in the pulmonary capillaries and the amount that is shunted through or around the lungs.

A right-to-left shunt occurs when blood passes from the systemic venous to the systemic arterial circulation. This can occur because of anatomic defects in the heart (e.g., cyanotic congenital heart disease), with a persistently patent ductus arteriosus in the presence of pulmonary arterial pressures that are higher than systemic arterial pressures (pulmonary hypertension), or when pulmonary capillary blood perfuses poorly expanded alveoli (e.g., intrapulmonary shunts). **Shunts lower the final arterial oxygen saturation. The usual degree of shunting in a newborn is 15% to 20% of the cardiac output.**

Acid-Base and Oxygenation Disorders

Ventilation **is defined as the amount of gas leaving the lungs per unit of time (e.g., minute ventilation). Minute ventilation is equal to the product of the tidal volume and respiratory frequency in breaths per minute.** The tidal volume is composed of (1) gas in the airway and nonperfused alveoli *(physiologic dead space)* and (2) gas in the alveolar space.[10,17] ***Alveolar ventilation*** **is defined as the ratio of CO_2 production by the body to the $Paco_2$. Alveolar ventilation is inversely related to $Paco_2$.** When $Paco_2$ doubles, alveolar ventilation is approximately one half of the original value. If the $Paco_2$ triples, alveolar ventilation is approximately one third of the original value, and so forth.[1]

RESPIRATORY ACIDOSIS

When the lungs become less effective at removing carbon dioxide, $Paco_2$ increases, and respiratory acidemia ensues. The causes of respiratory acidosis can be separated into pulmonary and nonpulmonary causes.[17] The most common pulmonary cause of respiratory acidosis in term newborns is obstructive lung disease, such as meconium aspiration[48] and transient tachypnea[43] of the newborn. For newborns delivered prior to 34 weeks' estimated gestational age, surfactant deficiency and immature parenchymal lung and neuromuscular development are the most common reasons for respiratory acidosis. Obstructive lung disease occurs in the recovery phase of uncomplicated respiratory distress syndrome (RDS) and in bronchopulmonary dysplasia.[47] Also included in the pulmonary causes of hypoventilation are conditions that interfere with the expansion of the lungs, such as diaphragmatic hernia, phrenic nerve paralysis, a space-occupying mass, or pneumothorax. These limit the tidal volume.[17]

A nonpulmonary cause of carbon dioxide retention is poor respiratory effort. A decreased respiratory drive may be secondary to medications such as opioids, sepsis, intracranial hemorrhage (including intraventricular hemorrhage), prematurity, hypothermia, and metabolic disturbances, such as hypoglycemia.[17] Even if the respiratory drive is

appropriate, newborns may have an inadequate neuromuscular ability to ventilate. Ineffective respiratory mechanics may be related to prematurity, systemic illness with multiorgan dysfunction, and conditions that decrease muscular tone and strength such as those found in certain genetic syndromes (Prader-Willi), maternal conditions (Graves' disease), and medication side effects (magnesium sulfate for maternal preeclampsia).

RESPIRATORY ALKALOSIS

In respiratory alkalosis, carbon dioxide clearance is increased, and thus $Paco_2$ is below normal.[20] Respiratory alkalosis occurs as a result of hyperventilation, which may be caused by (1) excessive ventilatory support; (2) central nervous system (CNS) stimulation that increases the respiratory drive (e.g., hyperammonemia from a genetic abnormality of the urea cycle);[11] and (3) hypoxemia, which stimulates respiratory centers through chemoreceptors.[20]

NONRESPIRATORY (METABOLIC) ACIDOSIS

In nonrespiratory (metabolic) acidosis, the metabolic component results from either adding nonvolatile acid (an acid other than carbonic acid) or losing base (bicarbonate).[35,48,53] The underlying mechanisms of metabolic acidosis are (1) the loss of base in urine or stool, (2) exogenous acid that is unable to be effectively secreted by the kidneys (high levels of amino acid administration), and (3) abnormal metabolism that leads to an increase in nonvolatile acid levels. Nonvolatile acids originate from lactic acid in circulatory shock and hypoxia, organic acids in inborn errors of metabolism, and ketoacids in diabetic acidosis. Loss of bicarbonate occurs in renal tubular acidosis (inability of the renal tubules to reabsorb bicarbonate appropriately), with stool loss (diarrhea), or through urinary excretion.[50,52,54]

Measurement of the anion gap helps identify the mechanism of metabolic acidosis.[15,18,29,54] The anion gap is variably calculated as the serum sodium concentration minus the serum chloride concentration minus the serum bicarbonate concentration[33,54] or, alternatively, sodium plus potassium minus chloride minus bicarbonate.* The upper limit of the normal anion gap with the first method is given as 14 mEq/L[54] and with the second method as 15 mEq/L.[26] Addition of nonvolatile acids is associated with an increased anion gap. **Loss of base or excess chloride [Cl^-] is the likely mechanism of acidosis with a normal anion gap.**[46,54] The advantage of measuring the anion gap in understanding the effect of excessive chloride administration is clear. Given that there must be a balance between blood cations and anions to preserve electroneutrality, [Cl^-] in excess simply displaces [HCO_3^-], resulting in metabolic acidosis.[54] In normal anion gap acidosis, low serum potassium indicates loss of base (e.g., diarrhea), and high serum potassium points to a renal defect (e.g., renal tubular acidosis).[33]

Albumin is a major component of the anion gap. Hypoalbuminemia, common in critically ill neonates and children, may mask the presence of the anions of lactic and organic or other nonvolatile acids.[15,16,18,26,33] A "normal" anion gap in combination with low serum albumin indicates that a nonvolatile acid anion is making up the difference for "absent" anions that albumin would ordinarily provide. Correcting the anion gap for hypoalbuminemia is accomplished by adding 2.5 mEq/L to the anion gap for every g/dL that the concentration of serum albumin is reduced below the normal value of approximately 3.5 g/dL.[15,52]

NONRESPIRATORY (METABOLIC) ALKALOSIS

Nonrespiratory (metabolic) alkalosis is caused by either a loss of acid or an increase of base, principally bicarbonate.[30] Alkalosis occurs when excessive amounts of bicarbonate, acetate, citrate, or lactate are given; metabolism of the latter three anions in the liver generates bicarbonate. **Loss of acid occurs with gastric fluid removal or prolonged vomiting, as can be seen with pyloric stenosis. Acid loss by renal mechanisms can occur through the influence of diuretics, digitalis, or corticosteroids.**[20] Urine electrolytes, especially chloride, are useful in the differential diagnosis of metabolic alkaloses. Low urine Cl^- (<20 mEq/L) is associated with chloride (saline)–responsive metabolic alkalosis from acid loss (e.g., vomiting, nasogastric suction), whereas high urine Cl^- is associated with chloride (saline)–unresponsive metabolic alkalosis from renal acid loss (e.g., diuretics).[18,33]

*References 9, 15, 17, 21, 23, 40.

OXYGENATION

Inadequate cardiac output, anemia, an increased hemoglobin affinity for oxygen, and hypoxemia (decreased Pao_2) may cause tissue hypoxia. **Hypoxemia results from lung disease or cyanotic congenital heart disease. The most common lung abnormality is mismatched ventilation and perfusion.**[10] In newborns, there is always some degree of ventilation and perfusion mismatch. Two extreme examples are (1) ventilated and oxygenated alveoli without perfusion (e.g., pulmonary emboli) and (2) perfused but nonventilated alveoli (atelectasis). The former is an example of wasted ventilation, and the latter represents an intrapulmonary shunt. Either extreme is incompatible with life. Clinically relevant degrees of ventilation-perfusion mismatch lie somewhere between those extremes.[10]

Hypoxemia, resulting from ventilation-perfusion mismatch, can be overcome with supplemental inspired oxygen. An increased inspired oxygen concentration will eventually displace nitrogen from even the most poorly ventilated alveoli, and alveolar and then arterial oxygen tension will increase. **However, when an extrapulmonary shunt bypasses the lungs, Pao_2 does not increase.** This is important because clinicians can differentiate parenchymal lung disease from cyanotic congenital heart disease as a cause of hypoxemia: the latter will not have a significant increase in Pao_2 even with the administration of 100% oxygen.

To perform the *hyperoxia test,* the clinician should place the neonate in 100% oxygen for 10 to 15 minutes and obtain a right radial arterial blood sample. If the Pao_2 rises to more than 150 mm Hg, cyanotic congenital heart disease is very unlikely, and lung disease is the most common etiology.

Central hypoventilation from narcosis may cause hypoxemia. As alveolar carbon dioxide rises, PAo_2 falls, and Pao_2 decreases. This condition should be clinically evident and should not be confused with lung or congenital heart disease. Other causes of hypoxemia, such as decreased inspired oxygen tension with increasing altitude and oxygen diffusion limitation, are uncommon in the infant.

PREVENTION

Prevention of acid-base and oxygenation disturbances and maintenance of acid-base homeostasis require attention to detail. A clinician must have an understanding of the physiologic principles of acid-base homeostasis and oxygenation to identify the underlying mechanism and treat with the appropriate medical intervention(s).

With respiratory disturbances, immediate assessment and prompt therapy, including supplemental inspired oxygen and assisted ventilation, may help improve oxygenation and the respiratory component of acid-base disturbances (see Chapter 23). Careful monitoring of fluid and electrolyte intake and output, minimizing blood loss, and observing for sepsis help the clinician prevent the development of nonrespiratory acid-base disturbances (see Chapters 4 and 22).

DATA COLLECTION

Monitoring inspired oxygen concentrations and arterial oxygen tension and supplying appropriate concentrations of additional inspired oxygen will prevent hypoxemia and hyperoxemia (see Chapter 23). Monitoring may be accomplished intermittently through indwelling arterial catheters or continuously by transcutaneous oxygen monitors and pulse oxygen saturation devices (see Chapter 7). Monitoring hemoglobin concentrations and blood loss, with appropriate replacement, helps ensure adequate blood oxygen content.

Reviewing the patient's history, performing a physical examination, and evaluating laboratory data augment each other in the assessment of disturbances in acid-base homeostasis and oxygenation (Box 8.2).

History

An adequate obstetric and perinatal history may warn of potential acid-base and oxygenation disturbances in the newborn:

- Premature delivery predisposes the infant to infection and respiratory insufficiency.
- Meconium staining may portend infection, lung disease, and right-to-left shunting with associated pulmonary hypertension.
- Prolonged rupture of membranes, maternal diabetes, or abnormal maternal bleeding may be associated with either metabolic or respiratory acid-base disturbances and hypoxemia.
- A neonatal history of vomiting, diarrhea, or other gastrointestinal disturbances can cause acid-base disturbances.

BOX 8.2 EVALUATION OF ACID-BASE DISTURBANCES AND OXYGENATION PROBLEMS IN NEONATES

1. History
   a. Obstetric and perinatal
   b. Neonatal
   c. Family
2. Physical examination
   a. Vital signs
   b. General appearance
   c. Respiratory effort
   d. Pulmonary examination
   e. Cardiac examination
   f. Abdominal examination
   g. Neurologic examination
3. Laboratory
   a. Chest x-ray film
   b. Arterial blood gases
   c. Urinalysis
   d. In selected cases: sepsis evaluation, serum electrolytes, serum albumin, urine electrolytes, and urine osmolality

- The infant's general appearance, feeding habits, and activity level may indicate sepsis or CNS injury, both of which promote acid-base disturbances and hypoxemia.
- Nosocomial infections and pneumonia may significantly influence acid-base and oxygenation disturbances.
- A family history of inherited renal problems such as tubular acidosis may suggest an acid-base disturbance.
- A family history of salt-losing endocrinopathies may produce an acid-base disturbance.

Physical Examination

SIGNS AND SYMPTOMS

Signs of acid-base disturbance vary widely and often go undetected. Hypothermia, hypotension, tachycardia, bradycardia, or poor peripheral perfusion should alert caretakers to the possibility of metabolic acidosis. **An altered respiratory rate and pattern, grunting respirations, nasal flaring, and chest wall retractions raise the possibility of respiratory acidosis or respiratory compensation for metabolic acidosis.** Abnormalities on auscultation of the heart may point to congenital heart disease and resulting acid-base and oxygenation abnormalities. Lethargy, seizures, and abnormal neurologic signs increase concern for acid-base disturbances or hypoxemia.

LABORATORY DATA

Chest Radiograph: A chest x-ray examination may assist in identifying a respiratory or cardiac cause for an acid-base disturbance and hypoxemia.

Urinalysis: The routine urinalysis records urine specific gravity and complements monitoring of urine output. Urine electrolytes and pH are helpful in differentiating among the pathophysiologic mechanisms of metabolic derangements.

Arterial Blood Gases: **Interpretation of the arterial blood gases will point to the primary acid-base derangement and may reveal a secondary compensation and define the degree of hypoxemia.**[9,28,37,49] Presently, methods for monitoring the components of acid-base analysis comprise both invasive and noninvasive techniques. Intermittent arterial punctures or indwelling catheters in various vessels (often the umbilical artery or vein) supply data. However, we can continuously measure transcutaneous Po_2 or O_2 saturation. Monitors can continuously measure expired end-tidal CO_2, which corresponds to the alveolar CO_2. (Alveolar and arterial CO_2 are equivalent unless respirations are excessively rapid.) In addition, skin electrodes are available that measure Pao_2 and $Paco_2$ with varying success (see Chapter 7).

Although the pathophysiologic condition of the acid-base disturbance is determined through the analysis of arterial blood gases, further assessment of the infant is necessary, as follows:

- Respiratory alkalosis or acidosis can be suspected on the basis of obstetrical and family history, physical examination, and chest x-ray or diagnosed by arterial blood gas analysis.
- Metabolic acidosis often accompanies shock and septicemia. The anion gap and urine electrolytes may provide additional information to delineate causes. Blood pressure measurement, a complete blood cell count, an infectious work-up, serum and urine electrolytes and pH, serum albumin and glucose determinations, and assessment of intake and output of fluids are often needed to identify the source of metabolic acidosis.
- Oxygenation disturbances may be analyzed from the preceding laboratory tests and, when indicat-

TABLE 8.2 UMBILICAL VENOUS AND ARTERIAL CORD BLOOD GAS VALUES

	VENOUS	ARTERIAL
pH	7.25–7.45	7.18–7.38
Pco_2 (mm Hg)	26.8–49.2	32.2–65.8
Po_2 (mm Hg)	17.2–40.8	5.6–30.8
HCO_3^- (mmol/L)	15.8–24.2	17–27
Base deficit (BD) (mmol/L)	0–8	0–8

ed, an echocardiogram to evaluate for structural heart disease or pulmonary hypertension. If an echocardiogram is not readily available, performing a hyperoxia test to evaluate for the possibility of congenital heart disease may be necessary.

Another calculation, **the *oxygenation index (OI),* is used to assess critically ill neonates receiving ventilator therapy. The OI is (Fio_2 × 100 × mean airway pressure) divided by Pao_2 or, simply put, work/result.** In some centers, an OI of 25 or greater has been considered an indication for extraordinary ventilatory support, such as inhaled nitric oxide or extracorporeal membrane oxygenation (ECMO).[18]

CORD BLOOD GAS INTERPRETATION

Providers participating in delivery room stabilization, as well as subsequent care of at-risk newborns, benefit from a thorough understanding of cord gas interpretation, as well as familiarity with the perinatal conditions that may have an adverse effect on fetal outcome. Table 8.2 describes normal cord blood gas values.[38]

When reviewing **cord gas values, it is important to note that there is a broader range of normal values than with postnatal blood gas values, and the relationship between the venous and arterial norms is the opposite of that in conventional blood gases.[41] With fetal circulation, the umbilical vein transports oxygenated blood from the placenta (acting as the fetal lung) to the fetus. The umbilical arteries transport blood from the fetus back to the placenta for gas exchange. The most useful value of cord blood sampling for the clinician caring for the newborn is the umbilical arterial blood pH because it is indicative of the fetal metabolic condition just prior to birth and is most strongly associated with perinatal mortality and important morbidities.[22,37]**

UMBILICAL CORD BLOOD GAS SAMPLING

Controversy exists as to which perinatal circumstances warrant collection and review of umbilical cord blood gases. The American College of Obstetricians and Gynecologists' Committee on Obstetric Practice updated its opinion statement regarding cord blood gas analysis in 2012.[3] **Cord gas collection and review should occur in circumstances of cesarean delivery for fetal compromise, low 5-minute Apgar score, severe growth restriction, abnormal fetal heart rate tracing, maternal thyroid disease, intrapartum fever, or multiparous gestations.**

There are a few points to keep in mind when collecting and analyzing cord blood. Following delivery, immediate collection and analysis of cord blood ensure the greatest sampling accuracy. However, valid results can be obtained with samples collected and analyzed within 1 hour at room temperature or analyzed within 6 hours if the samples are refrigerated.[50] **The placenta continues to be metabolically active following delivery, and theoretically, if the blood being sampled is in close proximity to the placenta, there may be continued gas exchange, yielding cord gas results that reflect a dynamic state and not necessarily the prior fetal environment.**[5]

Over the past decade, **delayed cord clamping has become quite common and is now considered standard practice at the delivery of term and preterm newborns.** Umbilical blood vessel sampling is possible during delayed cord clamping,[4] but does delayed cord clamping, as compared to immediate cord clamping, affect the results and interpretation of arterial or venous cord blood samples? At the time of birth, dramatic physiologic changes occur as the fetus moves from a fluid-filled environment, which relies on the placenta for gas exchange, to an air-filled environment, whereby the newborn's cardiorespiratory system fulfills that role. **During delayed cord clamping, gas exchange may occur simultaneously through the placenta and the newborn's cardiorespiratory system, which has the potential to significantly alter sampled cord blood gas values such as pH, Po_2, Pco_2,** and **base deficit.** A recent study[51] compared paired samples of arterial and venous cord blood samples obtained immediately after

birth with those obtained after delayed cord clamping in term pregnancies. **Statistically significant differences were noted for pH, Pco_2, lactate, and base excess, but not Po_2. The mean differences noted between immediate cord clamping and delayed cord clamping were as follows: pH lower by 0.03, Pco_2 higher by 3 mm Hg, lactate higher by 3 mg/dL, bicarbonate lower by 0.3 mmol/L, and base deficit increased by 0.3 mmol/L.** In term deliveries, a significantly lower pH and higher Pco_2 have been found in cord blood samples obtained after vaginal delivery as compared to operative deliveries.[37] The results, although statistically significant, may not be clinically relevant; however, these differences should be considered when interpreting cord blood gas values obtained with delayed cord clamping after vaginal or operative deliveries.

CORD BLOOD GAS INTERPRETATION

Asphyxia results when there is an interruption of placental-fetal gas exchange. More specifically, asphyxia is defined as metabolic acidemia following birth measured by a pH of less than 7.00 and a base deficit of greater than 12 mmol/L.[41] General causes of intrapartum asphyxia are (1) impaired uteroplacental gas exchange (uteroplacental insufficiency), (2) inadequate umbilical blood flow (cord occlusion), and (3) impaired fetal cardiac output.

General principles of cord blood gas interpretation include the following:

1. Umbilical venous blood represents uteroplacental status.
2. Umbilical arterial blood represents fetal *and* uteroplacental status.
3. When interpreting an infant's paired cord gases, the cord venous gas will *always* have a higher pH, a lower Pco_2, and a higher Po_2 than the umbilical artery cord gas. If values do not align with these rules of interpretation, it is likely that the samples were from the same vessel or mislabeled.[8,40]

Uteroplacental Insufficiency. There are multiple perinatal and intrapartum factors that can lead to uteroplacental insufficiency. Some common clinical conditions include maternal hypotension or hypertension, maternal hypoxia, maternal medications, a hyperstimulated uterine contraction pattern, premature placental separation, and defects in placental development. On many occasions, uteroplacental insufficiency is mild in nature and has no lasting effect on neonatal outcome. However, if a critical threshold of uteroplacental insufficiency is reached, the fetus becomes hypoxic. **The degree and duration of the hypoxia will determine whether metabolic acidosis will occur.**[21] **When intrapartum asphyxia is the result of uteroplacental insufficiency, the umbilical venous and arterial blood gases will *both* reveal derangements in acid-base status. However, with fetal hypoxia, the arterial gas will demonstrate a lower pH, higher Pco_2, and lower Po_2 than the venous cord sample. On many occasions, the cord gases reveal a paired respiratory acidosis without a metabolic component, which indicates an acute (less than 30 minutes) event.**[8]

Cord Occlusion (see Chapter 2). Identification of true cord prolapse during labor is enough to raise even the calmest of clinician's heart rates. However, there are several less intuitive scenarios leading to functional cord occlusion that result from stretching or compression of the umbilical vessels. They include an anatomically short cord; breech presentation; occult cord prolapse; shoulder dystocia; nuchal cord; body cord; true knot in the cord; kinking of the cord; cord entanglement between monoamniotic/monochorionic twins; and following rupture of the membranes, any instance in which there is compression of the umbilical cord vessels.[41]

The most common cord occlusion scenario is compression of the umbilical vein and at least partial patency of the umbilical arteries due to the differences in the vessel wall structure. The vein is thin walled and more easily compressed as compared with the thicker, more muscular arterial wall, which is less prone to compression. Cord blood gas sampling in this scenario would yield a near-normal venous gas with an arterial sample demonstrating metabolic and respiratory acidosis to various degrees depending on the severity and duration of the vessel compression. **Overall, the hallmark cord gas findings in cord occlusion are a widened venoarterial pH, Pco_2, and at times, base deficit differences.**

Fetal Circulatory Failure. A myriad of causes can ultimately lead to fetal circulatory failure. Included

among these are fetal hemorrhage/anemia, structural heart disease, arrhythmias, cardiomyopathies, extracardiac malformations, and septic shock. For example, in progressive fetal anemia, as seen with Rh isoimmunization, the fetus compensates for the anemia by increasing cardiac output. As **the anemia worsens, oxygenation becomes inadequate to meet cellular metabolism, and heart failure occurs.** As cardiac output decreases and blood flow slows, there is increased oxygen extraction from the blood and increased production of CO_2. This phenomenon will create widened venoarterial pH, Pco_2, and Po_2 differences. **Cord gases following fetal circulatory failure have a similar appearance to gases obtained after cord occlusion.**[41]

PATHOLOGIC PREDICTIVE VALUE OF CORD BLOOD GASES

Cord blood gas data and analysis are useful for immediate management, but pH alone is poorly predictive of long-term outcomes. Infants who recover quickly with reassuring neurologic examinations tend to have good long-term outcomes regardless of cord blood pH.[25] Although low cord blood pH is clearly associated with poor outcome, association is not cause and effect. The underlying cause of both acidosis and organ damage is tissue hypoxia.[25,31] In **contrast, an arterial cord pH of less than 7.00 in combination with abnormal clinical signs and symptoms is strongly associated with adverse outcomes.**[57] Low et al. demonstrated that arterial base deficits of 12 to 16 mmol/L were associated with moderate or severe newborn sequelae in 10% of the neonates studied. That number increased to 40% of neonates once the base deficit reached greater than 16 mmol/L.[36] Conversely, mild acidosis is not usually associated with newborn complications. Although analysis of cord gases can at times be difficult, paired cord blood gases have a role in determining underlying etiologies, guiding further evaluation and appropriate treatment(s).

TREATMENT

In respiratory acidosis, the pathophysiologic mechanism is decreased alveolar ventilation. Treatment is directed at the underlying cause.[15] **Hypoxemia caused by ventilation-perfusion mismatch is treated with increased inspired oxygen concentration.** Techniques that may be of benefit to treat respiratory acidosis include continuous positive airway pressure (CPAP), standard ventilation, high-frequency ventilation, ECMO, inhaled nitric oxide, and others (see Chapter 23). **Treatment of respiratory alkalosis usually consists of reducing minute ventilation.** One of the causes of neonatal central hyperventilation that requires a high index of suspicion and urgent evaluation and treatment is hyperammonemia caused by an inborn error of urea cycle metabolism[11] (see Chapter 27).

Asphyxia often leads to a combined respiratory and metabolic acidosis. Ventilation will resolve the respiratory acidosis. Improved oxygen delivery and tissue perfusion usually resolve lactic acidosis without bicarbonate therapy. In narcosis, temporary ventilator support may be necessary. **Narcosis may be reversed with the administration of naloxone (Narcan) at a dose of 0.1 mg/kg if the possibility of chronic maternal opiate drug abuse has been ruled out.** With chronic intrauterine opioid exposure, neonatal Narcan administration may result in acute withdrawal and seizures (see Chapter 4).

With any acidosis and alkalosis, determining the underlying etiology is critical for effective management. If the cause of metabolic acidosis is septicemia, intestinal necrosis, or poor cardiac output severe enough to result in metabolic acidosis, successful treatment of the cause is of far more importance than buffer therapy for acidosis. Historically, sodium bicarbonate has been administered for neonatal metabolic acidosis. However, controversy exists on the true physiologic benefit from sodium bicarbonate administration.[7] **Sodium bicarbonate administration may conversely cause harm, especially with a bolus administration, because it is a hypertonic solution that may increase the risk of intraventricular hemorrhage.**[13,35,45] It should not be used if severe lung disease restricts carbon dioxide elimination (see Equation 3).

COMPLICATIONS

Unrecognized oxygenation disturbances may lead to increased mortality or morbidity rates in survivors. Unrecognized acid-base disorders are not as important in themselves as they are

because they serve as indicators of unrecognized serious, perhaps life-threatening pathology such as septicemia or poor cardiac output. For example, otherwise-normal newborn infants and trained athletes can be severely acidotic without consequences.[25,27] Everyday, clinical experience in neonatal intensive care confirms that chronic respiratory acidosis, even with extreme hypercapnia, can be tolerated for long periods. **It is not always appreciated that acute correction of chronic acid-base disorders can be more problematic than the disorder itself.** For example, **sudden correction of respiratory alkalosis results in potentially damaging acute increases in cerebral blood flow.**[23] Sudden correction of chronic hypercapnia was long ago shown to be problematic.[17,18,30,40,42] In short, **complications of the correction of the acid-base balance vary according to the disturbance and the treatment provided. The treatment of respiratory acidosis by assisted ventilation can produce all of the complications of assisted ventilation, including infection, trauma, oxygen toxicity, sepsis, air leak, and subglottic stenosis** (see Chapter 23).

Complications of oxygen therapy include hypoxemia and hyperoxemia. **Severe hypoxemia may cause pulmonary vasoconstriction, a change from aerobic to anaerobic metabolism (with eventual metabolic acidosis), bradycardia, hypotonia, and impaired CNS and cardiac function.** Prolonged high inspired oxygen concentrations can result in oxygen toxicity, which may be central to significant morbidities such as retinopathy of prematurity and bronchopulmonary dysplasia.[12,28]

EXAMPLE CASES

Case 1

You are caring for a 7-day-old, former 36-week female infant who has poor feeding, sleepiness, decreased urine output, and a new oxygen requirement with Fio_2 0.40 on 2-L/min nasal cannula. On exam, she is only mildly responsive to stimulation; has delayed capillary refill of 3 to 4 seconds throughout, with poorly palpable peripheral pulses, especially in her lower extremities; and has a respiratory rate in the 80s, with labored breathing and clear breath sounds. Blood pressure measured with a cuff on her right arm is 65/40, heart rate is regular in the 160s, and oxygen saturations range in the low 90s in the right upper extremity. You are concerned about her appearance and order a chest x-ray, complete blood count (CBC) with differential and platelets, electrolytes, blood culture, urine culture with Gram stain and microanalysis, C-reactive protein, and arterial blood gas. The first result that confirms your concerns is the arterial blood gas: pH 7.03, Pco_2 30, Po_2 55, calculated bicarbonate of 9, base excess of −16. Serum electrolyte results include the following: sodium of 134, potassium of 5.9, chloride of 95, and bicarbonate of 10. You calculate an anion gap of 35 (134 + 5.9 − 95 − 10). Your clinical suspicion is that this newborn has coarctation of the aorta that has become critical upon closure of her patent ductus arteriosus, which is confirmed by echocardiogram. The patient receives an administration of parenteral prostaglandin, establishment of arterial and central venous access, and a cardiology consultation. **In patients with metabolic acidosis, it is imperative to identify the cause of the acidosis,** which, in this case was due to decreased oxygen delivery to tissues below the level of the coarctation, resulting in a large anion gap metabolic acidosis from lactic acid production due to anaerobic metabolism.

Case 2

You attended the delivery of a 32-week, 1.6-kg infant after preterm labor with rupture of membranes and clear fluid 1 hour before delivery. The mother did not receive betamethasone or antibiotics before delivery. He was delivered vaginally, with Apgar scores of 5 and 7 at 1 and 5 minutes, respectively. He presented with poor respiratory effort and responded to drying, stimulation, and positive-pressure ventilation with 30% oxygen after color and oxygen saturation did not improve with free-flow oxygen. By 5 minutes, he was breathing spontaneously, with an oxygen saturation measured at 85%. He was admitted to the neonatal intensive care unit (NICU) and placed in a hood with 50% oxygen. On exam, he was grunting, with marked retractions; had decreased breath sounds with rales; and had a respiratory rate of 80 with an oxygen saturation of 82%. The rest of the examination was noncontributory. He was placed on continuous positive airway pressure (CPAP) of 5 cm H_2O and Fio_2 0.45, and oxygen saturations increased to the high 80s. Catheters were placed in the umbilical vein and artery. A chest x-ray revealed low lung volumes, a fine reticulogranular pattern, and prominent air bronchograms. The arterial blood gas at 2 hours of life shows a pH of 7.13, a Pco_2 of 66, a Po_2 of 51, a calculated bicarbonate of 14, and a base deficit of 5. You suspect the infant has respiratory distress syndrome based on symptoms beginning at birth, chest x-ray (CXR), and a blood gas revealing hypoxemia and, predominantly, respiratory acidosis. Additional supporting factors include prematurity, lack of antenatal steroids, and exam significant for retractions and poor air exchange. Your management includes surfactant replacement therapy and mechanical ventilation in addition to antibiotics and a follow-up blood gas. Respiratory acidosis is a classic finding in respiratory distress syndrome, especially in the preterm population. Treatment goals are aimed at normalizing both oxygenation and ventilation and treating for the possibility of infection.

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9 DIAGNOSTIC IMAGING IN THE NEONATE

JASON P. WEINMAN, BRIDGET M. BRONSERT, AND JOHN D. STRAIN

Imaging is an important part of the diagnosis and treatment of medical problems in newborns. The ability to noninvasively screen for and diagnose disease, monitor the effects of therapy, and help define prognosis has made imaging an essential part of neonatal care. With refinements in diagnostic equipment and capabilities, the role of imaging has expanded significantly in recent years. There are many ways to assess any problem, and the vast potential of the new imaging modalities makes appropriate imaging a constant challenge (Table 9.1). New modalities have been introduced, and advancement in computer technology has added sophistication to established modalities. Nearly 60% of diagnostic imaging involves modalities that were not even available 30 years ago.

Many excellent reference books and textbooks on neonatal imaging address specific questions.* This chapter reviews the various imaging modalities available for diagnosis and intervention. A short summary of each imaging modality includes background information and the risks and benefits of each. For clarity, this thumbnail description of each modality provides a concise, tailored discussion of the physics of image acquisition. Each section addresses the most common usage of the modality in neonates, followed by a focused discussion of one or two aspects of image interpretation.

Because there is often more than one appropriate way to evaluate any given problem, it is essential to understand the inherent advantages and limitations of each modality to decide which might be most effective. Understanding some of the challenges associated with diagnostic imaging can lay the foundation for a focused problem-solving approach with appropriate collaboration between clinicians and radiology that will result in the best care for the patient.

*References 3, 4, 8, 9, 22, 24, 27, 29–32.

RADIOGRAPHY

Background

The 1896 introduction of the roentgenogram was met with great enthusiasm, and x-ray examination quickly became an indispensable clinical diagnostic tool throughout the world. Until 35 years ago, the field of radiology was based almost exclusively on the use of the x-ray.

A beam of ionizing radiation from a source (x-ray tube) passes through the patient, and various structures within the body interact to attenuate the x-ray before it is received on the other side. The x-rays pass through the patient and then expose a film, just as light exposes a negative in black-and-white film photography. The film is developed, and the resultant image (radiograph) is a map that corresponds to the transmitted x-ray (that portion of the x-ray not attenuated by absorption or scattered as it passes through the patient). Somewhat analogous to the shadows that result from objects in the sun, the images from x-ray are a shadow of the object being radiographed.

Bone attenuates a greater amount of the x-ray (or allows the penetration of fewer x-rays) than lung tissue does, resulting in a film on which the rib is white and the lung is black. In some ways, this can be compared with the different shadows cast by the trunk of a tree and by its leaves. With radiography, the spatial resolution is exquisite,

BLUE type highlights content that is particularly applicable to clinical settings.

TABLE 9.1 COMPARATIVE ANALYSIS OF IMAGING MODALITIES

IMAGING MODALITY	IONIZING RADIATION	SPATIAL RESOLUTION	CONTRAST RESOLUTION	COST	SEDATION	MISCELLANEOUS
X-ray	Very low	Excellent	Fair	Low	Never	Very fast acquisition eliminates motion
Fluoroscopy	Low	Excellent	Fair	Moderate	Never	Evaluates motion in real time
Ultrasonography	None	Good	Fair	Moderate	Never	Portable; evaluates motion real-time
Computed tomography	Low	Good	Good	Moderate to high	Sometimes	Cross-sectional imaging
Magnetic resonance imaging	None	Good	Excellent	High	Frequent	Multiplanar (i.e., in multiple planes) imaging, flowing blood without contrast
Nuclear medicine	Very low	Poor	Excellent	Moderate to high	Sometimes	Physiologic imaging

although the contrast resolution is lacking. One can capture 10 to 20 line pairs per millimeter with film radiography, although **only five different densities can be routinely distinguished: air, fat, water (which includes all solid viscera—liver, spleen, kidney, pancreas, and heart), bone, and metal.**

More recent developments in x-ray technology include computed radiography (CR) and digital radiography (DR). Although the physics of x-ray generation is essentially the same, the receiver has changed. With CR, a phosphorescent plate replaces film, and the latent image is captured digitally. With DR, the image is directly captured by a digital detector. The introduction of these products was driven by the desire to capture, archive, distribute, and display digital images. Almost all medical imaging is now digital, and a *picture archiving and communication system (PACS)* has become an essential component of any imaging department.

Clinical Utility in the Neonatal Intensive Care Setting

Radiography is the simplest and most reliable way to define tube and line position. Radiopaque markers are incorporated into most of these devices. **From peripherally inserted central catheters (PICCs) to endotracheal, thoracostomy, and feeding tubes, a simple radiograph can quickly identify suboptimal line or tube placement, allowing for repositioning and helping to eliminate complications** (Table 9.2). **Chest radiographs are most commonly used to evaluate the heart and lungs. Abdominal imaging allows a limited assessment of the solid viscera (the liver, spleen, and kidneys), as well as the bowel gas pattern, which is useful in evaluating a neonate with a feeding intolerance** (Fig. 9.1). **The bones of the trunk and extremities are easily assessed with plain-film radiology.**

TABLE 9.2 POSITION OF LINES AND TUBES

LINE/TUBE	POSITION
Endotracheal tube	1 cm above the level of the carina
Umbilical artery catheter	Descending aorta between T8 and T10
Umbilical venous catheter	Junction inferior vena cava and right atrium
Central line	Junction superior vena cava and right atrium
PICC line	Junction superior vena cava and right atrium
Nasogastric tube	Antrum of the stomach

PICC, Peripherally inserted central catheter; *T8* and *T10*, thoracic vertebrae 8 and 10.

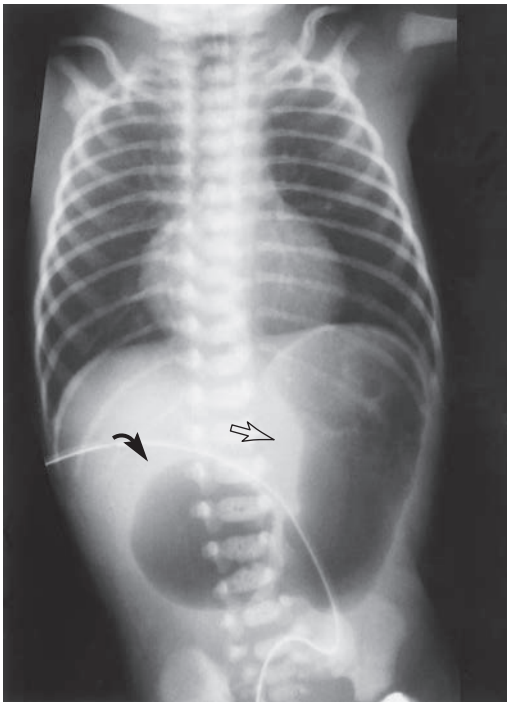

FIGURE 9.1 Frontal chest and abdomen show gaseous distention of the stomach *(open arrow)* and duodenal bulb *(curved arrow)*, the classic double bubble seen in duodenal atresia. Incidental note is made of 13 pairs of ribs in this patient with Down syndrome.

Focused Discussion: Chest Radiographs

The most common use of x-ray imaging in the neonatal unit is for evaluation of the chest to help define abnormalities that might contribute to respiratory distress. Respiratory distress in newborns can be divided into three categories: conditions that are managed medically, those that are managed surgically, and iatrogenic respiratory distress.

MEDICALLY MANAGED RESPIRATORY DISTRESS

Table 9.3 **summarizes plain-film diagnosis of respiratory distress in newborns.** The use of this approach takes advantage of the fact that only a limited number of changes can be identified radiographically, and a constellation of findings can define a specific group of etiologic factors. **A systematic analysis of these various characteristics helps determine a specific group that has a fairly limited differential diagnosis** (Box 9.1).

SURGICALLY MANAGED RESPIRATORY DISTRESS

Respiratory conditions that are managed surgically can be subdivided into three groups: (1)

TABLE 9.3 PLAIN-FILM DIAGNOSIS OF MEDICALLY MANAGED CAUSES OF RESPIRATORY DISTRESS IN THE NEWBORN (CHIMP DIFFERENTIAL)

		GESTATIONAL AGE	HEART SIZE	LUNG VOLUME	NATURE OF INFILTRATE	PROGRESSION	ANCILLARY FINDINGS
C	Congenital heart disease		Increased	Normal or increased	Increased pulmonary vascularity or edema	Stable or progressive	Abnormal situs, aortic discordance
H	Hyaline membrane disease*	<36 weeks		Decreased	Diffuse granularity with air bronchograms	Progressive over first 24 hours	No pleural effusions or body wall edema
I	Immature lung	<26 weeks	Normal	Decreased	Diffuse granularity	Progressive	Absent thymus from stress
M	Meconium aspiration	≥39 weeks	Normal	Increased	Streaky and patchy	Stable	Air leak (i.e., pneumothorax)
P	Neonatal pneumonia		Normal or increased		Either diffuse or focal		Pleural effusions and body wall edema

*Surfactant deficiency disease.

BOX 9.1 CHIMP DIFFERENTIAL DIAGNOSIS MODEL

Congenital heart disease
  Transient tachypnea of the newborn (resolves over first 24 hours)
  Extracardiac shunts
Hyaline membrane disease*
  Diffuse atelectasis
Immature lung
  Represents anectasis rather than atelectasis
Meconium aspiration
  Amniotic fluid aspiration
Pneumonia
  Diffuse
    Birth asphyxia
  Focal
    Pulmonary hemorrhage
Bronchopulmonary dysplasia represents the chronic lung disease that may result from any of the causes of respiratory distress.

*The use of exogenous surfactant modifies the picture of hyaline membrane disease (idiopathic respiratory distress syndrome [IRDS]) significantly. The irregular distribution after endotracheal administration causes a much less uniform infiltrate, and the patchy pattern that results has a look similar to that in meconium aspiration, which might be seen in a term or postterm infant.

those associated with aspiration, such as cleft palate, laryngeal cleft, or tracheoesophageal fistula (TEF); **(2) those that compromise functional lung volume,** including congenital diaphragmatic hernia (CDH), congenital lobar emphysema (Fig. 9.2), pulmonary sequestration, and congenital pulmonary airway malformation (CPAM); and **(3) those associated with tracheal or bronchial narrowing,** such as a double aortic arch and other vascular rings and slings, congenital tracheal stenosis, and bronchogenic cyst (Box 9.2).

IATROGENIC RESPIRATORY DISTRESS

Most iatrogenic respiratory distress results from either a misplaced catheter or tube or from barotrauma. An endotracheal tube (ETT) can be placed too deep and will preferentially ventilate only a single lung. An ETT may even be placed inadvertently into the esophagus, resulting in inadequate ventilation (Fig. 9.3), which is further compromised by distention of the esophagus and small bowel, limiting lung expansion.

Air leaks are often the result of barotrauma (Fig. 9.4). Although barotrauma occurs much less frequently because of the availability of exogenous surfactant, high-frequency ventilation, and nitric oxide therapy, air leaks continue to be a problem that causes significant concern. Appropriate ventilation management requires timely and accurate diagnosis. **One goal in the review of a chest x-ray is to define the location of any extrapulmonary gas. Abnormal extrapulmonary gas can include any one or a combination of the following: pulmonary interstitial emphysema, subcutaneous emphysema, pneumomediastinum, pneumothorax,**

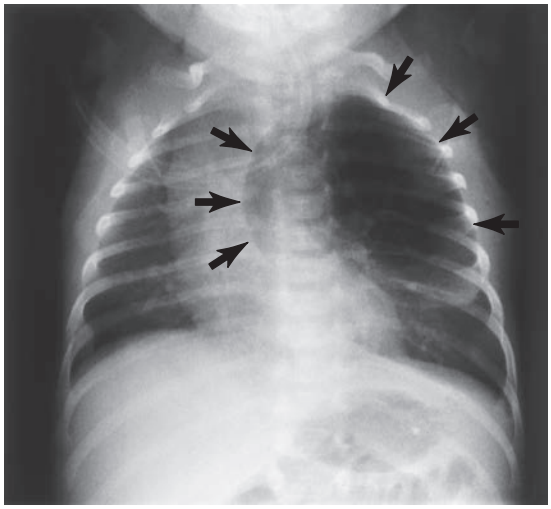

FIGURE 9.2 Frontal view of the chest shows a hyperaerated lucent left upper lobe *(arrows)* associated with mediastinal shift from left to right and is characteristic of congenital lobar emphysema.

BOX 9.2 SURGICALLY MANAGED RESPIRATORY DISTRESS

1. Associated with aspiration
   a. Cleft palate
   b. Laryngeal cleft
   c. Tracheoesophageal fistula
2. Compromised functional lung volume involvement
   a. Congenital diaphragmatic hernia
   b. Congenital lobar emphysema
   c. Congenital cystic adenomatoid malformation
3. Cause tracheal or bronchial narrowing
   a. Double aortic arch
   b. Tracheal stenosis
   c. Bronchogenic cyst

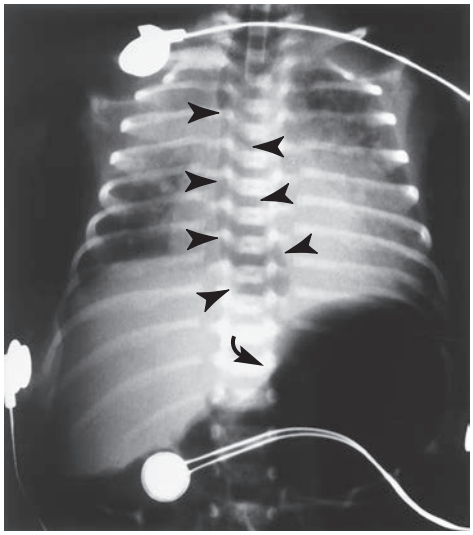

FIGURE 9.3 Frontal chest film. Although the endotracheal tube projects over the midline mediastinum near the thoracic inlet, the dilated esophagus *(arrowheads)* and distended stomach *(arrow)* associated with right upper lobe and left lower lobe atelectasis suggested esophageal intubation, which was diagnosed in this patient.

pneumopericardium, pneumocardia, and portal venous gas.

Focused Discussion: Skeletal Dysplasia

Skeletal dysplasias are a group of bone and cartilage disorders that, although rare individually, overall occur in approximately 1 in 5000 births. Today over 450 individual skeletal dysplasias are known and classified by their clinical, radiographic, and genetic findings. The accurate identification and classification of a patient with skeletal dysplasia can have important implications for the patient because some prove fatal in early life. **In patients for whom a complex skeletal dysplasia is suspected, a skeletal survey consisting of anteroposterior (AP) and lateral views of the skull, AP and lateral views of the spine, and AP views of the pelvis and all extremities (with separate AP views of the hands and feet) should be obtained.[21]**

The first step in assessing the radiographs in a patient with suspected skeletal dysplasia

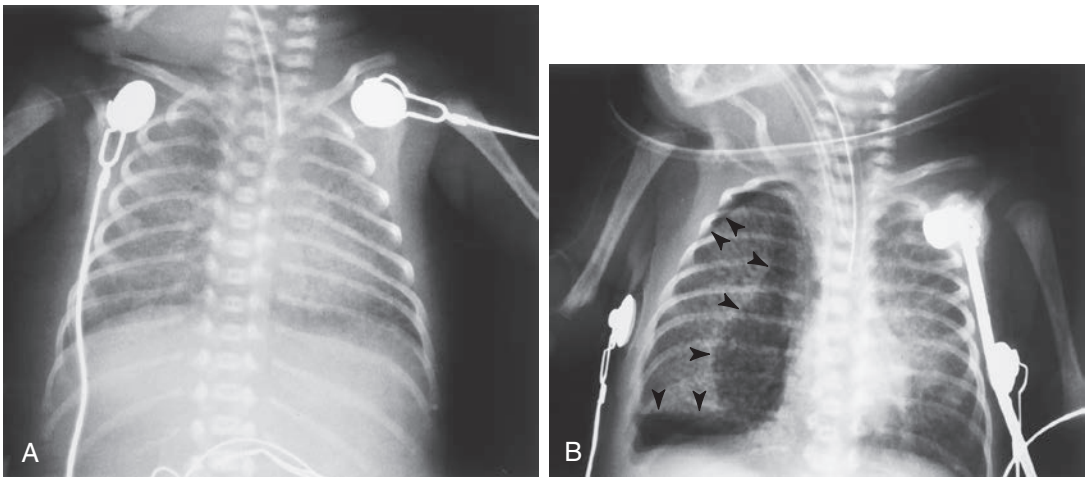

FIGURE 9.4 A, Frontal chest film. Surfactant deficiency disease (hyaline membrane disease) in this patient is defined by the diffuse symmetric granular infiltrates with low lung volumes. This patient required intubation, and the endotracheal tube tip projects in satisfactory position. B, Follow-up examination in the same patient demonstrates linear lucencies within the right lung resulting from pulmonary interstitial emphysema. A tension pneumothorax *(arrowheads)* is identified on the right with mild mediastinal shift from right to left. The lack of atelectasis on the right is the result of the extremely poor lung compliance that accompanies pulmonary interstitial emphysema. The endotracheal tube tip projects in a satisfactory position, but the nasogastric tube is in the midesophagus.

is to look for disproportion. A disproportionate appearance of the chest, such as a narrowed, elongated chest, can be an important diagnostic sign of dysplasia. Other signs include flattening of the vertebral bodies (platyspondyly), with short-trunk disproportion, and shortening of the extremities, such as rhizomelia (root or proximal limb shortening), mesomelia (middle limb), or acromelia (distal limb). **The next step is to evaluate epiphyseal, metaphyseal, and diaphyseal ossification.** Growth of long bones occurs at the ends, where the midshaft *(diaphysis)* is contiguous with the distal shaft *(metaphysis)* and separated by a radiolucent cartilaginous plate *(epiphyseal cartilage or physis)* from the distal end *(epiphysis)*. Ossification centers of the distal femur, proximal tibia, calcaneus, and cuboid are often present at birth. With these findings in mind, the patient can often be classified into a group of skeletal dysplasias. With the help of reference books on skeletal dysplasias, such as *Taybi and Lachman's Radiology of Syndromes, Metabolic Disorders and Skeletal Dysplasias,*[20] specific findings can lead to a diagnosis.

Achondroplasia is a relatively common dysplasia, with 2.8 cases per 100,000 births. **Achondroplasia is a disproportionate rhizomelic short-limbed skeletal dwarfism** (i.e., the proximal segment [humerus] is shorter than the middle [radius and ulna] and distal [wrist and hand] segments). Patients with achondroplasia also have a disproportionately large head, with a decreased size of the skull base and narrow foramen magnum. The lower lumbar spine demonstrates narrowing of the distance between the pedicles, which normally widen at the lower lumbar spine, and kyphosis (posterior angulation) at the thoracolumbar junction. Infants often suffer from respiratory difficulties due to adenoidal hypertrophy, narrow nasal passages, and a small thorax. Narrowing of the foramen magnum and cervicomedullary compression can lead to hydrocephalus and neurologic complications.

Thanatophoric dysplasia is also a disproportionate rhizomelic short-limbed dwarfism. Although the radiographic findings are qualitatively similar to achondroplasia, the severity of the manifestations helps differentiate the two. Classic findings in newborns with thanatophoric dysplasia include very short, bowed femurs with metaphyseal flaring (telephone receiver femurs); a narrow thorax; a large head with small facial bones; and flattened vertebral bodies with notched endplates. Thanatophoric dysplasia is frequently suggested on prenatal ultrasonography by shortened femurs and a narrow chest. This dysplasia has important implications in the neonatal intensive care unit (NICU) because infants will die within the first few days of life without respiratory support.

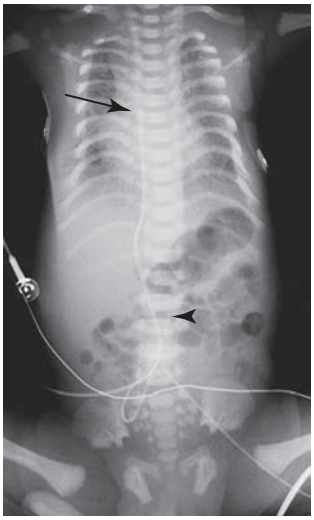

FIGURE 9.5 Anteroposterior film of the chest and abdomen of a patient with asphyxiating thoracic dystrophy (Jeune syndrome) demonstrates short broad ribs with a narrow thorax as well as shortened iliac wings with bony spurs. Also note the malpositioned umbilical venous catheter with its tip in the upper right atrium *(arrow)* and umbilical arterial catheter *(arrowhead)*.

In *asphyxiating thoracic dysplasia* (Jeune syndrome), presenting signs include a long, narrow thorax with short horizontal ribs and respiratory difficulties in infancy (Fig. 9.5). Shortening of the extremities, including the hands and feet, with occasional polydactyly (extra digits), also occurs and can present at birth or later in life. In the pelvis, the iliac wings are shortened in the craniocaudal direction, with bony spurs projecting from the acetabula. Complications of asphyxiating thoracic dysplasia in the neonate center on respiratory distress due to reduced lung volumes/small chest size. Later in life, respiratory infections become a problem, and progressive renal disease leading to renal failure may occur. Patients may also develop hepatic fibrosis, pancreatic fibrosis, and retinal degeneration.

FLUOROSCOPY

Background

Fluoroscopy employs an x-ray tube similar to that used for plain-film radiography. The x-ray is

generated in the same manner as in plain radiography, but it is received in most cases by a device that is similar to a TV camera or VCR. **Fluoroscopy allows real-time evaluation of a patient and can be performed with or without contrast material.** The spatial resolution in fluoroscopy is not as good as that in plain-film radiography, but it is still excellent. The contrast resolution is about the same: air, fat, water, bone, and contrast are the primary densities that can be separated. Contrast media can be given orally or per rectum, instilled into the urinary bladder, or given intravenously. The contrast attenuates the radiation beam to a variable extent related to physical properties and thickness of the attenuator. Most contrast agents are compounds that use either inert barium or iodine as the attenuator of the radiation beam. **The most important characteristic of fluoroscopic imaging is the ability to evaluate motion in real time. This is essential in the evaluation of swallowing function, gastrointestinal (GI) peristalsis, and diaphragmatic motion.**

Clinical Utility in the Neonatal Intensive Care Setting

The most common fluoroscopic examinations requested for neonates include the upper GI (UGI) series, contrast enema, and voiding cystourethrography. The UGI series (and modifications of it) is useful in the evaluation of swallowing, feeding intolerance, vomiting, and abdominal distention with possible bowel obstruction.

A contrast enema should be the initial diagnostic study of choice when low bowel obstruction is suggested clinically or on radiographs. A contrast enema can be diagnostic in many cases of low bowel obstruction, including distal small bowel atresia, meconium ileus, and small left colon syndrome. Findings suggestive of Hirschsprung disease can lead to further evaluation with punch biopsy and play an important role in surgical planning (Fig. 9.6). **In addition to a diagnostic role, a contrast enema can be therapeutic in small left colon syndrome and meconium ileus.**

A voiding cystourethrogram is used to evaluate the urinary bladder and the urethra and to look for vesicoureteral reflux (Fig. 9.7), which is associated with urinary tract infection. Vesicoureteral reflux is a common cause of hydronephrosis, which is now frequently identified during prenatal ultrasonography.

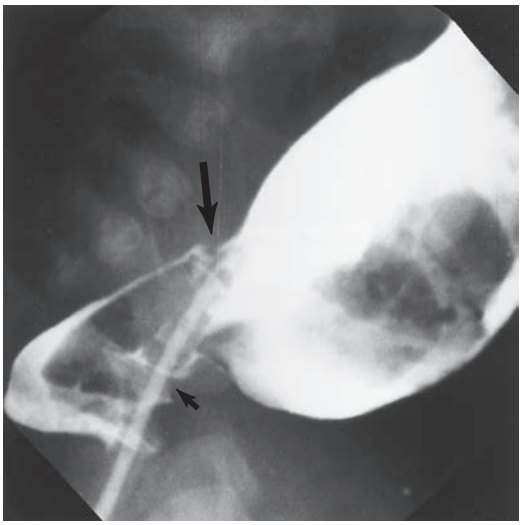

FIGURE 9.6 A lateral film from the early filling phase of a contrast enema demonstrates spasm of the distal rectal segment *(short arrow)* with a transition zone to dilated colon *(long arrow)*. These findings are characteristic of colonic Hirschsprung disease.

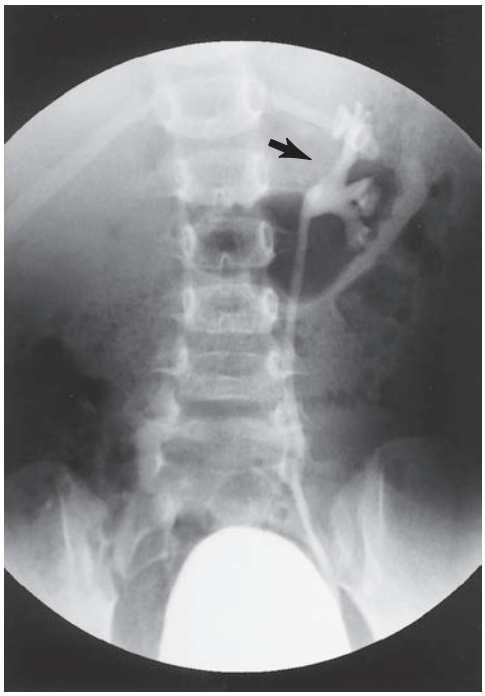

FIGURE 9.7 Frontal view from a voiding cystourethrogram demonstrates grade II vesicoureteral reflux on the left *(arrow)*.

Ureteroceles, periureteral diverticula, and posterior urethral valves all can be associated with hydronephrosis in the neonatal period and demonstrated with cystourethrography.

Air functions as a useful contrast agent, and the nasal and oral airway, as well as the trachea and proximal bronchus, can easily be evaluated fluoroscopically. Because the diaphragm is immediately adjacent to aerated lungs, diaphragmatic motion and its relationship to inspiratory effort help in the evaluation of phrenic nerve injury and diaphragmatic paralysis. Eventration of the diaphragm also can be evaluated fluoroscopically, but at times, it can be indistinguishable from diaphragmatic hernia.

Focused Discussion: Upper Gastrointestinal Series

Indications for performing a UGI fluoroscopic study include swallowing dysfunction, vomiting, choking, and apnea. An appropriately performed UGI series offers a systematic approach to the upper GI tract. Starting with the patient in a left-side-down recumbent position, deglutition, transport, aspiration, and laryngeal penetration all can be grossly assessed, with more detailed assessment reserved for a modified barium swallow using contrast material with varying thicknesses. The right-side-down position better separates the esophagus and the tracheal air column. However, if this position is used initially and the evaluation of the esophagus is prolonged, the stomach may empty, filling the proximal small bowel and obscuring the location of the ligament of Treitz. **The left-side-down position allows evaluation of swallowing and the esophagus without concern that the stomach may empty prematurely.**

Esophageal atresia **usually is diagnosed clinically;** plain-film observation of intraluminal bowel gas defines the most common form, which is associated with a distal tracheoesophageal fistula. **Often, an enteric tube that coils in the proximal esophageal pouch is the initial radiographic finding in patients with tracheoesophageal fistula.** The benefit of a proximal pouch study in esophageal atresia is controversial. There is a small incidence of fistula from the proximal pouch to the trachea; this incidence is independent of the presence or absence of a distal fistula. If the surgical approach to esophageal atresia repair includes direct visualization of the proximal pouch *(esophagoscopy),* the pouch contrast study is superfluous. If, on the other hand, esophagoscopy is not routinely performed, there is some value in evaluating the proximal pouch before surgery. In the absence of esophageal atresia, the location of the fistula (H type) is at the thoracic inlet. This is higher than the fistula that occurs at the level of the carina in the most common form of esophageal atresia.

The contour and caliber of the esophagus are evaluated next. Impressions on the posterior esophagus are suggestive of vascular rings and are correlated with side of the aortic arch to determine if further work-up for vascular ring is needed. Impressions on the anterior esophagus can be related to pulmonary artery slings. Esophageal contour, mucosal detail, and peristalsis are assessed. **The configuration of the gastroesophageal junction can indicate gastroesophageal reflux, and rare hiatal hernias can be diagnosed.**

Gastric emptying is evaluated, and gastric peristalsis is examined. Because the rotation and fixation of the bowel have important consequences in the newborn period, definition of the duodenal bulb, C-loop, and position of the ligament of Treitz is a critical part of a complete examination. Both the posteroanterior (PA) and lateral views are essential in localizing the ligament of Treitz. For proximal bowel rotation and fixation to be considered normal, the duodenal-jejunal junction (fixated by the ligament of Treitz) must be retroperitoneal (and therefore posterior), to the left of the spine, and at the level of the retroperitoneal portion of the second portion of the duodenum (just distal to the duodenal bulb).

The rotation of the proximal bowel may be independent of the rotation of the hindgut. **Therefore, if the clinical question is malrotation and possible volvulus, the UGI series is the examination of choice.** The caliber, contour, and fold pattern of the proximal bowel are evaluated, and the transit time is observed. This simple, systematic, yet comprehensive approach to the UGI series yields a tremendous amount of information.

ULTRASONOGRAPHY

Background

One of the most prominent mass-media introductions of ultrasound (US) technology came when Dr. Robert Ballard located the wreckage of the *Titanic*

using US to explore the ocean floor of the North Atlantic. Medical ultrasonography has its roots in sound navigation and ranging (sonar) developed during World War II.

In medical ultrasound, a transducer (essentially a piezoelectric crystal) converts electrons into a mechanical vibration that creates high-frequency sound waves within the body. The same transducer serves as both the transmitter of the sound wave and the receiver of the reflected sound. Within the body, these high-frequency sound waves propagate through the soft tissues until they meet a reflective surface that reflects some of those sound waves back to the transducer. The percentage of the sound beam reflected relates to the difference in the acoustic impedance of the material being evaluated. When the acoustic impedances of materials are similar, as is the case with the musculature of the abdominal wall (e.g., liver, kidney), most of the sound is transmitted, and a small percentage is reflected at each interface. As the sound wave travels through the abdominal wall to the liver, the abdominal wall–liver interface reflects a portion of the beam and transmits most of the sound through the liver to the liver–kidney interface. The small difference in acoustic impedance between the liver and kidney causes reflection of some of the beam and transmission of most of it to the posterior abdominal wall. This allows the visualization of multiple interfaces that are deeper than the first structure encountered. If the velocity of the sound beam in tissue is known, the distance to the reflective surface can be estimated by measuring the time it takes for the pulse to travel the distance to and from the object imaged.

Most of the tissues in the body have similar acoustic impedances; however, air has extremely low impedance, and bone has extremely high impedance. This means that there is a big difference in the acoustic impedance between these substances and the organs most commonly imaged. For this reason, both bone and air reflect nearly all of the sound that reaches them. This is why a coupling gel is used on the skin surface to eliminate the air gap between the transducer and the skin. This also explains why imaging through the liver gives a good acoustic window to deeper structures, but bowel gas obscures imaging lower in the abdomen. **For ultrasonographic imaging of the brain in a neonate, the anterior fontanel serves as the acoustic window because the bone of the skull acts as a reflective surface that limits through-transmission of US to deeper structures.** The mastoid fontanel serves as a window to the posterior fossa. Bulk fluids within the body, such as urine in the urinary bladder, bile in the gallbladder, or cerebrospinal fluid in the ventricles, have no internal interfaces and therefore are seen as solid black on conventional ultrasonography. Cysts have a sharp posterior wall and have increased through-transmission because the sound wave penetrates the fluid without any reflections to block transmission of the sound.

Doppler ultrasonography takes advantage of the physical principle that the US reflection from a moving object distorts the wavelength, with the distortion related to the velocity of the object being measured. This is the principle that causes the pitch of a train's whistle to change from high to low as the train passes an observer. It is the same principle used by radar guns to monitor the speed of a car or to measure the velocity of a pitcher's fastball. In fact, this same principle is responsible for the "red shift" observed by astronomers in determining that we live in an expanding universe. The Doppler evaluation in medical ultrasonography uses the distortion of the wavelength caused by moving red cells to identify flowing blood.

One of the major advantages of US imaging is the lack of ionizing radiation. Although most diagnostic imaging utilizes low doses of ionizing radiation, any radiation exposure is a concern and should be avoided when possible. The portability of US equipment has made it a valuable adjunct to diagnostic imaging in the neonatal intensive care setting.

Clinical Utility in the Neonatal Intensive Care Setting

Ultrasonography has had a major effect on the evaluation of the neonatal brain. Most of the early work focused on intracranial hemorrhage, which was a common occurrence in preterm neonates. **Even though the incidence has decreased, intracranial hemorrhage remains an issue for which US imaging is extremely well suited.** Ultrasound equipment has improved tremendously, and with the addition of color and pulse Doppler technology, great strides have been made in the refinement and sophistication of intracranial imaging. Numerous complex structural abnormalities can be recognized, and screening for developmental

abnormalities can largely be accommodated with cranial ultrasonography. Because bone reflects most of the sound, limiting through-transmission, the open fontanel is the window to the brain. As the fontanel closes over time, ultrasonography becomes less and less useful for intracranial imaging.

Renal imaging offers another major role for ultrasonography in the neonatal unit. The kidneys are well visualized ultrasonographically, either through a posterior approach or, more commonly, by using the liver or spleen as soft-tissue acoustic windows to the kidneys. **US is an excellent way to evaluate hydronephrosis**, which is now frequently picked up on routine prenatal evaluations. **US has a role in the evaluation of a jaundiced patient because it is ideal for evaluating cystic structures,** such as the gallbladder, and can readily identify dilated biliary ducts. Jaundice caused by biliary obstruction from a choledochal cyst, for instance, can be diagnosed readily with US. Because of the reflectivity of bone and bowel gas, US imaging is much more effective in the upper abdomen, in which the liver and spleen serve as the acoustic windows, or in the pelvis, in which the urinary bladder can function as the window.

Although US is limited by bone, **it has a significant role in the evaluation of the hips in the neonate.** Because the capital femoral epiphysis of the newborn is cartilage, the hip can be well imaged in a neonate. Maternal estrogen causes ligamentous laxity. This changes significantly during the first weeks of life; **therefore, the accuracy of hip ultrasound examinations improves after the first 3 to 4 weeks of life.** Ultrasonography is very good for the detection of developmental dysplasia of the hip and can be used to evaluate the degree of femoral head coverage, the acetabular angle, and any instability of the hip.

The use of US to provide the localization of central lines is becoming common practice. The types of lines frequently used for infants in the NICU include umbilical venous catheters (UVCs), umbilical arterial catheters (UACs), and PICCs. **Many complications can occur if the tips of these lines are not in the correct position, including pleural effusions, cardiac arrhythmias, cardiac tamponade, thrombosis, liver hematoma, liver injury, and portal hypertension.** The gold standard for assessing the position of lines and tubes has been radiographs of the chest, abdomen, or both. **The use of US has many advantages over radiography, including real-time assessment of the line; no radiation exposure; the ability to place and manipulate the catheter under US guidance; reduced insertion time; and fewer malpositions, manipulations, and complications.**[*] Bedside US can be accomplished with appropriate training. Numerous recent studies have suggested that the use of US for line placement has good sensitivity and specificity compared with radiographs.[†]

Focused Discussion: Cranial Ultrasonography

Ultrasonography is an ideal tool for evaluating the brain in a newborn. In general, an ultrasonographic examination is the first step in the imaging evaluation for any neurologic question. **A routine screening US is recommended at between 7 and 14 days of age in all premature infants born under 32 weeks' gestation and should be repeated at 36 to 40 weeks of gestational age.**[32] Structural abnormalities, intracranial hemorrhage, sequelae of anoxic or ischemic events, and infection are all well assessed via ultrasound. The most common approach is through the anterior fontanel, but additional information can be gained with axial imaging through the squamosa of the temporal bone. The posterior fossa can be evaluated through the posterior lateral fontanel. Familiarity with the normal anatomy is essential. Coronal and parasagittal views are obtained. **Normal structures can be easily recognized; their absence or deformity can define developmental abnormalities of the brain.** The ventricular size and configuration are assessed. Characteristic ventricular configurations can define lobar or semilobar holoprosencephaly. In addition, the ventricular configuration can suggest septo-optic dysplasia or agenesis of the corpus callosum. The corpus callosum can be visualized directly; abnormalities of the corpus callosum are commonly associated with *Chiari malformation* and other structural abnormalities of the brain, such as *Dandy-Walker malformation*. **Dilation of one or more of the ventricles can be an indication of a pathologic condition.** An obstruction of the flow of cerebrospinal fluid (CSF) in the region of the Sylvian aqueduct manifests with a disparity in ventricular size. The lateral and third ventricles are enlarged, whereas the fourth ventricle remains normal in size. Dilation of

[*] References 2, 10, 12, 16, 17, 18, 19, 23.
[†] References 2, 12, 16, 17, 18, 19, 24, 28.

one of the lateral ventricles, especially when associated with an area of *porencephaly,* is indicative of an in utero destructive event. **Seizures or apnea may indicate an anoxic or ischemic event in a neonate.** Certain structural abnormalities can suggest a specific diagnosis; for instance, periventricular nodules and cortical tubers define tuberous sclerosis. US examination is less sensitive than computed tomography (CT) and magnetic resonance imaging (MRI) in defining subtle areas of gray-matter heterotopia or focal pachygyria, examples of developmental abnormalities associated with seizures. **US imaging is very sensitive to intracranial hemorrhage, and areas of increased echogenicity can be demonstrated in areas of edema.** Intracranial hemorrhage is an important concern in a premature neonate (Fig. 9.8) and is classified into four grades; each grade is prognostically significant.[34] Grade I hemorrhage usually has a good outcome, whereas the prognosis with grade IV hemorrhage is frequently poor. **Grade I hemorrhage is confined to the germinal matrix in the caudothalamic groove. This is the last fetal germinal matrix to mature and is prone to hemorrhage in preterm babies. Grade II intracranial hemorrhage has intraventricular blood. Grade III hemorrhage is associated with ventricular dilation as the intraventricular clot enlarges the lateral ventricles. Grade IV hemorrhage is defined by parenchymal extension.** It has been hypothesized that grade IV hemorrhage may be the result of venous infarction that occurs from obstruction of the septal veins by the swollen germinal matrix hemorrhage. **White-matter injury of prematurity (periventricular leukomalacia) is a consequence of anoxic or ischemic injury to the brain that manifests as increased echogenicity in the deep periventricular white matter of the centrum semiovale. This may progress to cavitation and is then called *cystic leukoencephalomalacia*.** US can detect changes of leukoencephalomalacia, which is usually apparent within 2 weeks of birth.[33]

COMPUTED TOMOGRAPHY

CT was initially developed in 1972 in Middlesex, England, by Electric and Musical Industries (EMI), an industrial research company. After signing the Beatles in 1962, the company sold its computer business; however, it kept a researcher named Godfrey Hounsfield and funded his independent research through the revenue generated by the Beatles' success. Hounsfield imagined that he could determine what was inside a box by taking x-rays of the box at all angles. He then worked to build a computer that could reconstruct a slice of an object from the data of these x-rays acquired at various angles. He shared the Nobel Prize in Physiology and Medicine with Allan Cormack, who developed the theoretical mathematics for the invention of CT.

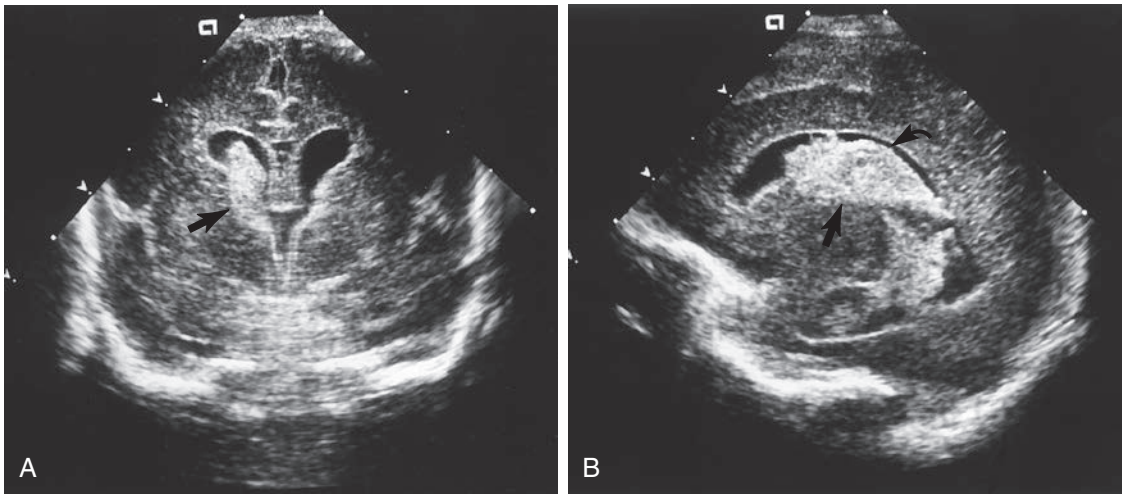

FIGURE 9.8 Coronal **(A)** and parasagittal **(B)** ultrasound images from a cranial ultrasound study demonstrate an echogenic clot *(arrows)* within the dilated right ventricle. The intraventricular clot with ventricular dilation defines a grade III hemorrhage.

Early CT scanners produced images by acquiring x-ray data in multiple positions in an axial plane, moving to a different level between acquiring slices. The initial EMI scanner solved mathematical equations representing the attenuation of the different x-ray beams, like a giant Sudoku puzzle. The complexity of mathematics involved as well as limitations in computers at the time contributed to the limited speed of the scanner; it took approximately 10 minutes to acquire and reconstruct each slice, and the resolution was limited to an 80 × 80 matrix. For comparison, today's fastest dual-source CT scanners can acquire 64 slices in about 0.07 second in the fastest scanning mode with a matrix of 1024 × 1024.

On modern multidetector helical CT scanners, image acquisition takes place as the patient is carried on a mobile table through a rotating gantry containing an x-ray source on the opposite side of the gantry from x-ray detectors. A ring of data is acquired as the patient is moved through the gantry; the path of image acquisition is in effect a helix, resembling a coiled spring, hence the term *helical* or *spiral* CT. Multidetector arrays of 4, 8, 16, 64, and even 320 elements allow rapid acquisition of multiple slices in a single rotation of the tube. This renders high-resolution isovoxel data sets (each volume element has the same width, height, and depth). Because the data are acquired in a continuous helix in an isovoxel data set, as if peeling an apple from top to bottom in one peel, the data can be reconstructed in any plane as well as rendered in three-dimensional (3D) format, just as you could imagine putting an apple peel back together to look like an intact apple. Reconstruction of the acquired data has undergone and continues to undergo revisions. In the most commonly employed method, filtered back-projection lines of gray representing the attenuation of the patient are layered on top of each other to create images, with different filters applied to accentuate different aspects of the image. This renders a cross-sectional slice that can show all of the structures within that slice. For instance, a slice through the upper abdomen may show the liver, spleen, pancreas, both kidneys, and the spine, each separated by a plane of fat and each with a subtly different density.

New technologies on recently introduced CT scanners include volumetric scanning, dual-source and dual-energy CT scanners, and technology designed to reduce the radiation dose to patients by limiting the patient's exposure during the scan or allowing for improved reconstruction of scans obtained at lower radiation doses. Volumetric scanning achieved with up to 320 detectors can allow for an area up to 16 cm to be scanned in a single rotation of the scanner gantry. Dual-source, dual-energy scanners can leverage two tubes and two detector arrays, either for an increased scanning speed of up to 0.07 second for 64 slices with both tubes at the same energy or improved tissue differentiation using different energies. **Given the recent attention to radiation effects from CT in both the medical literature and the lay press, there has been a renewed focus on technology to reduce the dose in CT scans.** This includes both improving the mechanics of the CT scanners themselves as well as developing more advanced reconstruction algorithms that allow scans obtained at lower doses to produce excellent-quality images.

These recent advances in CT technology have resulted in spectacular images and an explosion in CT utilization. The radiation dose in CT, however, is significantly higher than that in routine radiography. CT now accounts for more than 60% of the radiation exposure from medical imaging in the United States. Trailing this growth in the utilization of CT has been greater understanding of and concern for the effects of ionizing radiation in medical imaging. Evaluation of the risk associated with the low doses of ionizing radiation used in medical imaging is a complex and evolving topic. The majority of studies estimating risk from low doses of radiation have been based on models in which survivors of large known doses of radiation, such as from the atomic bombs in Japan, have been followed longitudinally to assess the risk of developing cancer. These models assume that by extrapolating the effects of large radiation doses to low doses, the risk for low doses can be assessed in what is called a linear no-threshold model. Although the accuracy and assumptions in this type of model have been questioned, with some investigators claiming that there is in fact no risk, or even benefit, with low doses of radiation, **more recent studies have suggested that there is a small increased risk of cancer associated with clinical medical imaging.**[5,6,13] **A retrospective cohort study that looked at the incidence of leukemia and brain tumors in pediatric patients who had undergone CT demonstrated an association between the radiation received from**

CT scans and leukemia and brain tumors.[25] Although there was a significant increase in relative risk suggested in this study, the absolute risk remained low.

Medical research suggests that the radiation dose currently used in diagnostic CT is associated with an increase in the risk for radiation-induced malignancy. Neonates, infants, and children are more susceptible to the effects of radiation than adults. This stems from the fact that for a given exposure to radiation, the smaller the patient, the greater is the effective dose because more of the radiation penetrates the patient. Also, longer life expectancy puts younger patients at an increased risk because there is a longer period of time for a radiation-induced complication to develop.

Ionizing Radiation in Perinatal Medicine

The effects of ionizing radiation on the fetus of a pregnant patient also present complex and important concerns. Although the use of ionizing radiation generally should be avoided in patients who are pregnant, there still exist indications for which the benefit of performing the examination may outweigh the risk to the fetus. Additionally, on rare occasions, a CT may have been performed on a patient who was not known to be pregnant before the examination. Although a comprehensive analysis of the risk and radiation exposure of a pregnant patient undergoing CT should be considered in consultation with a medical physicist, general guidelines have been provided by the American College of Radiology in conjunction with the Society for Pediatric Radiology, as briefly described in the following paragraphs:[1]

Before conception, there has been no documented genetically heritable risk in the human population. ***In the first 2 weeks*** after conception, the only potential risk is felt to be the loss of pregnancy. Doses associated with radiographic procedures have not been clearly associated with increased risk, although this is difficult to determine because approximately half of all conceptions are lost in this period, often without recognition of the loss by the woman.

Radiation exposure ***between 2 and 15 weeks*** after conception has more complex risk implications. In general, radiologic procedures outside of the abdomen and pelvis, including the head, neck, and chest, should result in only a very low dose to the fetus from scatter radiation. In a patient who is known to be pregnant, the study should be optimized to limit the dose to the fetus even further. When imaging of the abdomen and pelvis is indicated or has been performed, consideration of the risk to the fetus takes on greater importance. In centers that carefully manage their CT radiation dose, as do most children's hospitals, the dose to the fetus is thought to be below the level associated with any developmental abnormality. However, before counseling takes place, verification of the dose by a qualified medical physicist is recommended. If the dose is determined to be low, the majority of the risk associated with radiation exposure to the fetus is a small increased risk of cancer in later life, and termination of pregnancy would not be indicated. Doses associated with increased developmental disorders are uncommon in routine practice and usually occur in circumstances that have important implications for the pregnancy, such as in patients who require complex cardiology or interventional radiology procedures.

The effects of radiation exposure to the ***fetus more than 15 weeks*** after conception are even smaller, with risk to the developing nervous system occurring only at very high doses, usually beyond what would be typically encountered even with multiple radiology procedures. Therefore, after 2 weeks' gestation, the predominant concern with low-dose diagnostic imaging is the small increase of developing cancer over a lifetime.

Although concern for the deleterious effects of radiation is important, it should always be viewed in the context of the patient as a whole. CT can be a powerful tool in evaluating the pediatric patient. Caution is the key: (1) image only when indicated; (2) limit the scan to the region of concern; and (3) be cognizant of dose and use as low peak kilovoltage (kVp) and milliampere-second (mAs) as possible, and use dose-reduction technologies while maintaining diagnostic-quality examinations.

Clinical Utility in the Neonatal Intensive Care Setting

Cranial imaging is the most common use of CT in most neonatal intensive care settings. CT adds significant specificity to the abnormalities

recognized with ultrasonography. Concern about ionizing radiation and the fact that CT equipment is generally not portable makes obtaining a CT more difficult than obtaining a sonogram. **CT is more accurate in assessing the nature of extra-axial fluid collections and is very helpful in further defining structural abnormalities of the brain, particularly those associated with the abnormal distribution of gray or white matter.** It is also very good for evaluating intracranial hemorrhage and infection. Exquisite bone detail defines craniofacial anomalies, choanal atresia and stenosis, and abnormalities of the petrous bone associated with hearing loss.

Focused Discussion: Computed Tomography Angiography of the Chest

Chest CT angiography (CTA) is becoming much more frequent in the NICU. CTA is often used to evaluate abnormalities detected during intrauterine US, chest x-ray, and echocardiogram examinations, such as congenital lung lesions and potential surgical lesions such as vascular rings identified on chest x-ray films.[7,11]

Through carefully controlled administration of intravenous (IV) contrast, CTA can supplement, and in many cases replace, the need for traditional catheter angiography.[15] Uses include describing the vascular supply to congenital lung lesions such as bronchopulmonary sequestrations, defining vascular and airway anatomy for surgical planning in patients with vascular rings, and surgical planning in patients with complex cardiac disease.

Congenital lung lesions are a spectrum of developmental abnormalities of the lung that include bronchial atresia, congenital pulmonary airway malformations, and bronchopulmonary sequestration, among others. Often suggested on prenatal sonography and, in some cases, characterized on fetal MRI, **CTA is often used in the postnatal period to further characterize the lesion and plan surgical intervention.**[11] Bronchial atresia can be diagnosed on CTA when an atretic bronchus is identified, often in association with a dilated, mucus-filled segment or "bronchocele/mucocele" distal to the atretic airway. Although often found in isolation, studies have identified bronchial atresia in up to 77% of other congenital lung lesions.[20] Cystic pulmonary airway malformations (CPAMs) have been traditionally defined by the size of the cysts within the lesion, with type 1 having cysts greater than 2 cm, type 2 with cysts less than 2 cm, and type 3 appearing solid; more recent alternative classification systems have been proposed, and the pathology of type 3 has been disputed. CPAMs can have a multilobar and rarely bilateral distribution. **CTA can define the cyst size and distribution as well as provide a roadmap for surgical planning.** Rare malignant potential for type 1 CPAMs has been reported, as has recurrent infection. Bronchopulmonary sequestrations were traditionally defined as portions of the lung with a systemic arterial supply and then further characterized as either extralobar or intralobar. Extralobar sequestrations most often appear as a wedge-shaped mass with systemic arterial supply with a pleural margin, often on the left and below the otherwise normally formed lung. Intralobar sequestrations are thought to be developmental abnormalities of the lung composed of isolated nonfunctional lung tissue, sometimes accompanied by cystic change within an otherwise-normal lobe. CTA provides excellent identification and characterization of both the vascular supply and associated parenchymal change in these lesions.

Although vascular rings are often initially suggested on chest x-ray or upper GI, CTA and MR angiography have largely replaced other techniques in the characterization of vascular rings.[7,14] CTA has the advantages of easy availability, improved depiction of the airway and lung parenchyma, and short scanning times, which in some cases can eliminate the need for sedation. Disadvantages include the use of ionizing radiation and iodinated contrast. MR angiography is a viable alternative in some cases in which the need for a detailed evaluation of the airway and lung parenchyma justifies the need for sedation.

In embryonic development, the ventral and dorsal aorta are connected by six pairs of aortic arches. Normally there is regression of some of these arches to result in the normal left-sided aortic arch. The sixth arch forms the ductus arteriosus and proximal right and left pulmonary arteries. Failure of regression or inappropriate development of these primitive vascular structures leads to the development of vascular rings and slings.

Vascular rings are formed when vessels, either patent or atretic, encircle the trachea and esophagus, with the potential to result in esophageal or tracheal compression. The most common

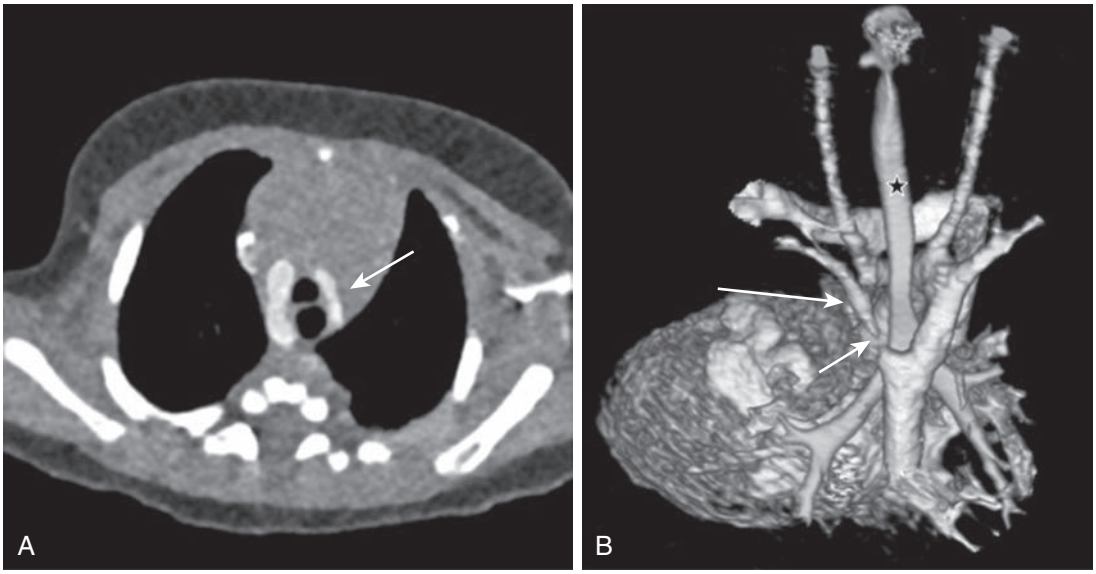

FIGURE 9.9 Axial **(A)** and volume-rendered three-dimensional **(B)** images of a computed tomography angiogram of the chest demonstrate a double aortic arch with hypoplastic left arch (*long arrow,* **A** and **B**) with atresia of the posterior aspect of the left arch (*short arrow,* **B**). The volume-rendered image (viewed from behind) better demonstrates the spatial relationships of the arches to each other as well as to the encircled trachea *(star)*.

symptomatic vascular ring is a double aortic arch (Fig. 9.9).[14] In most cases the right arch is dominant and higher than the left, although the arches can be the same size and one arch can be atretic. The second most common vascular ring is a right-sided aortic arch with aberrant left subclavian artery and left-sided ligamentum arteriosum. Less common vascular rings include left-sided aortic arch with aberrant right subclavian artery and right-sided ligamentum arteriosum and right-sided aortic arch with mirror-image branching and left-sided ligamentum arteriosus as well as circumflex aortas. In several of these conditions, the sidedness of the ligamentum arteriosus or other atretic structures determines if a complete vascular ring is present. The atretic structure itself usually cannot be visualized. Instead, the presence of a *dimple* on the aorta or pulmonary artery, *diverticulum* of the subclavian artery, or position of the *descending* aorta on the side opposite the arch (also referred to as the three "Ds") determines the position of the atretic segment.

Ultrasonography remains the first-line diagnostic tool for the evaluation of the kidneys, liver, and spleen, but when a pathologic condition of the abdomen is a concern and a good acoustic window for US imaging is not available, CT is frequently the examination of choice. CT can be performed with significantly less sedation than that necessary for MRI. CT eliminates many of the artifacts, including those of vascular flow, respiratory motion, and even bowel peristalsis, that limit the utility of MRI. **Skeletal lesions are well visualized with CT. Ultrasonography is the method of choice in the evaluation of congenital hip dysplasia, but CT can be very helpful in evaluating the position of the femoral heads after reduction and treatment of congenital hip dysplasia when the patient is immobilized in a plaster cast.**

CT can be very helpful in identifying the organ of origin of a specific pathologic condition.[14] This is, of course, the first step in narrowing a differential diagnosis. The addition of IV contrast can define the presence and extent of tumor and infection or abscess. CT can also evaluate for adenopathy, as well as the presence of tumor thrombus in renal arteries and the inferior vena cava, which may affect the surgical approach to renal and hepatic neoplasms. The findings on CT often lead to a specific diagnosis. The multiplanar, cross-sectional rendition of anatomy, which allows structures to be distinguished from one another, and the improved

contrast resolution make CT a useful tool when clinically indicated.

Focused Discussion: Intracranial Blood

Noncontrast CT is extremely sensitive and specific for the detection and localization of intracranial blood (Fig. 9.10). Blood from acute hemorrhage has a density on noncontrast CT (measured in Hounsfield numbers) higher than any normal structure except bone and calcium. The increased contrast resolution of CT allows the differentiation of gray matter from white matter and lends itself to a detailed structural evaluation of the brain. The ventricles are low in density (0 Hounsfield units, equal to water), the white matter is denser, and the gray matter is even more dense still, followed by blood from acute hemorrhage and, finally, calcium and bone. **Blood from acute hemorrhage is visualized as white as soon as a clot is formed, and this high density will slowly decrease over time.** For instance, the blood in a subdural hematoma after 2 to 3 weeks will become lower and lower in density until it is indistinguishable from water and CSF. **MRI can differentiate blood from a chronic subdural hematoma for a longer time than CT because the protein within a chronic subdural hematoma modifies the signal on MRI for an extended period.** Although all intracranial blood does change density over time, the compartment in which the blood is found affects the rate of change to some extent. **Therefore, the timing of an event responsible for the blood cannot be precisely determined based on density alone.**

The location of the blood is the next issue. **CT is the most accurate imaging method for detection of subarachnoid blood.** The presence of subarachnoid blood postpartum is common, even after a relatively nontraumatic birth. Unfortunately, on rare occasions, subarachnoid blood can cause vasospasm of vessels near the skull base, which can result in relative ischemia or hypoperfusion of the peripheral cortex. Areas of edema can be detected by looking for the loss of the normal gray–white differentiation or by finding a focal area of brain edema characterized by relatively low density resulting from the addition of low-density water to an otherwise-normal area of the brain.

The shape of a collection of blood is important in evaluating intracranial hemorrhage. Subarachnoid blood assumes a configuration that follows the arachnoid space. Therefore, it is most frequently seen in the suprasellar cistern, the ambient cistern, the Sylvian fissure, or the interhemispheric fissure, or layering on the tentorium. The most sensitive locations for identifying subarachnoid blood are in the region of the quadrigeminal plate cistern, the posterior aspect of the third ventricle, and the interpeduncular cistern. Subdural hematomas occur most frequently over the convexities or along the interhemispheric fissure. Those over the convexity can be differentiated from epidural hematomas by their crescentic configuration as opposed to the lenticular configuration of an epidural hematoma. The dura is the periosteum of the inner table of the skull; therefore, an epidural hematoma is limited by the adhesion of the periosteum to the skull and hence the lenticular configuration. This also explains why epidural hematomas are most often associated with higher-pressure arterial bleeding and why subdural hematomas frequently are associated with venous bleeding. Another key to differentiating the compartment is the relationship to cranial sutures. **An epidural hematoma will not cross a suture line because of the anatomic limitation of the dura by the suture. A similar limitation by the dural attachment at suture lines helps distinguish a cephalohematoma from a caput succedaneum.** The direct sagittal imaging of MRI has revealed the high prevalence of subdural blood in the posterior fossa.

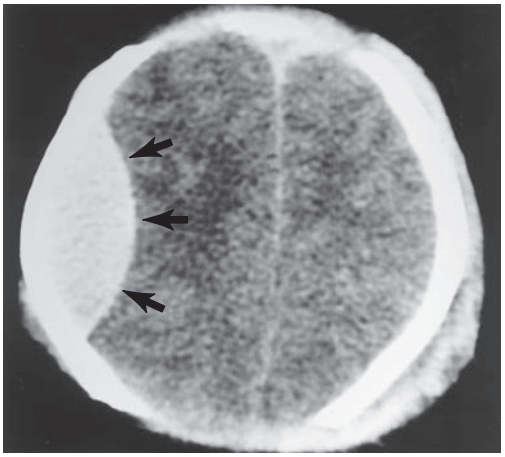

FIGURE 9.10 A single axial image near the vertex demonstrates a high-density lenticular mass *(arrows)* in the extra-axial space over the right cerebral cortex. The lenticular configuration is that of an epidural fluid collection and the high-density characteristic of blood from a chronic hematoma.

MAGNETIC RESONANCE IMAGING

Background

MRI is a modality that images protons or hydrogen ions within the body. The rapid development of magnetic resonance was a result of, in part, the transfer of sophisticated reconstruction algorithms used in CT and the computer power developed in other fields, such as the 3D graphics used in animation, cartography, and seismology. These technologic advances allow tremendous amounts of information to be manipulated quickly enough to make image reconstruction a reality. **MRI is essentially hydrogen imaging, and because the human body is 98% water, much hydrogen is available to image.**

MRI is performed by placing a patient in a strong magnetic field, which varies slightly from the head to the foot. Each proton acts as a small magnet, and just as the needle on a compass orients itself in one direction when placed next to a magnet, the protons in the body align when placed into a strong magnetic field. This alignment of protons is essential to create an environment that has a net electromagnetic field. Without the alignment of protons by the magnetic field, the random orientation of protons would have no measurable net field effect when stimulated and therefore would create no signal to image.

Once the patient is in the magnetic field, a radiofrequency (RF) pulse is delivered. In current imaging systems, the pulse wave has the frequency of an FM radio wave. Less than 1 in 1 million hydrogen ions will absorb any energy, and only certain RFs will allow the transfer of energy from the RF pulse to a hydrogen ion.

An analogy of this energy transfer can be seen on a schoolyard playground. Visualize a child on a swing. When pushing the swing in rhythm or resonance with the natural frequency of the motion of that swing, the swing will absorb the energy, and the child will swing higher and higher with each push. This natural rate of harmonic motion depends on the length of the rope on the swing and the mass of the swing and the child. If you were to push at a rate that was not synchronous with the swing's natural rhythm, pushing would not allow the energy to assist in propelling the swing higher and higher, and in fact, you would disrupt the normal rhythm of the swing.

In a famous TV commercial for Memorex in the 1970s, the playback of Ella Fitzgerald's voice caused a goblet to break, demonstrating the absorption of resonance frequency by the crystal in the goblet. The absorbed energy caused the goblet to shatter. In MRI, the FM RF energy is used to stimulate hydrogen ions or protons in the body.

Because the field strength of the magnet used for imaging varies slightly from one end of the patient to the other and the resonance frequency depends on the field strength of the magnet, one can selectively stimulate various locations within the patient. By changing the RF slightly, a different specific group of protons is stimulated. Protons stimulated by an RF pulse absorb energy and move to an unstable higher-energy state. They give up the absorbed energy as an RF pulse or "echo" of the pulse they received. The echo is received by an antenna, just as with a radio receiver, and converted to an image. The signals or echoes received are the result of T1 and T2 relaxation times, which are simply physical parameters that describe the environmental interactions that influence the signal released from a proton. Such spin-echo pulse sequences are frequently used sequences in routine MRI.

An analogy of a spinning top can help to explain the T1 and T2 relaxation times that result in spin-echo imaging. Each hydrogen ion has a dipole moment (a positive pole and a negative pole) and therefore acts like a small magnet within the powerful magnetic field of the imaging magnet. These protons spin or precess with a precessional frequency that is related to the field strength of the magnet. Electromagnetic energy can be transferred to these protons if the energy is delivered at the resonance frequency. Once an RF pulse of resonance frequency is delivered, a small number of protons will absorb this energy and move to a higher-energy state. The T1 relaxation time reflects the time it takes for these excited protons to give up their higher energy and return to baseline.

T2 relaxation times relate to a second parameter of physical interactions. Although the protons are rotating at a frequency proportionate to the magnetic field in which they exist, they are not in phase. In other words, there is no net direction of polarity from all of these spinning magnets. Once the RF pulse perturbs or stimulates these protons, they begin to spin synchronously and therefore create a net magnetic field. This spinning net magnetic field generates an electromagnetic wave that can be

picked up by the RF antenna of the imaging system as an "echo" of the original RF pulse delivered. (The principle of a spinning magnet inducing an electromagnetic pulse is the basis for the turbines of hydroelectric generators.)

Because its immediate electromagnetic environment affects each proton differently, these protons will remain synchronous in their precession for a very short period. As they move out of phase or synchrony, the net magnetic field that was created dissipates; therefore, the signal received by the RF antenna diminishes. The T2 relaxation time indicates the time it takes the protons to go from a state of synchronous rotation, when maximal signal is created, to random, out-of-phase precession, with zero net magnetic field and hence no signal. The requirement of a net magnetic field to create a signal is used to evaluate flowing blood without the need for contrast. An RF pulse saturates the protons in the field being imaged. The saturated blood within the vessels of that field flow out of the field and are replaced with nonsaturated blood from an adjacent slice. Consequently, there is no signal from the vessel containing the blood flowing perpendicular to the slab being imaged.

Diffusion-weighted sequences have proven to be very sensitive in defining neonatal pathology. Diffusion weighting is the most sensitive technique in the identification of early anoxic-ischemic injury. Diffusion weighting takes advantage of the random Brownian motion of molecules in fluid and the restriction of Brownian motion by anatomic barriers or edema. Water within the ventricular system will diffuse homogeneously in all directions (i.e., no restricted diffusion) and will be a low signal on a diffusion-weighted sequence and high signal (white) on an apparent diffusion coefficient (ADC) map. An acute or subacute infarction, for instance, will cause restricted diffusion in the affected region as fluid rushes into cells due to failure of the cells' homeostatic mechanisms, such as ion pumps. The restricted diffusion caused by acute cell death will be a high signal on the diffusion sequence and a low signal on the ADC map. Late findings after infarction will demonstrate facilitated diffusion with a high signal on both the diffusion and ADC map as the infarcted cells burst and therefore no longer restrict the movement of water molecules. Diffusion tensor imaging measures diffusion in at least six planes simultaneously. From that data, a map of the magnitude and direction of water movement can be generated. The axons within white-matter tracts will allow diffusion in the direction of the axon but will restrict diffusion in any direction other than the course of the axon. This allows one to map the white-matter tracts and has been studied in relation to developmental abnormalities in the brain, the relationship of intracranial neoplasm to white-matter tracts, and the plasticity of the developing brain in response to injury.

The key feature of the physics of MRI is that images are acquired without ionizing radiation, which is particularly important in pediatrics. No known harmful effect of either magnetic exposure or RF exposure at the levels used in MRI has been observed. **However, MRI is still relatively new, and one should be cautious in using MRI for fetal and newborn imaging. Energy deposition is a concern, and protocols have been established that limit patient exposure.** Another concern is the effect a magnetic field might have on electronic instrumentation, such as pacing devices and metallic surgical clips. The torque on metallic implants can be quite high, but this is rarely of clinical significance. However, the artifact caused by the disturbance of the magnetic field can be significant. The most important and real safety concern is that of the magnetic-field attraction of ferromagnetic material. Pens, stethoscopes, or even oxygen canisters can act as projectiles when inadvertently brought too close to a magnetic field.

The main drawback of current MRI technology is the time it takes to acquire an image. Motion-free imaging is necessary for optimal image quality, and because image acquisition in MRI takes minutes, sedation frequently is necessary. Respiratory and cardiac gating can help for physiologic motion, but even physiologic motion can be problematic.

Focused Discussion: Practical Considerations

The physics of MRI is complex, and multiple variables influence the signal received (Fig. 9.11). These influences variably affect the T1 and T2 relaxation times in spin-echo imaging. Imaging sequences tend to be called *T1* or *T2 sequences,* depending on which physical parameter has the most influence on the appearance of the image. A helpful simplification of spin-echo imaging is that in T1-weighted spin-echo sequences, fluid is black,

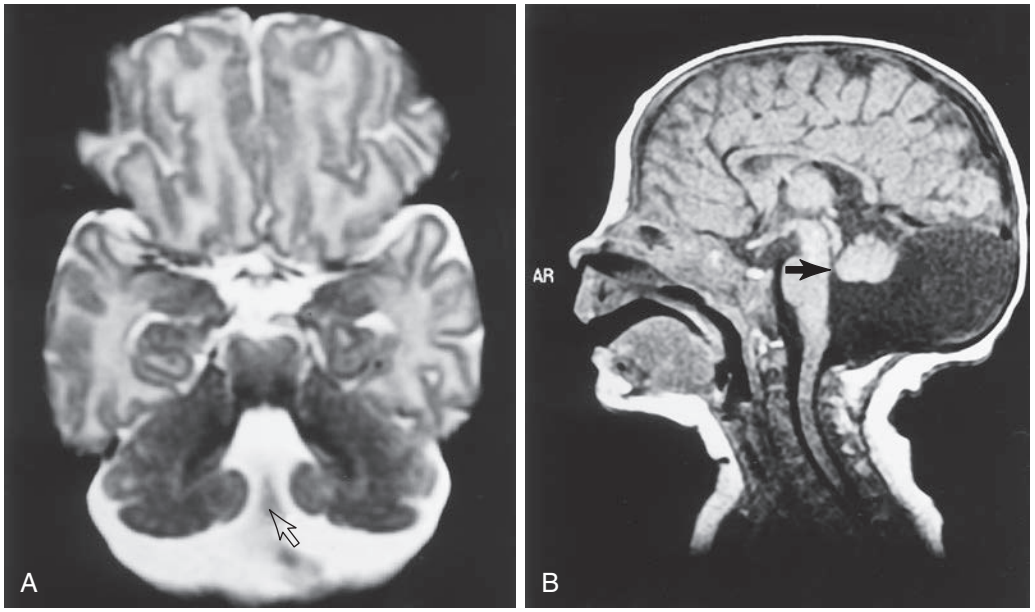

FIGURE 9.11 Axial T2-weighted image through the posterior fossa **(A)** demonstrates the high-signal cerebrospinal fluid in the posterior fossa cyst, which communicates with the fourth ventricle more anteriorly *(open arrow)*. Midsagittal T1-weighted image **(B)** demonstrates a Dandy-Walker variant in this patient. The partial formation of the vermis seen best on the sagittal image defines a Dandy-Walker variant *(black arrow)*.

whereas in T2-weighted imaging, fluid is white. **Most pathologic conditions are characterized either by the distortion of the normal anatomy or by edema, which is manifested as increased fluid in an otherwise normal structure or within the particular lesion.** Therefore, if one looks for a fluid collection (e.g., CSF in the ventricles of the brain, such as CSF in the subdural space around the cord; orbital fluid of the aqueous humor; or fluid in the heart or urinary bladder), one usually can determine whether the imaging sequence is T1 weighted, in which the fluid appears black, or T2 weighted, in which the fluid appears white. On T1-weighted sequences, a pathologic condition is seen as a black or lower signal because a pathologic state is associated with increased water in the area of abnormality. In T2-weighted sequences, the pathologic lesion tends to be white.

Focused Discussion: Fetal MRI

Historically, US has been the most effective and informative imaging modality in fetal medicine. However, as the field of maternal-fetal medicine evolves, fetal MRI is becoming an essential part of the imaging armamentarium (Fig. 9.12). The explosion in fetal MRI is the result of advanced instrumentation, imaging sequence development, and expertise in interpretation. The newer equipment and modified sequences shorten acquisition time and therefore minimize artifact, yielding better-quality images.

US continues to offer the advantage of availability, portability, and real-time acquisition. MRI, like US, is performed without ionizing radiation. Although fetal US continues to be the screening modality of choice, MRI as an additional modality can clarify US findings. **Literature also has demonstrated that fetal MRI can identify additional abnormalities not seen by fetal US, particularly in the central nervous and genitourinary systems.** A fetal MRI examination takes much longer to perform than an US study, and in general, the imaging is not real-time. However, **MRI offers a number of advantages. Tissue characterization with MRI is superior to that of US.** This is particularly helpful when evaluating the fetus for developmental anomalies of the

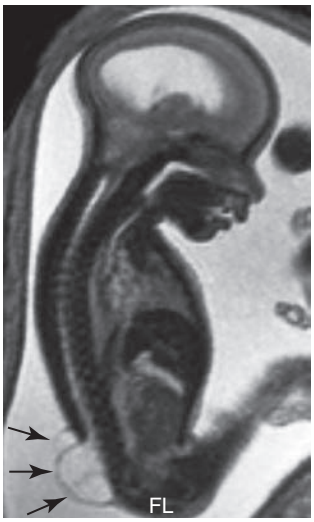

FIGURE 9.12 Sagittal T2-weighted fetal magnetic resonance imaging demonstrates a defect within the lumbosacral spine with associated cystic structure consistent with a lumbosacral myelomeningocele. The associated findings of a small posterior image with dilatation of the lateral ventricles, consistent with a Chiari II malformation, are also partially visible.

central nervous system. Cerebral sulcation, cortical and white-matter development, and ventricular size and configuration can be readily displayed with fetal MRI. **MRI can clarify spinal abnormalities suggested by screening US.** MRI is an essential part of the Management of Myelomeningocele Study (MOMS Trial) comparing the results of prenatal versus postnatal repair of myelomeningocele. **Another important role of fetal MRI relates to imaging of the airway and lungs.** Valuable information concerning the degree, location, and nature of bronchial obstruction can have a significant effect on ex utero intrapartum treatment (EXIT) procedures to deal with complex anatomy that could result in fatal airway compromise after birth.

NUCLEAR SCINTIGRAPHY

Nuclear scintigraphy is the most physiologic of the tools commonly used in neonatal imaging. A pharmaceutical is tagged with a radiotracer, which is a radioactive isotope that can be detected by a nuclear medicine camera. The pharmaceutical may be injected intravenously, given orally, or delivered directly into the urinary bladder. The pharmaceutical is distributed in the body based on the parent compound to which the radioisotope is chelated or bound. The patient then is imaged using a detector that maps the distribution of the tagged isotope in the body.

The radiation dose in scintigraphy is small. With the doses used for diagnostic purposes, there is little risk to the individual and no risk to anyone who is in immediate contact with the patient. The pharmaceutical agents have both a biologic half-life related to the natural elimination of the parent compound from the body and a radioactive half-life determined by the isotope used to label the pharmaceutical. The spatial resolution is poor, but the contrast resolution is exquisite because the radiopharmaceutical is distributed so specifically within the body.

Clinical Utility in the Neonatal Intensive Care Setting

Three common investigations for which nuclear medicine is well suited are renal scintigraphy, hepatobiliary imaging, and splenic imaging. In patients with the syndrome defined by vertebral, anal, cardiac, tracheal, esophageal, renal, and limb (VACTERL) anomalies, renal scans can be helpful in determining the number and location of the kidneys. Renal scintigraphy can be used to quantify relative renal function. **Scintigraphy is a functional way to evaluate the degree of obstruction in hydronephrosis.** Nuclear cystography has a very low radiation dose; therefore, it is a good method for following vesicoureteral reflux. Fluoroscopic cystography usually is performed for the initial evaluation because the excellent spatial resolution can assist in defining anatomic abnormalities that may be responsible for reflux (e.g., that might be missed with the poor spatial resolution of nuclear imaging).

Hepatobiliary imaging can assist in the evaluation of the jaundiced patient. The radiopharmaceutical is extracted from the blood pool by the liver and excreted like bile, allowing one to determine transit time and flow of the bile from the liver into the gallbladder, through the common bile duct, and into the duodenum. **Hepatobiliary imaging can help distinguish neonatal hepatitis from biliary atresia. In neonatal hepatitis, there is limited clearance of the pharmaceutical agent from the blood by the liver;** therefore, the liver shows little activity compared with the background, but a small amount of activity is excreted into the bowel. **In**

biliary atresia, the clearance or extraction of the radiopharmaceutical agent from the blood is closer to normal, but the isotope never leaves the liver, and therefore no activity is seen in the duodenum and small bowel, even on delayed images. A choledochal cyst accumulates radiotracer and is diagnosed by an intense area of focal activity and a dilated biliary system more proximally.

Splenic imaging can be performed with technetium sulfur colloid, which is taken up in the Kupffer cells in the liver and spleen. Alternatively, radiolabeling of red blood cells can be used for splenic images because damaged cells are sequestered in the spleen. Splenic imaging frequently is helpful in patients with complex congenital heart disease and situs abnormalities to diagnose asplenia or polysplenia.

Focused Discussion: Renal Scintigraphy

The radiopharmaceutical choices for renal imaging are either cortical agents that bind in the renal cortex, filtered agents that transit the cortex and then are excreted into the collecting system, or a combination of both cortical and filtered agents. Cortical agents are useful in defining the size, number, location, and relative function of the kidneys (when there are two kidneys). The US characteristics of multicystic dysplastic kidney (MDK) usually are diagnostic; however, renal scintigraphy (Fig. 9.13) occasionally can help differentiate the hydronephrotic form of MDK from severe ureteropelvic junction (UPJ) obstruction. A combination agent, such as mercaptoacetyltriglycine (MAG3), is useful in the evaluation of hydronephrosis because one can determine the relative function of each kidney and evaluate the degree of obstruction. Addition of the furosemide (Lasix) washout study augments the evaluation of hydronephrosis by rendering a washout curve that is indicative of the severity of obstruction. In evaluating hydronephrosis, it is generally helpful to place a catheter in the urinary bladder to prevent possible vesicoureteral reflux from confounding the examination results. Although all of these tests can be performed in the newborn period, the concentrating ability of the newborn kidney is marginal. Therefore, the tests often are reserved until the patient is 3 to 6 months of age to improve their accuracy and prognostic capability.

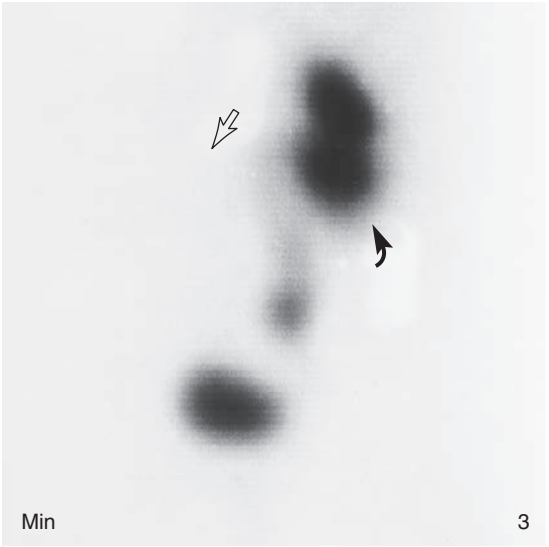

FIGURE 9.13 This posterior image from a diethylenetriaminepentaacetic acid (DTPA) renal scan demonstrates the collecting system, ureter, and urinary bladder associated with the functioning right kidney *(black arrow)*. The multicystic dysplastic kidney on the left shows no functional renal tissue *(open arrow)*.

POSITRON EMISSION TOMOGRAPHY

Background

Clinical utilization of positron emission tomography (PET) in neonates and young infants has been limited because the radiation dose is significant. Nonetheless, the recent growth of and interest in PET for specialized applications argue for its understanding.

The concept of PET was initially proposed in the early 1950s, and medical PET was first attempted in the mid-1970s. The physics of PET involves the introduction of a positron-emitting radiopharmaceutical combined with a biologically active substance. These short–half-life radiopharmaceuticals require a cyclotron to produce and are therefore less available than the pharmaceuticals most commonly used in routine nuclear scintigraphy. A positron is a particle with the opposite charge of an electron that travels only a very short distance within the body until it hits an electron. The collision of the positron with an electron results in two annihilation electrons (gamma rays) of the specific energy 511 keV being emitted in opposite directions at equal velocity. The location in space of the point source of the electrons can be calculated from the

fractional difference in the time it takes for the electron to reach the detector. The positron-emitting tracer attached to a metabolically active substance is introduced into the body intravenously, and the radiotracer is distributed throughout the body with the active metabolite. After 30 to 60 minutes of redistribution within the body, a scintillation scanning device detects the nearly coincident paired gamma rays. In the body, bones and other attenuators block some of the electrons from reaching the detector. Therefore, a means of identifying the blockers is needed.

CT happens to be a very efficient means of locating bones and other blockers but has the added benefit of rendering anatomic images. This allows for more precise localization of signal and its relationship to internal structures. Because of the ability to acquire both anatomic and metabolic information simultaneously, the combination of PET and CT (PET/CT) has been responsible for the rapid growth of PET in recent years. Not only can one identify regions of high metabolic activity, but also the location can be more precisely correlated with the internal anatomy, with significant improvement in diagnostic accuracy. In humans, the most common pharmaceutical used is fluorodeoxyglucose (FDG), which is a glucose analog. FDG is distributed like glucose throughout the body. Regions of abnormal metabolic activity can be identified and, with CT, localized to a specific structure in the body. A metabolically active tumor, for instance, would demonstrate a focus of increased activity in a PET image. For example, if it were localized in the anterior mediastinum, it would be consistent with the diagnosis of lymphoma.

Clinical Utility in the Neonatal Intensive Care Setting

The relatively high radiation dose associated with PET has limited its use, but it has been effectively utilized in staging neonatal neoplasm. The role PET will play in the evaluation of hypoxic-ischemic injury and the evaluation of neonatal seizures is yet to be determined.

INTERVENTIONAL RADIOLOGY

Intervention is one of the newest but most rapidly growing subspecialty areas in medical imaging. Interventional radiology has assumed an important role as a minimally invasive way to treat disease. Imaging can also direct the surgical approach. From a practical standpoint, **there are four major areas of radiology intervention: (1) vascular access; (2) tissue sampling for minimally invasive diagnosis of neoplasm or infection; (3) catheter or needle drainage of fluid collections or abscesses; and (4) directed delivery of cells, chemotherapy, or embolic material, which may be used to diminish flow to a vascular lesion.**

Any of the imaging modalities may be used to guide the intervention, but the most commonly used are fluoroscopy, ultrasound, and CT.

Clinical Utility in the Neonatal Intensive Care Setting

Vascular access is the most commonly requested radiologic intervention in most pediatric institutions. Ultrasound or fluoroscopy can be used to visualize veins for venous access. Although bedside catheter placement with confirmation of placement by ultrasound or radiography is often possible, placement in interventional radiology is sometimes necessary in difficult cases, such as patients with aberrant anatomy, vascular narrowing, or occlusion.

***Tissue sampling* is often performed to diagnose neoplasm.** In general, utilizing ultrasound, fluoroscopy, or CT, a needle is placed into an area of abnormal tissue to obtain either a fine-needle aspirate or, often in solid tumors, a core needle biopsy. The advantage of a core needle biopsy is that the tissue obtained is frequently large enough to complete many of the pathologic studies necessary in the pretreatment evaluation of the neoplasm. This can be particularly helpful in patients in whom a neoplasm, once defined, can be pretreated before definitive surgical resection is performed.

***Cysts or abscesses can be drained,* obviating the need for an open surgical procedure and thus minimizing morbidity and shortening recovery time.**

A *gastrostomy or gastrojejunostomy tube* also can be placed in a minimally invasive manner, rather than a more invasive surgical procedure. This can be an ideal approach for the placement of a temporary feeding tube.

***Directed delivery of chemotherapy* has been used in neonatal units for the treatment of hepatoblastoma.** Chemotherapy can be directed through the hepatic artery into the involved lobe and the tumor reduced in size before excision. By reducing the size of the tumor preoperatively, a previously nonresectable tumor can sometimes be removed.

Another example of directed delivery is the *embolization* of infantile hepatic hemangioma. Infantile hepatic hemangioma is a rare cause of congestive heart failure resulting from an extracardiac shunt in the neonatal period. It is possible to embolize the benign neoplasm, thereby diminishing the shunt and correcting the heart's failure. Vein of Galen malformation is another extracardiac vascular shunt that frequently predisposes the patient to high-flow cardiac failure. A spectrum of vein of Galen malformations exists, and the success of embolization is highly dependent on the degree of vascular insufficiency resulting from the steal associated with a high-flow lesion. In patients who present early and in florid heart failure, the outcomes are predictably worse than in patients who present later with an abnormality discovered during a routine physical examination, in which an intracranial bruit might be identified.

Finally, directed delivery for cell implantation and genetic engineering shows great promise. These areas are early in their development, but the ability to direct a catheter to a specific organ for cell implantation or gene therapy will clearly have a role in future applications of interventional radiology.

Focused Discussion: Vascular Access

The availability of ultrasonographic equipment can allow placement of PICCs or central venous catheters in vessels as small as 2 mm. With US imaging, the vessel is visualized directly. Fluoroscopic guidance requires limited venography by injecting contrast through a peripheral IV line. After visualization with either ultrasonography or fluoroscopy, a 21-gauge needle is placed into the selected vessel. Once good blood return confirms the intraluminal position of the needle tip, a 0.18-wire is passed through the needle. The needle is removed, and the tract is dilated. Next, a peel-away sheath is placed over the wire. The catheter is sized and then passed through the peel-away sheath. The location of the catheter tip is confirmed fluoroscopically.

PICTURE ARCHIVING AND COMMUNICATION SYSTEMS

The widespread use of picture archiving and communication systems (PACSs) has had a significant effect on diagnostic imaging and medicine throughout the United States and the world. Simply put, a PACS is the process of image display, distribution, and archive as it relates to radiology (Box 9.3). **PACS allows images obtained by CT, MRI, ultrasound, nuclear imaging, and plain radiography to be distributed to any location for simultaneous access by any number of caregivers and specialists.** Images can be distributed via a local network within a hospital, over a regional network to a group of providers, or over the Internet for viewing anywhere in the world. Systems have been developed that offer resources never before possible with film. Archives are protected for patient privacy and safety.

BOX 9.3 PICTURE ARCHIVING AND COMMUNICATION SYSTEM

- Acquires, displays, distributes, and archives patient images
- Displays digital images on computer monitors (soft copy)
- Enables manipulation of images to enhance visualization
- Provides brightness, contrast, magnification
- Makes simultaneous viewing at multiple sites possible
- Improves efficiency and accelerates results reporting
- Enhances decision support, which improves patient management

For a number of years, CT, MRI, and US images have been acquired digitally or, at a minimum, were handled digitally after an analog-to-digital conversion. Before computerized radiography (CR) and digital radiography (DR), x-ray images obtained on film could be converted into a digital format by scanning the film in a laser scanner. Fluoroscopic and x-ray images are now captured digitally with CR or DR and thereby become immediately available for soft-copy reading from a computer monitor as opposed to viewing a radiograph on film at a view box, known as *hard-copy reading.* CR is very similar to conventional radiography except that it replaces film with a phosphorescent imaging plate that transfers the latent image into a digital format when developed. DR provides for direct conversion of the x-ray into an electronic digital format that requires no processing of the imaging plate.

The flexibility provided by digital imaging permits extensive manipulation of images. The contrast and brightness (window and level) can be adjusted to optimize visualization of selected images or even portions of an image. These parameters can be changed when viewing an image to enhance a particular structure or finding. The window and

level can be changed when viewing a chest x-ray image, for example, to accentuate the lung, bones, a central catheter, an endotracheal tube, or a gastrostomy button. Images can be magnified, rotated, inverted (black to white and white to black), and even screened by sophisticated computer programs to improve the detection of pathology. Radiology reports can be transcribed with voice-recognition software, allowing the radiologist to edit and sign a report within minutes of acquisition. The reports then are associated with images from the examination. **It is now common to have images and interpretations available on a computer monitor in the NICU by the time the patient returns from radiology.** Reports and images then are assimilated into the patient's electronic medical record. PACS is a powerful tool that improves medical management by translating bits of data into clinically relevant information. It enhances medical care and decision support by making images and interpretations available simultaneously in numerous locations, including in the NICU and often at the bedside, in a fraction of the time previously necessary.

FAMILY EDUCATION AND INVOLVEMENT

The NICU team can have a positive effect on imaging by helping educate the parent. When parents understand a procedure and know what to expect, they can be very helpful. Not only is the quality of the imaging better, but also the experience of the parent and patient is improved. **An informed parent can effectively assist in the imaging process when included in the treatment plan.**

An optimal study requires motion-free imaging. Even with fluoroscopy and ultrasonography in which motion is recorded, the actual acquisition of the image must be free of extraneous motion. With x-ray and CT studies, shortening the acquisition time helps to accomplish this. Respiratory motion can be limited by taking the image at the end of inspiration. Some modalities cannot acquire the image data fast enough to eliminate motion. These examinations frequently require sedation. **The most common modalities to require sedation are MRI, nuclear scintigraphy, and CT.**

Sedation protocols vary from institution to institution, but certain aspects of sedation are universal. **The patient must be given nothing by mouth (NPO) for a period of time before sedation.** It is simply unsafe to sedate a patient who has eaten recently. Failure to keep a patient NPO is one of the most common reasons that a scheduled examination has to be canceled and rescheduled. **Parents generally are informed of the need for sedation and asked for consent (verbal or written).** The choice of sedation depends on many factors. These include the length of the examination, the fragility of the patient, and the experience and training of the individual responsible for sedation. The route of administration also is variable and includes IV, intramuscular (IM), oral (PO), rectal, and inhalation. **The sedated patient is monitored throughout the procedure and recovery. Recovery can occur in the imaging suite, a recovery area, or newborn center, but the patient must be monitored until fully recovered.**

Some unique aspects of newborn care require special attention in the imaging suite that might not be as important in older patients. These important issues are of even more concern in the sedated patient. Thermoregulation is always of concern in the neonate. Imaging suites frequently are cold. **Maintaining body heat is especially problematic in studies that require prolonged imaging times and in those in which the patient could get wet, such as cystography and fluoroscopic GI procedures. Blankets and overhead warmers can mitigate the problem, but providers must anticipate the issue.**

Fluid administration also can be problematic in the neonate. **Newborns need dextrose in their IV lines, especially if they are not feeding. Therefore, it is important in these patients to keep IV lines open and functioning. Most IV pumps are not compatible with MRI, and many cause interference that degrades image quality. However, it is not appropriate to suspend fluid administration for the duration of the study.** The issue should be anticipated and addressed in a timely fashion.

Care of a critical newborn in the imaging suite can be challenging. It requires cooperation between the NICU staff (nursing and medical) and the imaging staff. Parental education enables the parents to participate in the care of

their newborn and has a positive effect on the newborn's imaging experience.

Numerous imaging alternatives are available for the evaluation of any patient condition. The best imaging choice varies depending on local expertise and availability. A clear understanding of the clinical question, patient condition and comorbidities, and the differential diagnosis being considered is essential for optimal imaging and interpretation. **The clinician should consider the pros and cons of each modality and consult with a radiologist if there is any uncertainty as to the best method of imaging.**

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10 PHARMACOLOGY IN NEONATAL CARE

LAWRENCE C. KU, CHI HORNIK, AND DEANNE BUSCHBACH

Optimal pharmacotherapy involves dosing drugs to deliver the maximum intended beneficial effects with the minimum toxicities. Determining the optimal pharmacotherapy for neonates is problematic in that much of the data have been extrapolated from research in adults, children, and laboratory animals. **Neonates show significant differences in processing and responding to drugs compared with older children and adults.[39,46] There is also great variability in the response to pharmacotherapies among neonates. Gestational age, chronologic age, and disease state alter a neonate's ability to metabolize medications and affect the response to the drug.[46,72]**

This chapter discusses neonatal pharmacology, illustrating how rational decisions can be made for pharmacotherapies used in neonatal intensive care unit (NICU) patients. The chapter also includes discussions on strategies to avoid medication errors, strategies for drug delivery, information on how therapeutic hypothermia affects pharmacokinetics, and a summary of recent pharmacokinetic studies in NICU patients.

PHYSIOLOGY

Pharmacodynamics and Pharmacokinetics

The drug-receptor theory states that the amount and duration of exposure of a drug to a receptor determine its effectiveness. ***Pharmacokinetics* describes what the body does to the drug (exposure over time),** which then determines how a drug is available to the receptors and for what length of time (Fig. 10.1).[37,78] ***Pharmacodynamics* describes what the drug (or its active metabolite, such as caffeine for theophylline or morphine-3 and morphine-6 glucuronide for morphine) does to the body at certain concentrations (effect over exposure).** The drug's effectiveness also depends on receptor availability, the affinity of the drug for the receptor, and cellular functions in response to the drug–receptor interaction.

***Antagonist* drugs block a receptor's cellular and physiologic activity (e.g., naloxone), whereas *agonist* drugs elicit the receptor's action (e.g., cardiovascular agents such as dopamine and epinephrine).** Some drugs act with receptors to increase or decrease gene expression (e.g., antenatal steroids such as betamethasone), whereas others affect cell membrane permeability. Some drugs, such as methylxanthines, increase or decrease the amount or activity of second-messenger molecules within cells. Antibiotics and antiviral agents act through some of these mechanisms to reduce the viability of pathogenic organisms by changing vital characteristics and functions. Readers should note that most drugs have more than one effect, so although the desired therapeutic effect may occur, the drug's other effects can limit its usefulness. *Side effects,* which can vary from minor to prohibitive, occur within the therapeutic range of concentration. *Toxic effects* result from a drug overdose or serum concentrations higher than the recommended therapeutic range.

Individual infants may have *idiosyncratic responses* to medications, which are rare and unpredictable reactions, as well as expected responses. Different,

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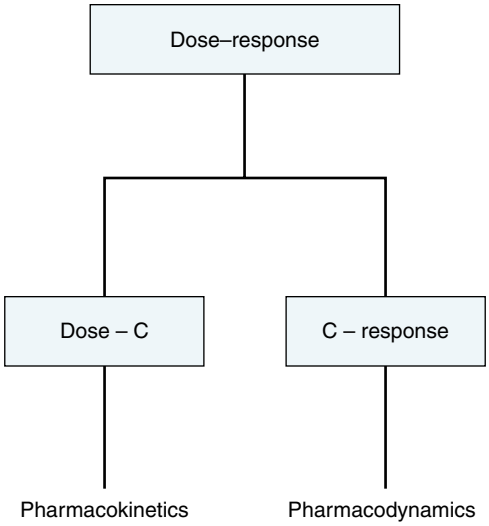

FIGURE 10.1 Variability in dose–response relationship can be the result of differences in pharmacokinetics or pharmacodynamics. *C,* Drug concentration (plasma or serum).

competing mechanisms related to postmenstrual age (PMA) in weeks, postnatal age (PNA) in days, disease, genetics, and drug interactions can lead to infants who exhibit a drug response less than that expected for a usual dose and other infants who exceed the expected response for a given dose and drug level. Unpredictable adverse reactions differ from expected responses. Patients may become tolerant to a given drug dosage, as is commonly seen with opioids. ***Tachyphylaxis*, a rapid decrease in drug response without a dosage change,** may be related to limited receptors or other intracellular mechanisms.[14,33]

Developmental differences related to infant physiology are responsible for significantly different pharmacokinetics in infants compared with adults and older children. Characteristics affecting drug disposition in infants include total serum protein available for binding to drugs, body water composition, kidney function, and skin thickness affecting the intradermal absorption of drugs; these characteristics change drastically over a period of days, weeks, and months after birth.[16,40,85] Many enzymes responsible for the metabolism of drugs prescribed to infants also undergo significant changes in levels of expression and activity with age.[13] In many cases, these enzymes will have significantly reduced activity at birth that slowly increases with postnatal age. As a result, drugs that are predominantly metabolized by these enzymes will demonstrate different rates of elimination among infants of different ages.

Developmental differences in the number and function of receptors and intracellular mechanisms are also critical to estimating drug actions.[77] For example, neonates may have increased sensitivity to morphine compared with adults due to higher levels of expression of the *mu* opioid receptor in neonates.[54] **Changes in alpha- and beta-adrenergic receptors also occur with gestational and chronologic age and must be considered in determining dosages with vasopressors and inotropes.**[8]

A clinician determines a drug regimen and dosage largely on the likelihood of achieving the desired therapeutic response with minimal toxic effects in the "average" patient. In concept, the clinician does this by targeting a drug concentration in the body compartment where the desired effect is wanted.

Plasma concentration is often used as a surrogate for effect when the relationship between concentration (C) and effect has been demonstrated in similar patients. The *minimum effective concentration (MEC)* **is the concentration at which 50% of patients exhibit the desired response** (Table 10.1). The maximum safe concentration (MSC) **is that at which 50% of patients exhibit a toxic response** (Fig. 10.2). The *therapeutic index* is calculated as the ratio of MEC to MSC. Drugs with a **narrow therapeutic index (i.e., where the MEC is close to the MSC) will require careful considerations during patient care, such as drug-level assessments or close monitoring for signs of toxicities.**

To elicit the desired therapeutic effect, the drug must be delivered to the receptor and remain available for an appropriate amount of time.[88] If a clinician aims **to continue the therapy beyond a single dose, then plasma concentration at steady state (Css) is targeted within the MEC and the MSC, where most patients exhibit the desired effect and few suffer toxic effects. With ideal maintenance therapy, the drug administered should equal the drug elimination. The time-dependent variability around the Css depends on the dose, dosage interval, and drug disposition. Even before clinicians consider the age-related changes in drug metabolism when prescribing maintenance therapy for neonates,**

TABLE 10.1 ABBREVIATIONS

ABBREVIATION	ABBREVIATION DEFINED	UNIT OF MEASUREMENT
C	Drug concentration (plasma or serum)	mg/L
Css	Steady-state concentration (average)	mg/L
MEC	Minimum effective concentration	mg/L
MSC	Maximum safe concentration	mg/L
F	Extent of drug availability (0-1): how much active drug gets to the systemic circulation	Unitless
Vd	Volume of distribution: relates to loading dose	L/kg
Cl	Clearance: relates to maintenance dose	L/kg/h
$t_{1/2}$	Drug elimination half-life: relates to the time course of changes in drug concentration	Hours

L, Liter = 1000 milliliters; *mg,* milligram = 1000 micrograms.

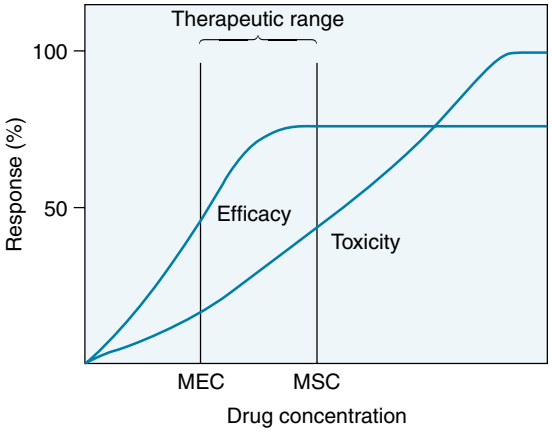

FIGURE 10.2 Percentage of patients with desired and toxic responses as a function of drug concentration. Therapeutic range is bounded by minimum effective and maximum safe concentrations. *MEC,* Minimum effective concentration; *MSC,* maximum safe concentration.

clinicians should anticipate the need to adjust dosages regularly for changes in infant body weight and composition. There is a 10-fold variation in weight range among NICU patients (0.5 to 5 kg). For term newborns, the weight is expected to double in the first 3 to 4 postnatal months, whereas in premature infants, the rate of weight gain can be more rapid.[87]

The target Css is influenced by the amount of drug bound to plasma protein. It is only the free, unbound drug that exerts its effect on receptors and is subject to elimination in the body. In a newborn, **unconjugated bilirubin can displace numerous drugs of lower protein affinity,** including ampicillin, penicillin, phenobarbital, and phenytoin,[80] whereas **other drugs can displace unconjugated bilirubin, which can worsen hyperbilirubinemia and its potential for toxicity,** as observed with ceftriaxone, ibuprofen, benzyl alcohol, and sulfisoxazole.[3,5] **Intravenous (IV) lipid infusions also can affect the protein binding of both bilirubin and some drugs,** such as nafcillin and ceftriaxone. The drug concentration measured in most available assays is usually the total drug concentration, which includes both protein-bound and free forms; therefore, the available concentration at the receptor (i.e., free drug) usually is somewhat less than the total serum concentration. This changes over time for NICU patients with changes in bilirubin production and changes in the amount and types of plasma proteins that come with age. The **lower affinity of fetal albumin to weak acids and the displacement of drugs from binding to albumin by bilirubin can lead to higher levels of freely circulating active drugs** (e.g., protein binding of ampicillin, phenytoin, and phenobarbital in neonates is about half of that noted in adults).[40,77]

The effect of differences in protein binding on drug pharmacokinetics can be illustrated using micafungin as an example. Micafungin is an antifungal agent that disrupts fungal cell walls. It is highly protein bound and highly metabolized by several enzymes known to have lower expression in neonates compared with adults. It would be expected that, based on decreased metabolizing enzyme activity in neonates, the elimination of micafungin would be slower, and lower doses would therefore be needed in neonates compared with adults. However, pharmacokinetic studies in premature infants demonstrated that premature infants had 1.7- to 2.6-fold-greater

micafungin clearance compared with older patients and required a threefold-higher dose than adults to achieve similar drug exposures.[34,77] **Decreased protein-bound micafungin in neonates could explain why neonates have higher clearance rates compared with adults.** Neonates demonstrate a lower fraction of protein-bound micafungin compared with adults (96.7% vs. 99.6%). Because there is a greater amount of unbound micafungin in neonates, more of the drug is available to the elimination mechanisms, resulting in much faster elimination in the younger population. Due to these differences in neonatal physiology, the micafungin doses needed for treating neonates (10 to 12 mg/kg IV daily in extremely low-birth-weight infants) differ greatly from the doses used to treat adults (100 to 150 mg IV daily, which would be 1.5 to 2 mg/kg/dose based on a 70-kg average adult patient).

DOSE–CONCENTRATION–TIME CONSIDERATIONS RELATED TO AGE

In the NICU, doses and intervals must be adjusted based on changes in the dose–concentration and the concentration–response relationships. Measurements of total drug concentrations using therapeutic drug monitoring (TDM) enable a more accurate and precise response to changes in dose–concentration effects. Unfortunately, not all drugs have TDM assays readily available for clinicians. As with the micafungin case, clinicians must observe for clinical effects and assess the influences of other factors that can affect free drug concentrations to estimate drug efficacy and the responsiveness of receptors and cellular processes to the drug.

As noted earlier, pharmacokinetics describes the delivery and removal of a drug to and from the body. **Four major processes can affect a drug's disposition: drug entry (absorption), distribution, biotransformation (metabolism), and elimination.** Doses and dose intervals are expressed mathematically by pharmacokinetic parameters related to absorption, distribution, biotransformation, and elimination, such as the time to reach maximum drug concentrations, volume of distribution, clearance, and half-life. There are many factors unique to newborns that can alter the dose–concentration relationships seen in this population.

Absorption

The process of *absorption* defines the rate and amount of a drug that enters the bloodstream. In the NICU, various routes are used for drug administration. Drugs are frequently given directly into the bloodstream by IV injection. When a drug is given through IV injection, it is said to have **100% bioavailability, meaning that all of the drug given reach the circulatory system.** Drugs are also frequently given by other means that do not introduce drugs directly into the bloodstream, including intramuscularly, via inhalation, intranasally, intrarectally, topically, and subcutaneously. When extravascular administration methods are used, the drug must overcome physical, chemical, mechanical, and biologic variables to enter the circulation. Oftentimes, these obstacles can result in a bioavailability that is less than 100%, meaning that not all of the drug administered will reach the bloodstream. When considering **extravascular administration, clinicians must keep in mind the clinical and developmental stage of the patient.** For example, in extremely premature infants, transdermal absorption is much greater than in term infants due to a thinner stratum corneum and less adipose tissue, but intestinal absorption in the extremely premature infant may be less due to slower transit time and delayed gastric emptying.[40,77]

Bioavailability is represented by the parameter *F*, indicating the percentage of administered drug that becomes available in the systemic circulation, with *F* = 1 indicating the drug is 100% available. Systematic studies of absorption in critically ill newborns are lacking, and differences in absorptive processes are expected but generally remain unmeasured. Some differences in newborns that potentially affect bioavailability include developmental changes in the surface area and permeability of gastrointestinal (GI) mucosa, age-dependent changes in acid secretion in the stomach (neonates have higher gastric pH than in older children and adults in the first postnatal days), changes in gastric emptying time and total GI transit time, and the composition of intestinal microflora. Drugs such as ranitidine and metoclopramide also affect the absorption of other medications by altering gastric and intestinal pH and gastric emptying time and intestinal motility (faster transit time results in less absorption).[77]

First-pass elimination occurs when a drug is eliminated after administration but prior to reaching the systemic circulation. Common sites of first-pass metabolism for orally administered drugs include the liver and the gastrointestinal tract. Other sites of first-pass elimination include the

vascular endothelium and lungs.[64] **Different drugs are absorbed at different rates, and different formulations of the same drug may be protected from first-pass metabolism.**[37] The first-pass phenomenon is why many drugs (e.g., furosemide, propranolol, morphine) require larger doses when given orally compared with intravenously.

Distribution

Medications rely on many factors for distribution to their sites of action, including blood flow, organ size, presence of drug transporters, and drug permeability. The *volume of distribution* (Vd) for a drug is a parameter that relates the total amount of drug distributed throughout the body to the serum or plasma concentration.[14] It is an attempt to quantify the space in which the drug can go. Strictly defined, the volume of distribution is the hypothetical volume of body fluid necessary to dissolve the total amount of drug as found in the serum. The ***volume of distribution* must be used to estimate the amount of a loading dose or a change in plasma concentration with any bolus dose.**

The *volume of distribution* usually is expressed as a function of body weight, with units of volume per kilogram. **Major factors that affect the volume of distribution include plasma protein binding and body composition.**[8] Changes in body composition happen throughout fetal and newborn life. **Total body water as a percentage of body weight decreases with increasing age: 85% in extremely preterm infants; 70% in term infants; and 55% in most adults.** Total body water may increase with conditions such as the syndrome of inappropriate antidiuretic hormone (SIADH) excretion. About half of the total body water is found in the extracellular space in a healthy term neonate, where large, water-soluble drugs will tend to accumulate. **Intravascular water makes up only about 10% of the body weight; protein-bound medications are trapped in this smaller compartment.** Preterm infants have more total body water as a percentage of body weight compared with term infants, and water-soluble drugs such as penicillins, aminoglycosides, and cephalosporins have greater volumes of distribution in preterm infants than in older infants. Preterm infants also have greater volumes of distribution for these water-soluble drugs and require a higher dose per kilogram than term infants to achieve the same exposure.[51,77]

Plasma protein amounts and binding capacities also differ with gestational and chronologic age. Protein binding is decreased in newborns due to lower total amounts of albumin. Additionally, fetal albumin has less capacity to bind certain drugs. Acidic drugs such as ampicillin, phenytoin, and phenobarbital bind less to fetal albumin, thus increasing the unbound fraction of the drug, thereby increasing the amount of free drug available to exert the drug's effect. **Changes in pH also can affect a drug's affinity for albumin.**

Fat content varies with gestational age and degree of illness. For fat-soluble drugs, increased adipose tissue increases the volume of distribution for lipophilic drugs such as propofol and fentanyl. [40,77]

As described previously, the interaction of circulating unconjugated bilirubin and protein-bound drugs is particularly concerning in neonates. **Several anionic drugs, like ceftriaxone, bind to albumin and can displace bilirubin, increasing free bilirubin and increasing its potential for neurotoxicity.** For other drugs, bilirubin can have a higher affinity for albumin than the drug; it may displace these drugs from albumin, increasing the concentration of unbound drug and, therefore, the potential to reach toxic levels.[3,5]

Biotransformation

***Biotransformation*, or *drug metabolism*, occurs most commonly in the liver. Drug metabolism results in the modification of the structure of drugs in the body, leading to their eventual elimination from the body.** Phase I metabolism describes the nonsynthetic metabolism of medications and includes oxidation, reduction, and hydrolysis reactions. Phase I metabolism does not always inactivate the drug; in some cases, the metabolite formed can retain active properties sometimes more potent than the parent drug. Phase II, also known as conjugation, is synthetic metabolism, in which small molecular moieties are added to the drug in the body to aid in its elimination; examples of phase II metabolism include glucuronidation, sulfation, and acetylation. **The enzymes responsible for these reactions change with age, disease states, and interactions with certain drugs.** For example, many enzymes responsible for the **oxidation**

and glucuronidation of drugs are decreased in newborns.

Drugs that rely on these reactions for elimination, such as acetaminophen, phenobarbital, and phenytoin, will be eliminated more slowly and result in higher exposures in the neonate compared with the adult. The possibility of prolonged peak concentrations of available drug or active metabolites for many pharmaceuticals mandates careful monitoring of drug levels and clinical conditions to titrate doses. Additionally, a decrease in plasma protein binding (or any other change in the volume of distribution) may increase the hepatic metabolism and subsequent clearance of a drug, as seen with the micafungin example.

Clearance (Elimination)

***Drug clearance* or *elimination* occurs by excretion of the active drug or biotransformation to an inactive metabolite.** Most drug-elimination pathways can become saturated if the dose is too high or if the dose intervals are too frequent. Most drugs used in the NICU have therapeutic doses less than those necessary to saturate the elimination system. When clearance mechanisms are not saturated, the Css in plasma is proportional to the dose. **Clearance equals the rate of drug elimination divided by the drug concentration.**[37] Just as the volume of distribution relates to the loading dose and initial concentration, **clearance relates to a maintenance dose that keeps a drug's concentration at steady state.** The appropriate dose rate can be calculated if the clinician can specify the desired steady-state plasma concentration and knows the clearance and bioavailability of a drug (from peak and trough levels in a particular patient).

RENAL EXCRETION

The kidney is the primary route of excretion for many drugs commonly used in the NICU. The kidney clears drugs through glomerular filtration and tubular secretion. Examples of medications eliminated through the kidney are aminoglycosides, digoxin, diuretics, and penicillins. Doses and dose intervals of drugs that have renal excretion must be adjusted for age and disease state. **The glomerular filtration rate (GFR; the amount of blood filtered by the kidney in a unit of time) is low at birth and gradually increases over the first few weeks. In preterm infants, the GFR starts even lower than in term infants, with a significant increase occurring around 34 weeks' PMA.** Nephrogenesis begins at 5 to 6 weeks of gestational age, with over 60% of nephrons being formed during the last trimester.[68] Preterm infants born before 36 weeks' gestational age are at risk of having a decreased nephrogenic potential.[1] Tubular secretion also matures with increasing gestational age and depends on tubular function. In adults, aminoglycosides may be dosed based on creatinine clearance, but in neonates less than 1 week old, serum creatinine may reflect maternal levels, as well as renal impairment. Acidosis and a history of hypoxia or ischemia also may modify an infant's renal function, slowing excretion and altering pharmacokinetics. Again, measuring levels through TDM in cases of suspected renal impairment, whether from suspicious history or laboratory values, is important in determining an appropriate dosage strategy.

Half-Life

A drug's *half-life* ($t_{1/2}$) is the time necessary for the drug concentration to decrease by 50%. The half-life is used to predict and interpret the time course of changes in plasma drug concentrations and is related to both the volume of distribution (Vd) and clearance (CL). For example, the time to reach Css with repeated dosing is 4 to 5 half-lives. The half-life is useful in selecting dosing intervals and determining whether a loading dose is necessary. This concept is illustrated in Fig. 10.3.

Loading doses help expedite the attainment of the desired therapeutic concentrations, especially for drugs with long half-lives, in which a desired effect is needed immediately. For example, caffeine is a drug used to treat apnea of prematurity in premature infants. In this patient population, the half-life of caffeine can be as long as 3 to 4 days. Given that the time to reach Css is 4 to 5 half-lives, administering just the maintenance dose will require 12 to 20 days to reach the target concentration and presumably achieve a therapeutic response. For this reason, a loading dose is given to reach the target concentration immediately to achieve a rapid therapeutic response. For drugs with one-compartment distribution that stay in the circulation and are not stored in cells or tissue, the loading dose may be given as a single dose. Drugs that are fat soluble or stored intracellularly are more

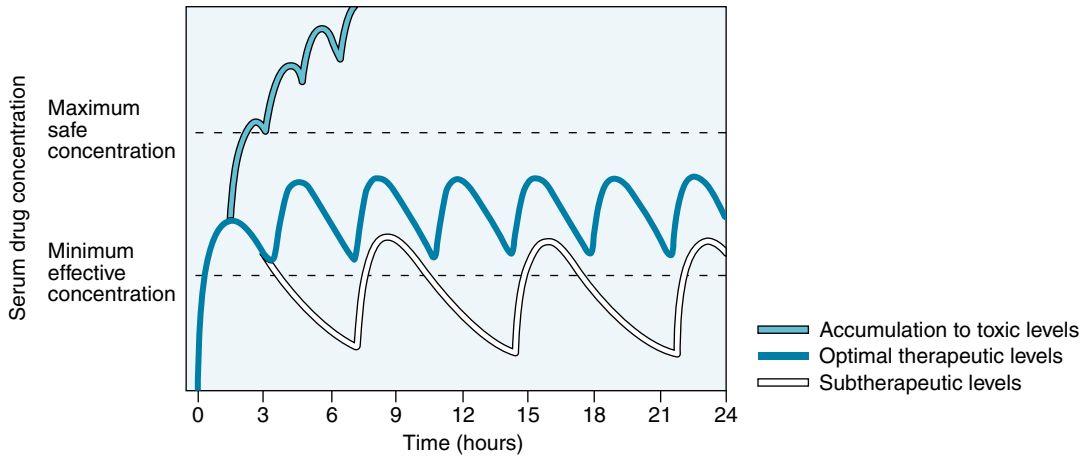

FIGURE 10.3 Effect on serum drug concentration of multiple dosages along with different time intervals between doses. (From Roberts RJ. *Drug Therapy in Infants*. Philadelphia: WB Saunders; 1984.)

difficult to assess, and the volume of distribution of those drugs must be included in the loading-dose assessment.

If the volume of distribution for caffeine in preterm infants is 0.8 L/kg, 20 mg/L is the desired concentration, and *F* for an IV dose is assumed to be 1, a loading dose can be calculated as follows:

$$LD = (Vd \times C) / F = 0.8\ L/kg \times 20 mg/L$$
$$= 16\ mg\ of\ caffeine/kg$$

In certain clinical conditions, such as a birth-depressed **newborn undergoing therapeutic hypothermia, the prolonged half-life of medications is due to significantly reduced metabolism and clearance.** For example, studies have shown that phenobarbital has a prolonged half-life of 8 to 22 days in these patients.[23,74] Similarly, the decreased clearance and longer half-life of gentamicin in cooling infants mandates spacing out the dosing intervals to every 36 hours versus the standard dosing of every 24 hours to prevent accumulation.[26]

Pharmacogenetics and Pharmacogenomics

In the 30,000-plus known genes, there are over 4 million "common" variants (occurring in more than 1% of the population), many of which directly affect the function of the coded proteins. **In certain cases, these genetic differences can result in changes in the expression and function of proteins involved in the absorption, distribution, metabolism, and elimination of certain drugs.** These changes can lead to significant clinical consequences. *Pharmacogenetics* **is the study of the role of inheritance in the individual variation in drug response.** *Pharmacogenomics* **is the study of the influence of multiple genes, and their interaction with each other and the environment, on drug effects.**[15,68,77]

Genetic variations affecting the ability of patients to metabolize drugs have been well described. Over 40 years ago, one of the first reports of a genetically caused variation in drug metabolism focused on *butyrylcholinesterase*, the enzyme responsible for the hydrolysis of succinylcholine. One in 3500 people is homozygous for the gene encoding an atypical form of butyrylcholinesterase. Patients with the atypical form of the enzyme are poor metabolizers of succinylcholine and thus eliminate succinylcholine much more slowly than people with the normal enzyme variant. Because metabolism is significantly hindered in patients with the atypical enzyme form, succinylcholine levels in patients with the atypical variant are more likely to accumulate to levels that can lead to prolonged muscle paralysis.

The cytochrome P-450 (CYP) enzymes are a group of enzymes responsible for the metabolism and subsequent elimination of many of the drugs used to treat patients. CYP2D6 is an example of a CYP enzyme with genetic variations resulting in clinically significant consequences. Codeine is an opioid used in the treatment of pain. For codeine

to achieve its clinical effect of pain relief, it must first be converted by CYP2D6 to its active form, which is morphine. Certain patients have genetic variants of this enzyme that result in decreased function of CYP2D6, thus making these patients poor codeine metabolizers and, therefore, poor responders to codeine. There are also patients who have genetic variants that result in increased function of CYP2D6, thus making these patients ultra-rapid metabolizers of codeine. These patients can metabolize codeine into morphine much faster than the normal patient, resulting in faster formation and accumulation of morphine and increased risk for toxicity. This can have especially important consequences in breastfeeding women. **A breastfeeding woman who is an ultra-rapid metabolizer of codeine can develop morphine levels high enough to transfer to her infant through the breast milk and lead to signs of opioid toxicity in the infant,** such as sleepiness, poor feeding, and even respiratory depression. In the worst cases, this has resulted in infant death due to morphine toxicity.[47] In 2007, the U.S. Food and Drug Administration (FDA) issued a public health advisory on life-threatening side effects in nursing babies of some women who were prescribed and taking codeine. Since then, the FDA (and the European Medicines Agency)[21] issued a strengthened warning in 2017 for codeine and a new warning for tramadol in breastfeeding mothers due to the same concern with ultra-rapid metabolizers.[83]

A genetic variant in mitochondrial DNA, the A1555G mutation, has been linked to a risk of hearing loss associated with aminoglycoside toxicity. The frequency of this mutation in the general population is estimated to be between 1% and 3%, but among deaf subjects tested, the concurrence of deafness with the aminoglycoside treatment associated with this mutation is more common. This suggests that in the future, testing for the mutation before the use of aminoglycosides might be warranted. However, it is currently unknown whether tighter control of aminoglycoside levels in these patients would reduce the risk of hearing loss. No recommendations can be made until more extensive, population-based studies are done. Such studies must include controlling for drug levels and duration and genotypes in the assessment of the risk of hearing loss.[56]

In addition to drug metabolism, genetic variants can also affect the expression and function of drug targets. These include adrenergic and dopamine receptors and enzymes, such as acetylcholinesterase, and are likely to have effects on the response to drugs targeting these proteins, such as bronchodilators, vasopressors, and inotropes, and angiotensin-converting enzyme (ACE) inhibitors such as enalapril and captopril.

There have been few studies focused on pharmacogenomics in neonates, particularly those who are premature. However, genetic differences with clinically important consequences have been described in premature infants.[4] For example, polymorphisms in the enzyme UGT2B7, which is responsible for the metabolism of morphine, have resulted in pharmacokinetic differences in infants treated with morphine.[48] Also, polymorphisms affecting the expression of the opioid receptors upon which morphine exerts its effects have resulted in differences in the need for rescue doses of morphine among premature infants on mechanical ventilators.[49] Still, very little is known about the clinical effects of many genetic polymorphisms among infants; pharmacogenetics and pharmacogenomics are areas deserving more study in infants.

DATA COLLECTION

Monitoring Safety and Efficacy of Pharmacotherapies in the Clinical Setting

Clinicians must be aware of a medication's desired therapeutic effects, side effects, and toxicities; know when these are expected to occur; and continuously monitor for these effects. Whether or not a dose effect occurs requires documentation. **The exact time when therapeutic drug monitoring is conducted should be recorded in order to accurately evaluate the dose–plasma concentration.** If the drug's serum concentration relates to clinical response, the plasma concentration should be monitored in addition to clinical signs. To optimally assess drug serum levels, the expected plasma concentration is calculated from the dosage history, and patient variables that may affect pharmacokinetics and the timing of blood samples are considered. A comparison of expected values with measured values allows rational adjustment of future dosages.[15] Potential explanations for differences

BOX 10.1 POTENTIAL EXPLANATIONS FOR DISCREPANCIES BETWEEN MEASURED AND EXPECTED DRUG CONCENTRATIONS

- Inadequate compliance
- Inadequate medication delivery
- Inappropriate timing of samples
- Laboratory error
- Revision in initial estimates of necessary pK required

pK, Pharmacokinetics.

between measured and expected concentrations are listed in Box 10.1.

Even if predictable pharmacokinetic and pharmacodynamic changes are considered, other factors may influence a drug's effect. Clinical end points must be followed and recorded, with dosage regimens adjusted accordingly. One example is the monitoring of renal function with indomethacin dosage; an indication for using IV indomethacin is for treatment of hemodynamically significant patent ductus arteriosus (PDA). Some of these infants may exhibit compromised perfusion to their kidneys because of the PDA steal phenomenon. However, **if clinical signs of renal dysfunction (a potential side effect of indomethacin) are noted, the drug is not administered. A pharmacist on the caregiving team can clarify the dose and disposition parameters for individual neonates with a variety of conditions.**

If a suboptimal clinical response is noted in conjunction with a subtherapeutic plasma concentration, revised estimates of clearance require adjustments with one or two available plasma concentrations. If a single level is drawn after drug absorption and distribution are complete or concentrations are near steady state, then the maintenance-dose formula can be rearranged to calculate the revised clearance. The commonsense approach suggests that if a patient has half the expected concentration of a drug, then perhaps the clearance is twice the initial estimate. If the patient has twice the expected concentration, the clearance likely is half the initial estimate. However, this technique is misleading if a steady state has not been reached. **If a drug's level is higher than expected and higher than what is considered safe, or if toxicity is noted, the drug should be discontinued until the concentration decreases to the appropriate target range.**

Examples

The following examples illustrate the need to pay close attention to issues of dose and clinical effects. The following examples are for caffeine citrate in neonates. The half-life of caffeine citrate in premature neonates is 3 to 4 days, the *Vd* is *0.8 to 0.9 L/kg,* and clearance is *0.008 L/kg/h*.

EXAMPLE 1: A 15-day-old, 1-kg preterm infant receives oral caffeine for apnea of prematurity. After the loading dose of 20 mg/kg, the infant has received 5 mg every 24 hours of caffeine for 5 days. At 8 AM on the fifth day, 4 hours after the last dose, the baby's heart rate is more than 180 beats/min, but apnea has not been a problem. Clinical and laboratory evaluation of tachycardia includes consideration of caffeine toxicity. A blood sample for caffeine is sent to the laboratory. To estimate the concentration of caffeine, use the following formula:

Necessary data (assume $F = 1$):

$$\text{Total body weight} : 1\,\text{kg}$$
$$\text{Vd} = 0.8\,\text{L/kg} = 0.8\,\text{L in this patient}$$
$$\text{Cl} = 0.008\,\text{L/kg/hr} = 0.008\,\text{L/hr in this patient}$$
$$t_{1/2} = 0.7 \times \text{Vd} / \text{Cl} = 0.7 \times 0.8\,\text{L} / (0.008\,\text{L/hr})$$
$$= 70\,\text{h}$$
$$\text{Time to steady state (Tss)} = 4t_{1/2} = 280\,\text{h}$$

Therefore:

$$\text{Css} = F \times \text{Dose} / (\text{Dose interval} \times \text{Cl})$$
$$= 1 \times 5\,\text{mg} / (24\,\text{hr} \times 0.008\,\text{L/hr})$$
$$= 26\,\text{mg/L}$$

The Css was estimated using average Vd and Cl values reported in similar infants, adjusted for this infant's weight. If this infant has diminished clearance relative to the "average" infant, toxicity may result from the standard dose. Toxicity may not have been noted until day 5 because of the estimated time to steady state (Tss) of 115 hours.

EXAMPLE 2: When the next dose of caffeine is due at 4 AM, 24 hours after the last dose, a caffeine concentration of 27 mg/L is reported. This is within the therapeutic range for caffeine in neonates, but this infant is exhibiting tachycardia, a side effect of the

drug, at this level. His heart rate is now consistently >190 beats/min. The patient is stable on room air, with no occurrence of apnea. Because of the slightly higher-than-expected level, it is most likely the result of decreased clearance. Using this concentration, estimate the time when the concentration will decline to 20 mg/L, and determine a 24-hour dosage schedule to maintain that concentration. The 4 AM dose is held, and the tachycardia resolves 24 hours later.

$$\begin{aligned}\text{Clearance revised} &= F \times \text{Dose} / (\text{Interval} \times \text{Css}) \\ &= 1 \times 5\,\text{mg}/(24\,\text{h} \times 27\,\text{mg/L}) \\ &= 0.008\,\text{L/h}\end{aligned}$$

$$\begin{aligned}\text{Revised } t_{½} &= 0.7 \times \text{Vd}/\text{C1}_{\text{revised}} \\ &= 0.7 \times 0.7\text{L}/0.008\,\text{L/h} = 70\,\text{h}\end{aligned}$$

Therefore, the concentration 70 hours later should be one half of the measured 27 mg/L, or about 13.5 mg/L. To maintain a concentration of 20 mg/L:

$$\begin{aligned}\text{Dose} &= (\text{Interval} \times \text{C1}_{\text{revised}} \times \text{Css}) / F \\ &= (24\,\text{hours} \times 0.008\,\text{L/h} \times 20\,\text{mg/L})/1 \\ &= 3.8\,\text{mg caffeine PO q 24 h}\end{aligned}$$

EXAMPLE 3: Before the new oral regimen is initiated, another blood specimen is drawn 70 hours after the first and is found to be 14 mg/L. Because tachycardia has resolved, an oral regimen based on the last two levels is resumed to maintain a caffeine concentration of 20 mg/L. Estimate the necessary maintenance dose: The concentration fell 50%, from 27 to 13.5 mg/L in 70 hours, which confirmed our original estimate of half-life. Although caffeine has a wide therapeutic index, clinicians can use TDM and pharmacokinetic calculations to help individualize dosing regimens to provide optimal clinical responses while minimizing side effects.

PHARMACOLOGY AND BREASTFEEDING CATEGORIES

Breastfeeding mothers may require treatment with medications for acute or chronic conditions, resulting in concerns for safety with exposures to drugs excreted in breast milk. In all cases, **the benefits of breastfeeding must be weighed against the risk of drug exposures to the infant.** When possible, certain considerations may be taken to lessen the risk of unintended drug exposures to the infant through breast milk, including the following: avoidance of long-acting medication formulations, timing medications with breastfeeding to achieve minimum concentrations at the time of feedings, choosing medications that will accumulate the least in breast milk, providing a therapeutic interchange with another medication that has a safer profile in neonates, and monitoring the infant closely for abnormal signs and symptoms related to the medications being taken by the mother.[66,67,71]

Although most medications are safe for mothers and the nursing infant, some drugs are known to potentially cause harm to the nursing infant and are contraindicated during breastfeeding, such as anticancer drugs and drugs with radioactivity.[87] Lactation risk categories can be assigned to drugs based on available information.[32] Categories range from safest, designated as L1, to hazardous, designated as L5. Only drugs categorized as L5 are contraindicated during breastfeeding. Other categories require balancing of risk versus benefit to the mother and the infant in the decision on whether to allow breastfeeding in conjunction with the medication being questioned. **Table 18.7 provides information about specific maternal drugs excreted in breast milk.**

DRUG CATEGORIES

Antimicrobial Agents

Antimicrobial agents inhibit microbial growth or kill microorganisms; they include antibacterial, antiviral, and antifungal agents. *Bacteriostatic* agents limit microbial growth, allowing host defenses to control spread; this will not reliably eliminate a pathogen but can prevent its proliferation. *Bactericidal* agents kill the pathogen. Bactericidal agents at low concentrations may be bacteriostatic. The *minimum inhibitory concentration (MIC)* is the lowest concentration of an antimicrobial that stops the spread of an organism in laboratory culture media. This cannot be directly measured in an infected neonate and depends on tissue concentration and the number of bacteria present. The *minimum bactericidal concentration (MBC)* is the lowest concentration of antimicrobial that reduces the microbial number in laboratory media by 99.9%. Pathogens can develop *resistance* to antimicrobials by changing their cellular structures or producing enzymes that reduce antimicrobial activity.

For effective antimicrobial action, the drug must reach an adequate concentration in the infected tissue. The ideal concentration elicits a maximum effect on the pathogen with minimum effects on the patient. Selection criteria for antimicrobials include the microorganism's sensitivity, the availability of the drug to the target tissue (e.g., when treating central nervous system (CNS) infections, it is important to note that some antibiotics do not cross the blood–brain barrier), the bioactivity of the antimicrobial in the target tissue, the known MIC and MBC relative to side-effect and toxic-effect levels for the medication, and the infant's biologic state—that is, whether the systems of absorbance (e.g., intestinal integrity) and elimination (e.g., kidney and liver function) are working adequately for effective and safe drug delivery and removal. **When the use of antimicrobial agents is planned in an infant, as with other drugs, consideration must be given to clinical status and PMA and PNA in order to appropriately select the right drug at the right dose for the right indication for the right duration.**

In particular, the pharmacokinetics of antifungal drugs in neonates have been studied, and these data have guided optimal dosing in the neonatal population for an infection associated with high morbidity and mortality rates.[6,20,44] For example, one cited study on the use of fluconazole, a synthetic triazole, suggested that a loading dose (25 mg/kg) prior to starting maintenance dosing achieved the therapeutic target more rapidly than without a loading dose in infants.[63] When treating *Candida* infections in neonates, immediate attainment of the target level of fluconazole (area under the concentration curve/MIC) is paramount. As more pharmacokinetic studies of commonly used antimicrobials in critically ill neonates are completed, such as with clindamycin, metronidazole, piperacillin-tazobactam, and meropenem, dosing regimens based on PMA and PNA continue to be updated and improved in the NICU.[17,18,29,52,76]

Diuretics

Diuretics are used in the NICU to remove excessive extracellular fluid. Diuretics commonly cause a loss of electrolytes along with water. **Response to any diuretic depends on renal function and the drug's ability to reach its target in adequate amounts. Most diuretics work within the tubule, but any drug that increases GFR can increase water loss.** Drugs that increase cardiac output without decreasing renal perfusion, and others that specifically increase renal blood flow, can also cause diuresis.

In infants, renal tubular function improves with increasing chronologic and gestational age. Poor absorption and response to aldosterone (especially in extremely preterm infants) and electrolyte losses can be clinically significant with the addition of a loop diuretic such as furosemide or bumetanide. The ongoing losses may lead to hypochloremic metabolic alkalosis and less response to the diuretic.

Delivery of diuretics to the kidney loop increases with increasing chronologic and gestational age. Most diuretics rely on secretion from the proximal tubule and filtration through the glomerulus to reach their site of action. Both these functions improve with age. Enteral absorption of some diuretics is limited, so clinical effectiveness and electrolyte stability must be monitored closely to help determine safe and effective dosage regimens. The kidney also is responsible for diuretic excretion, again through tubular secretion and glomerular filtration. These functions are age dependent; the clinician must ensure that the clearance time is adequate to avoid toxic levels.

Cardiovascular Drugs

Medicines used to improve cardiovascular function include digitalis and the sympathomimetic amines, which include drugs such as dopamine, dobutamine, and epinephrine. ***Antiarrhythmics,* including digoxin, act to control the electrical conduction within the myocardium.**

The sympathomimetic amines bind to β and G receptors; the number and availability of receptors determine response. A β_1 receptor response leads to constriction of vascular smooth muscle. β_2 receptors cause a decrease in GI motility. Stimulation of the G1 receptor stimulates cardiac contractility, and the G2 response includes vascular and bronchial smooth muscle relaxation. The response in any individual, and in any individual's specific organ system, depends on the relative amount of these receptors. Receptor numbers and their linked response elements within cells vary with gestation and clinical condition, and the response must be monitored to aid in dosage decisions. Prolonged administration of sympathomimetic amines can lead to a decreased response—an example of tachyphylaxis.

***Antihypertensive* agents occasionally are used in neonates for essential hypertension and occasionally to decrease afterload in infants with heart failure.** These include volume reducers such as diuretics, inhibitors of physiologic regulators of blood pressure like enalapril, and drugs that decrease vascular resistance through β and G receptors. ACE inhibitors, such as enalapril, should be avoided in preterm infants because they are at significant risk of acute renal failure after exposure to this class of drugs.[41,43,45]

The pathophysiology of neonatal disease should direct the choice of cardiovascular agent. Extremely close monitoring of physiologic effects helps determine the safety and efficacy of therapy. Monitoring must include very frequent, if not continuous, monitoring of blood pressure, heart rate, perfusion, and oxygen saturation (preductal and postductal in some cases). **Other drugs are often given concomitantly while a neonate is receiving cardiovascular medicines; thus, thorough knowledge of possible drug interactions is mandatory.** The absorption of cardiovascular drugs is unpredictable. **The sympathomimetic amines, such as epinephrine, must be given by the IV route unless used in an emergency situation in which endotracheal (ET) administration is indicated.** Once dosed, the drug must be delivered to the target organ system. Infants in shock may not have the circulatory wherewithal to deliver the medication to elicit the desired therapeutic response. Due to the variability in β- and G-receptor development and distribution, undesired side effects in various organ systems may accompany desired responses. **Rapid metabolism of the sympathomimetic amines demands continuous IV infusion, and infiltration of IV fluids may lead to significant tissue damage.** Along with the physiologic effects, these IV lines must be carefully monitored to prevent adverse effects as well as to ensure the infant receives the drug.[46,72]

Also related to the cardiovascular system are drugs used to treat patent ductus arteriosus (PDA) in neonates. The ductus arteriosus is a vascular connection between the aorta and the pulmonary artery. In utero, the ductus arteriosus serves the important function of bypassing blood flow away from the nonfunctioning fetal lungs and back into the systemic circulation through the aorta, where the blood can then travel to the placenta. The ductus arteriosus typically closes spontaneously after birth. If the ductus arteriosus fails to close after birth, the resulting PDA can result in shunting of blood away from the body and back to the lungs and cause significant problems to the infant, including pulmonary overcirculation and decreased perfusion to vital organs such as the kidneys. The presence of prostaglandins is known to keep the ductus arteriosus patent, which can be produced endogenously by the infant at the ductus arteriosus or be administered as a drug for certain congenital heart defects.

Pharmacotherapies are used to treat a PDA when more conservative treatments, including volume restriction and diuretics, have failed. These pharmacotherapies are directed at inhibiting the formation of prostaglandins at the ductus arteriosus. Indomethacin, a nonsteroidal anti-inflammatory drug (NSAID), is often used to treat a PDA in these cases. Indomethacin works by inhibiting the enzyme cyclooxygenase, which prevents the formation of prostaglandins, allowing the PDA to close.[50] **When indomethacin is used, close monitoring is necessary for several important side effects, including decreased kidney function and thrombocytopenia. Contraindications against the use of indomethacin include extremely elevated serum creatinine levels, severe oliguria or anuria, and severe thrombocytopenia. Studies have also demonstrated an increased risk in the development of spontaneous intestinal perforations among premature infants treated with indomethacin and hydrocortisone concomitantly; the use of indomethacin with hydrocortisone, and likely other corticosteroids, in this population should be avoided if possible.**[86]

More recently, there has been increased use of acetaminophen/paracetamol for the treatment of PDA in infants. Acetaminophen may cause PDA closure through the inhibition of prostaglandins, although the exact mechanism of how acetaminophen results in PDA closure is still unknown. A recent Cochrane review evaluating eight studies that included a total of 916 preterm infants demonstrated that **acetaminophen performed similarly to ibuprofen or indomethacin and better than placebo for successfully treating PDAs.**[59] Furthermore, acetaminophen may be safer than ibuprofen or indomethacin, without the adverse effects related to NSAIDs, including decreased renal and mesenteric blood flow. However, the authors of the review concluded that further studies, including long-term neurodevelopment

outcome studies, must be conducted before acetaminophen can be recommended as a standard treatment for PDAs.[59]

Central and Peripheral Nervous System Drugs

Nervous system drugs include **analgesics, which decrease pain sensations; *anesthetics,* which control pain peripherally or in the CNS; *sedatives/hypnotics,* including barbiturates (phenobarbital) and nonbarbiturates (lorazepam), which do not control pain and can control some seizures; and *antiepileptic* agents, which are designed to control seizures (phenytoin, fosphenytoin).** These drugs are associated with problems of addiction, tolerance, dependence, and withdrawal.

Neonates are incapable of developing addiction but are able to develop tolerance, dependence, and withdrawal to these medications. *Addiction* is a complex lifestyle change that involves drug-seeking behavior, which is not applicable to neonates. Tolerance occurs with many drug types. *Tolerance* exists when increasing doses and serum concentrations of a medicine are necessary to achieve a desired effect. A patient is *dependent* on a medication when regular drug administration is necessary for physical well-being. *Withdrawal* is a collection of physiologic and behavioral signs attributed to the absence of a medication in a dependent individual. There are two distinct types of withdrawal in neonatal patients. **Neonatal abstinence syndrome is secondary to in utero exposure to illicit substances,** such as heroin, or prescribed medications, such as methadone or buprenorphine, taken by mothers during pregnancy. **Iatrogenic withdrawal is induced by prolonged exposure to opioids, benzodiazepines, and other sedatives used in sick infants who often require prolonged mechanical ventilation.** Withdrawal has been identified for many medications, but it has been classified and described, along with weaning protocols, for opioid analgesics and benzodiazepines[22] (see Chapter 11).

The mechanism of most CNS medications is not clearly known. Again, careful monitoring of therapeutic effects relative to dose, duration, and serum concentrations is extremely important. **Significant respiratory depression can occur with most CNS medications, so appropriate resuscitation equipment must be available.** Variations in hepatic metabolism and the volume of distribution are important in the ongoing assessment of dose response. Some medications are highly fat bound and are slowly released into the circulatory system, causing prolonged effects, both therapeutic and undesired (e.g., respiratory depression, poor gastric motility, and abnormal neurologic function such as feeding difficulties).

If therapeutic hypothermia is used for infants with hypoxic-ischemic encephalopathy (HIE), evidence suggests that opioids accumulate in the circulation in excess of the accumulation in similar infants with HIE who are not cooled. Therefore, when using opioids in cooled infants with HIE, opioid levels are likely to be higher than expected for a given dose, and the expectations for the neurologic examination must be modified given the accumulation of high levels and delayed neurologic findings.[68]

Pharmacokinetics During Hypothermia

In recent years, **therapeutic hypothermia has become the standard approach in NICUs for term newborns with neonatal HIE.[72] (see Chapter 26) Therapeutic hypothermia entails lowering the core body temperature below 34°C for the first 72 postnatal hours, followed by gradual rewarming.**[73] Neonatal HIE is often accompanied by metabolic acidemia in the first postnatal hours to days, along with kidney and liver injury. This complex combination of end-organ injury and cooling below the usual physiologic core body temperature influences the pharmacokinetics of commonly used medications in the NICU.[89]

Antiepileptics, opioids, and antibiotics are among the more commonly used medications for infants with HIE. In adults, the systemic clearance of drugs metabolized by cytochrome P-450 is decreased between approximately 7% and 22% per degree Celsius below 37°C during cooling. Several studies have assessed specific medications often used for term neonates with HIE.

Hypoxic newborns are at high risk of seizures. Clinicians who are treating these infants with HIE should understand the antiepileptic agents and their dosing and pharmacokinetic profiles. **Phenobarbital (PB) administered to newborns under whole-body hypothermia results in higher plasma concentrations and longer half-lives**

than expected in normothermic newborns. In the report on phenobarbital pharmacokinetics for neonates cooled for HIE, C_{max}, C_{min}, and C_{avg} were higher, and half-lives were longer, than reported in normothermic newborns in earlier studies. **Clinicians using PB to treat seizures in such newborns should be aware of the risks of elevated serum PB concentrations with doses of 40 mg/kg or higher.[23]** Other antiepileptics with a better safety profile, such as levetiracetam, may be used adjunctively to treat refractory seizures in infants who have been administered PB.[84] This may decrease the need to push PB doses to suprathera-peutic levels in this cohort.

Even in noncooling infants, morphine should be used judiciously in neonatal patients due to its many known adverse effects. In the Total Body Hypothermia Study (TOBY), one center measured and reported morphine pharmacokinetics for the infants enrolled in the study.[69] All of the infants were treated with a continuous infusion of morphine, with the rate adjusted according to clinical status. Serum morphine concentrations reached a steady state after 24 hours in normothermic infants with HIE but continued to increase throughout the assessment period in the hypothermia group. The authors concluded that **infants with HIE have reduced morphine clearance and elevated serum morphine concentrations when morphine infusion rates are based on the clinical state. Potentially toxic serum concentrations of morphine are more likely with the combination of HIE, moderate hypothermia, and infusion rates greater than 10 micrograms/kg per hour** than with HIE not treated with hypothermia.[69] To reduce the accumulation of morphine, a loading dose of 50 mcg/kg followed by 5 mcg/kg/hour was predicted to achieve target serum concentrations in neonates with HIE receiving therapeutic hypothermia.[25]

Gentamicin is a common antibiotic used to treat early-onset sepsis in infants. In a study of 29 infants treated with hypothermia for HIE, **gentamicin clearance was decreased in neonates with HIE treated with hypothermia** compared with previous reports in nonasphyxiated, normothermic full-term neonates. At a 36-hour dosage interval, a dose of 4 to 5 mg/kg was predicted to achieve target gentamicin peak and trough concentrations in more than 90% of neonates.[27] In a subsequent study, this group demonstrated that a gentamicin dosage strategy of 5 mg/kg every 36 hours in neonates with HIE receiving therapeutic hypothermia improved the achievement of the target trough concentration of less than 2 mg l(–1) compared with dosage every 24 hours while still providing high peak concentration exposure.[26]

From these few examples, **the effect of hypothermia on the pharmacokinetics of important drugs in a very vulnerable population is evident.[19]** An ongoing, multicenter study in the Netherlands is investigating how therapeutic hypothermia influences the pharmacokinetic and pharmacodynamic time profiles of analgesics, sedatives, antibiotics, and antiepileptic drugs in infants with HIE.[19] So far, these studies have demonstrated that therapeutic hypothermia results in significantly decreased clearance rates for the antibiotics gentamicin, amoxicillin, and benzylpenicillin, resulting in the need to adjust to lower dosing for all three drugs during therapeutic hypothermia and rewarming.[9-11]

PREVENTION OF THERAPEUTIC MISHAPS

The Institute of Medicine (IOM) estimates that more individuals die each year in the United States from medical error than from motor vehicle accidents, breast cancer, or AIDS-related illness.[35] **Many medical errors are medication errors. Neonatal patients are at a higher risk for errors given the narrow margin of safety in very small, fragile patients with an immature organ system and clinical illness.[64]** For example, a decimal point error in dosing that may not cause adverse effects in an adult could cause significant harm to a preterm neonate. **Between 20% and 50% of neonates in the NICU experience medication errors, with the youngest, smallest, and sickest neonates being the most affected.[69]**

Medication errors can occur at any stage in the medication-use process: (1) prescription/transcription, (2) preparation/dispensing, (3) administration, and (4) monitoring.[70]

Prescription and Transcription

A recent descriptive study of common medication errors in the NICU found that the majority (98.5%) occurred in the prescribing phase, with 58.7% due to calculation errors.[62]Additionally, wrong-patient orders are more common in the NICU than in

non-NICU pediatric settings.[2] Dosing references; administration guidelines, such as IV compatibility and infusion rate guidelines; and other drug resources should be made available to all clinicians in the NICU.[12,70] Building dosing recommendations and clinical guidelines into order sets within a computerized order-entry system (CPOE), even the use of a "preselected prescription" concept, reduces errors in prescribing and assists in standardizing and optimizing clinical outcomes.[30] Designing the ordering system to reduce complexity and provide rule-based order screening and double-checking of calculations and developing effective information delivery may be more effective than traditional education or process-improvement efforts that target interventions after an error occurs.[22,28]

The use of a CPOE system with an approved neonatal formulary, prompts, and clinical decision support decreases errors by making the prescribing legible, guides the prescriber in the safest and most cost-effective medications, and enables the prescriber to become proficient with a selected number of drugs.[70] CPOE systems can be customized to a specific NICU and use only "acceptable" or no abbreviations, write out or use capital letters for "look-alike/sound-alike" drugs, and use both generic and brand names of the drugs in the neonatal formulary. **Electronic generation of medication administration records (MARs) by pharmacists after checking the medication order improves accuracy in the transcription process and ensures legibility compared with handwritten MARs.** Pharmacist participation in NICU patient rounds enables multidisciplinary communication and clarification of new medications to be ordered and any therapeutic drug monitoring that needs to be done. **Neonatal clinical pharmacist participation in NICU rounds and clinical care has been shown to decrease errors by 80%.[74]**

Preparation and Dispensing Medications

Even after making a correct choice of medication, one must pay attention to the appropriate dose and interval based on factors that affect a drug's pharmacokinetics and pharmacodynamics.

Investigators estimate that 8% of drug doses calculated and administered by competent NICU nurses are at least 10 times greater or less than the ordered dose.[71] A system in which unit doses are prepared in the pharmacy, labeled, and delivered to the NICU is a safer system than having stock medications in the NICU that are reconstituted and/or diluted by the bedside nurse. **Pharmacist interventions can reduce medication errors and adverse drug events.[12,59,81,82]** In the pharmacy, unit doses are checked by two pharmacists[12,36,81,82] to ensure accuracy, scanned using barcode technology, and placed in the automated dispensing system (ADS). Emergency medications are available in the ADS, which is accessed by the nurse for dispensing; the drug is then prepared by the nurse (reconstituting or diluting), and the appropriate dose is measured and double-checked with a second nurse before administration.[36,57,82,81] When unit-dose patient labels are integrated with the CPOE system, labels contain the dose, volume, concentration, route, preparation instructions, and time of administration.[70]

BOX 10.2 THE "SIX RIGHTS" OF DRUG ADMINISTRATION

Right drug
Right patient
Right route
Right dose
Right time
Right response

Administration of Medications

Completing the "six rights" of medication administration (Box 10.2) **in the NICU is essential and may be complicated by the small doses and dosage adjustments based on infant weight or body surface area.** Many drugs used in neonatal care must be diluted because they are ordered in amounts that are not commercially available. The rate of drug entry, or absorption, also varies, depending on the route of administration. Even with unit dosing, the **calculation of the medication dose received must be double-checked by two nurses at the bedside before administration. This redundancy of independent double-checking in the pharmacy and at the bedside is a strategy for reducing medication errors.[12,36,57,80,81]** Drug delivery must be ensured; this includes **appropriately prescribed**

orders or transcribed orders, appropriate dose calculations, appropriate mixing with diluents, and appropriate method of administration. The *Rule of Six* was developed originally for use with vasopressor agents in code situations, and its use has extended beyond that. The rule, which allows nurses to estimate a pediatric dose by using a factor of 6, is prone to error (Fig. 10.4).

Standardized drug concentrations are less error prone and safer for patients than the *Rule of Six*.[2] Because of medication errors, The Joint Commission (TJC) requires the use of standardized IV drug concentrations for pediatric patients prescribed medications for which the *Rule of Six* was routinely used.

The use of smart IV pumps reduces IV medication errors by 73%.[42] Smart pumps are used for both continuous and intermittent IV administrations. Smart pumps are programmed with each IV medication from the neonatal formulary and are separate from adult medication pumps. Proper training on use of medication pumps is crucial. Errors occur from poor training on pumps. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6318721/). In addition to **barcode scanning, visual verification of the medication label to ensure that the medication, dose, concentration, and route match the electronic order and the MAR information also prevents errors and increases patient safety.[42,70]** Access to medication references with administration guidelines, compatibilities, dilution guidelines, diluent information, and administration time is essential for all NICU staff.[70]

Monitoring Medication Effects

After medications are administered, all care providers must evaluate the neonate for drug interactions, incompatibilities, and untoward and adverse effects. The effects of therapy at the chosen dose and systematic monitoring for therapeutic and toxic effects must be included in NICU care when medications are used.

TDM is necessary for some medications to measure whether pharmacokinetic and pharmacodynamics goals are being met.[69] Blood is drawn at peak, trough, or random times, and medication doses are adjusted as necessary. Therapeutic ranges are specified for each drug, and doses are adjusted for maximum efficacy and the prevention of toxicity. **NICU staff must be educated in how and when to accurately and consistently monitor drug levels, as well as the appropriate interventions that are to be expected given laboratory values that are outside of therapeutic ranges.** When clinical pharmacists participate in patient rounds, they promote safety by effective monitoring with laboratory values as well as with education of the NICU staff.[42,70,75,79] Additionally, the **bedside nurse who is constantly with the sick neonate must be familiar with the adverse effects of all medications that are given so that the nurse is able to advocate for the patient who is showing symptoms of toxicity.** For example, a very low-birth-weight (VLBW) infant on caffeine therapy who has a resting heart rate of 180 beats/ minute and is vomiting after gavage feeding is symptomatic of caffeine toxicity and needs a caffeine level drawn; the next dose of caffeine should be withheld until results of the caffeine level are known.

A recent national survey found that of the 164 respondent NICUs, 85% adhered to practices designed to decrease and eliminate medication errors, yet some safety practices were not used.[31] The American Society of Health-System Pharmacists has published guidelines for preventing medication errors in hospitals.[12] These such include hospital-wide actions as the establishment of a clearly defined system for drug ordering, dispensing, and administration, with review of the original drug order before dispensing *and* administration. Confirmations of patient weight, drug dosage, and strength are also recommended. **Avoiding the use of the terminal zero to the right of the decimal point (e.g., writing *5* instead of *5.0*) and using a zero to the left of a dose less than 1 (e.g., using *0.1* rather than *.1*) will help reduce medication errors. Avoid abbreviations of drug names** (e.g., *MS* may mean either morphine sulfate or magnesium sulfate), **spell out dosage units rather than using abbreviations** (e.g., *units* rather than *U,* or *mcg* for microgram rather than *μg*), **and use generic medication names rather than trade names.** Avoid verbal orders whenever possible; verbal orders should only be used in emergency situations.[81] **See Table 10.2 for other interventions to reduce medication errors. For neonatal/pediatric nurses, recommendations include the following:[12,36,57,69,81]**

TABLE 10.2 INTERVENTIONS TO REDUCE MEDICATION ERRORS

STRATEGY	EXAMPLES
Establish an institutional and NICU culture of safety[12]: • Safety is valued • Medication safety leader • Structure for safe medication practices • Strategic plan	Medication safety is a priority that is supported by a system of safety that makes it easy to prevent an error and difficult to make an error[12]: • "Just" culture that evaluates systems flaws as well as human errors; a support system for second victims: care for health care providers traumatized by being involved in medication error(s) • Nonpunitive event-reporting system that includes "misses" and "near-misses" that undergo RCA to identify causes and devise strategies to prevent a recurrence • Interdisciplinary medication safety team to proactively assess risk, as well as systematically and collaboratively address medication safety within the NICU • Continuous quality improvement process regarding evaluation of errors/harm: use of technology that reduces risk and prevents patient harm. • Strong designs that assess and reduce risk and patient harm • reduce risk and patient harm • Use of electronic barcode scanning systems that reduce preventable adverse drug events by 50% to 80%[39,53]
Multidisciplinary staff education and teamwork training to establish, enhance, and/or sustain a culture of safety in the NICU	Administer the AHRQ's Survey on Patient Safety Culture before and after compulsory, multidisciplinary teamwork and communication training; compare unit data to AHRQ's national survey data[55]
QI projects	Collect data before and after QI interventions related to medication safety, such as double-checking and signing for all neonatal medications; use of barcode scanning
Random safety audits: safety tool to prevent adverse events	Collect data from smart (IV) pumps to assess the frequency of appropriate use of infusion pump safety systems[7]
Multidisciplinary team develops a neonatal/pediatric formulary	Neonatal/pediatric drugs to be used in NICU, age-specific dosage guidelines along with dilutions of common drugs. Use of standardized drug preparation and dosage, standardized nomenclature and CPOEs with alerts for unusual drug doses[70]
Develop written protocols and procedures that are easily accessible to all NICU staff	Use of smart pumps, insulin, skin care; monitoring of IV infusions and therapeutic drug levels; intervention for IV extravasation
Provide up-to-date references easily accessible to all NICU staff	Neonatal/ pediatric drug dosage handbooks, intranet resources, 24-hour access to pharmacist[70]
Use CPOE system with neonatal dosing regimens and order sets	Build national and local guidelines into admission order sets, disease-state order sets, and all commonly used neonatal medications

AHRQ, Agency for Healthcare Research and Quality; *CPOE*, computerized provider order entry; *IV*, intravenous; *NICU*, neonatal intensive care unit; *QI*, quality improvement; *RCA*, root cause analysis.

- Familiarizing oneself with the system for medication ordering and documentation
- Accepting only medication orders that specify not only the amount to be given but also the intended amount per kilogram so that intended dosing can be recalculated by the dispenser (pharmacist) and the administrator (nurse) of the medication
- Clarifying medication orders before the prescriber leaves the NICU
- Verifying drug orders before administration
- Confirming patient identity by two forms of identification before each dose
- Using electronic barcode scanning system to verify patient and medication before administration

- Verifying calculations, IV pump programming, and medication concentrations by using independent double checks with a second individual
- Verifying any unusually large volumes or dosage units for a single patient dose
- Verifying verbal orders by "reading back" the complete order to the prescriber
- Familiarizing oneself with the methods of drug administration: oral syringes that are unable to be connected to IV ports, smart pumps, unit dosing, oral measuring devices in metric system
- Listening to the patient, parent, or other caregiver
- Asking questions as to whether a drug should be administered—for example, discontinuing antibiotics after negative laboratory findings, including cultures in an asymptomatic neonate
- Maintaining familiarity with the operation of administration devices and the potential for errors with such devices

METHODS OF ADMINISTRATION

Once a clinician orders a medication and the drug and dose are found to be appropriate for that particular infant, the nurse's challenge is to administer the medication correctly. The following section addresses methods that help improve the accuracy of drug delivery.

Oral Administration

It must be noted that **all oral medications should be prepared and administered using only oral syringes and oral orogastric (OG) or nasogastric (NG) tubing. These oral syringes and tubing do not allow oral medications to be given inadvertently through an IV line.**[80] Variations in oral bioavailability and unanticipated and unmeasurable loss of the drug complicate the administration of oral medications to newborns. Loss of medication occurs when infants regurgitate or require gastric suctioning and lose residual fluid that may include medication. **If an infant is receiving OG or NG feedings, the medication should be placed into the center of the barrel of a syringe containing a small portion of the feeding to dilute the medication, thereby decreasing the osmolality of the medication and, subsequently, increasing the tolerance.** The nurse should document drug administration attempts and any possible loss of drug, with an estimate of the amount lost. **For infants receiving oral medications, documenting the color of the emesis or residual material helps determine the presence of medications that have a distinctive color.**

If an infant is bottle-fed, it is not recommended to put the medication in the full bottle. The concern is that if the infant fails to take the whole volume, he or she has not received the full dose. One option is to gently introduce very small portions of a dose into the cheek pouch and wait for the infant to swallow. **Another method is to put 5 to 10 mL of a feeding, with the medication, in a small bottle and let the infant take that amount, then continue with the remainder of the feeding. The medication also may be placed into a nipple with a small volume of feedings and then offered to the infant.** For breastfeeding infants, medications may be administered into the mouth as described previously, with or without a small volume of expressed breast milk.

Intramuscular Administration

A newborn infant has relatively little muscle mass to receive injections. **When IM injections are necessary, as with vitamin K, the anterior thigh is the site of choice. Comfort measures should be given before and after the injection** (see **Chapter 12**). For an infant weighing less than 1500 grams, the volume injected into one leg should not exceed 0.5 mL. The final step is to document the administration.

Intravenous Administration

IV medications can be given by push or pump infusion. Although drugs directly enter the bloodstream, the time necessary to complete drug delivery to receptors is a function of dosage volume, IV flow rate, and injection site (depending on particular IV methods).[87] Failure to recognize these potential time lags could result in inappropriate expectations of the timing of physiologic responses and peak and trough concentrations. **Certain drugs should either be avoided or cautiously administered into the umbilical vein or artery, and drug incompatibilities should be recognized before setting up multiple medications through the same IV line.** Appropriate flushing is necessary, especially in between intermittent medications that are incompatible. Careful monitoring for infiltrates and knowledge of drug-specific treatments for this complication are essential to safe IV drug

administration. **Some medications require central venous access to safely administer medications, and stable access may be required before administration.** Continuous IV infusion of vasopressors is common in the NICU, and because of their rapid clearance and physiologic importance, these infusions should never be interrupted or given by bolus **without orders.** A sudden influx of potent medication and flushes to clear lines with continuous infusions of sympathomimetic amines should be avoided.

PUSH INJECTION

IV push medications must be mixed in appropriate volumes, delivered through appropriately sized syringes, and followed with an appropriate flush solution.

The IV port closest to the patient should be used to administer an IV push injection. Administer a small volume of the appropriate flush solution, and then administer the medication over 1 to 2 minutes. Slow IV push rates must be specified by the ordering clinician. **A post-medication flush is given at the same rate as the medication to clear the line of remaining medication. IV push administration of many medications used in the NICU is *contraindicated* because of the possibility of immediate adverse reactions associated with rapid bolus injections. Opioids and sedatives should be given with great care and constant attention to respiratory and cardiovascular parameters. Check a pharmacology reference for any uncertainty.**

INTRAVENOUS INFUSION ON THE PUMP

To avoid delay of drug delivery, two methods of pump infusion using a mechanical infusion device allow control of drug amount and delivery rate. These devices consist of a pump that can be set to deliver a specific volume over a specific time, a syringe or other container that holds the medication or fluid to be delivered, and connecting tubing to connect the pump to a port for drug delivery. Because pumps vary by manufacturer and some may be used in a variety of ways, **each NICU should have a policy to ensure that each staff member carries out pump infusions in the same manner.**

INTRANASAL ADMINISTRATION

Some medications, such as midazolam or fentanyl, can be given through the intranasal route. **Although the intranasal route of delivery for these medications has not been approved by the FDA in neonates, this drug delivery route has been shown to be useful as a rapid and less invasive method of administering certain drugs,** especially in neonates who have limited IV access. The nasal mucosa has a rich vascular bed that allows rapid absorption of these drugs into the bloodstream.

OTHER CONSIDERATIONS REGARDING IV ACCESS AND ADMINISTRATION

Access via Peripherally Inserted Catheters (PICCs) or Peripheral Intravenous Lines (PIVs). PICCs have been used in the neonatal world for more than 30 years. PICC use has decreased mortality and morbidity and optimized care for infants requiring prolonged stable access for parenteral nutrition or IV pharmacotherapies. PICCs have proven to be **a reliable, safe method to deliver medications and fluids with high osmolarity.**[60] Training for PICC placement is accomplished through specialized courses that adhere to strict sterile techniques. IVs may be placed by a bedside nurse without the specific training course that is needed to place a PICC. **Common sites for IV placement in neonates include the hands, feet, arms, legs, or scalp veins. A trans-illuminator or ultrasound machine**[36] **may help locate vessels in extremities.** Always use nonpharmacologic comfort measures and consider local anesthetic or analgesia prior to attempting access (see Chapter 12).

Some vessels do not provide blood return. Babies in hemodynamic shock also may not have blood return. If the needle is thought to be in the vessel but no blood return is seen, then a small amount of flushing solution may be injected. If the needle is not in the vessel, the tissue will swell. **If it blanches, the vessel is most likely an artery.**

When securing a line, leave adequate visual access to the insertion site and allow monitoring for changes in color or edema that indicate complications such as infiltrates, phlebitis, or hematomas.

If a medication is to be administered intermittently and the line is not otherwise used, it may be heparin or saline locked and flushed per unit protocol with your unit's standard flush solution. Alternatively, a continuous heparinized fluid can be infused at a low rate of 0.5 to 1 mL/h to keep the access patent and can be used as a medication carrier fluid.

COMPLICATIONS OF INTRAVENOUS THERAPY

Complications of IV therapy include phlebitis, infiltration, hematomas, chemical burns, compartment syndrome, and emboli.[46] Long-term complications include disfigurement, contractions, and the need for surgical repair or amputation. Frequent *(at least hourly)* assessment of IV sites helps reduce, but does not absolutely prevent, all IV complications (Box 10.3).

Footdrop[24] and *compartment syndrome,* in which nerves and vessels are damaged by swelling of tissue within a limited space, have been associated with positioning a footboard along the lateral aspect of the fibula, with or without an IV infiltration. The use of rolled washcloths as footboards or extensive padding of IV boards with cotton or gauze may prevent excessive pressure. **Unnoticed infiltrations may result in significant tissue loss. Warm soaks are *contraindicated* because, when warmed, extravasated fluid may exacerbate the burn, maceration, and necrosis**. In addition, **heat increases oxygen demand in the already-compromised tissues.**

Elevating the infiltrated area increases venous and lymphatic drainage, helping to decrease the edema. Hyaluronidase[58] destroys extracellular barriers, allowing rapid diffusion and absorption of the infiltrated medication, such as calcium. For vasoconstrictive substances that extravasate, such as epinephrine infusion, local use of vasodilators like phentolamine can aid in reperfusion. Table 10.3 lists treatment approaches for extravasation.

Clinicians must remain attuned to additional concerns when administering IV medications. **Medications may require filters or protection from light sources or may have significant specific gravity osmolarity. A 0.22-micron filter may provide "cold sterilization"** (i.e., remove particulate matter and bacterial contamination). **Some medications cannot be administered through a filter because the filter removes the active ingredient.** Medications with a specific gravity less than that of the IV fluid have a tendency to accumulate at high points in the IV tubing, whereas those with a higher specific gravity settle into low tubing loops, in both cases resulting in delayed and inaccurate drug delivery.

BOX 10.3 CRITICAL ASSESSMENT
Intravenous Extravasation

- Check all indwelling lines hourly for signs of extravasation.
- Look for phlebitis, edema, burns, adequacy of perfusion to site, hardness of tissue, or inflammation at needle site.
- For scalp veins, check dependent side of head for trauma.

PARENT TEACHING/ COMMUNICATION

IV lines in newborns often frighten the newborn's parents, especially lines placed in a scalp vein. (Box 10.4). **Family members may need reassurance that an IV catheter/needle**, IV fluids, and possibly medications are going into large veins and not directly into the infant's brain. Parents may need

TABLE 10.3 TREATMENT APPROACH FOR EXTRAVASATION

DRUG SUPPLIED	DOSAGE/ADMINISTRATION	COMMENTS
Hyaluronidase (Amphadase) 150 units (mL)	1 mL (150 units) given as 4 or 5 intradermal 0.2-mL injections with a 25-gauge needle around the periphery of the IV extravasation site	Use with extravasation of hyperosmolar or extreme pH drugs. Administer within 1 hour of event. Not for use with vasoactive drugs.
Phentolamine (Regitine) 5 mg/mL in 1-mL vial	0.5 mg/ml given as 4 or 5 intradermal 0.2-mL injections with a 25-gauge needle around the periphery of the IV extravasation site	Prepare a dilution. Use with vasoactive drugs. May be given up to 12 hours after an event.

Modified from Roberts RJ: Intravenous administration of medication in pediatric patients: problems and solutions. *Pediatr Clin North Am.* 1981;28:23-34.

encouragement to touch and hold infants when IVs are in place.

Parents will need assurance that pain assessment and control are part of the caregiver's ongoing efforts and are always addressed during IV placement and maintenance.

Parents need to be aware that venous fragility, combined with the types of solutions used, can make the need to restart IV lines and or the need for multiple sticks per line relatively commonplace. **The potential for infiltration also should be addressed, and parents should be included in the effort to monitor the appearance of IV sites (see Chapter 12).**

As for an infant's treatment, the parents should be included in conversations regarding pharmacotherapy and nonpharmacotherapy choices in the NICU. Parents need not know the details of medication dosage and significant medications within their infant's treatment regimen. **At discharge, parents need to know the names, uses, dosages, frequency of administration, and side effects of each of their infant's medications and how to obtain refills.** Some medications for infants are not readily available. Caregivers must teach parents to administer prescribed medicines, and parents must demonstrate the parent's ability to safely and reliably draw up liquid medications using syringes and administer the prescribed doses to the infant. **The parents need to receive written drug information instructions, which may be developed by the unit for their families or may be commercially available. Instructions must include the name of the medication, treatment indications, dose, route of administration, dosage schedule, and potential side effects.**

BOX 10.4 PARENT/CAREGIVER TEACHING
Indwelling Lines for Parents

Talk with parent about indwelling lines. Discuss the following:

- Type of line, purpose, and any limitations on holding, handling, or feeding the infant
- Pain control measures for the placement of lines
- Need for restarting lines
- At discharge: The name of the medications, the dosages, purpose, routes, and any potential side effects
- At discharge: Medication administration and what to do if the infant does not receive the full dose of medication

NEONATAL RESUSCITATION MEDICATIONS

Name: _____ Weight: _____ Suction depth: _____

Date of birth: _____ ET tube size: _____

Drug	Strength	Dose	Route	Amount to administer
Epinephrine	1:10,000	0.1 mL/kg	IV, ET	_____
Atropine	0.1 mg/mL	0.1 mL/kg	IV	_____
Volume expanders		10 mL/kg	IV	_____

_____

Signature of preparer

FIGURE 10.4 Calculations for neonatal resuscitation medications. Other drugs and dosages could be added. *ET,* Endotracheal; *IV,* intravenous.

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11 DRUG WITHDRAWAL IN THE NEONATE

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When a neonate shows signs of withdrawal from a medication or drug taken by the mother during pregnancy, this does not necessarily imply that the mother was addicted or an "addict." Medications may be needed for maternal health reasons that pose a risk for withdrawal in the baby following birth. These risks and benefits must be known and discussed between the health care provider and patient before being used. Nonetheless, **the rising prevalence of illicit and prescription maternal substance use and abuse has affected pregnant women of all demographic backgrounds.**[25,103] The extent of drug use during pregnancy is often underestimated, as are the effects on the fetus and neonate. **Estimated illicit drug use suggests an annual prevalence of approximately 6% of pregnant women, with the highest use at 18.3% in women 15 to 17 years of age.** Illicit use decreases to 9% in those 18 to 25 years of age and 3.4% in those 26 to 44 years of age.[115] The Centers for Disease Control and Prevention (CDC) reported from 2011 to 2013 an average of 10.3% of all pregnant women 18 to 44 years of age voiced current alcohol use, with 3.1% engaging in binge drinking. Cigarette smoking, while decreased overall, has remained unchanged in the pregnant woman.[115] The National Survey on Drug Use and Health in 2013 showed that 15.4% of pregnant women 15 to 44 years of age smoked cigarettes in the previous month.[113]

Neonatal abstinence syndrome (NAS) parallels the national opioid epidemic. While the CDC's press report in 2018 shows opioid use disorder increased from 1.5 per 1000 hospital deliveries in 1999 to 6.5 in 2014, NAS escalated accordingly.[19] **NAS has increased from 1.2 to 5.8 per 1000 hospital births per year from 2004 to 2012.**[92] **Many infants are exposed to poly-substances that compound NAS.**[95] The national average length of stay for an infant requiring treatment for NAS has increased from 16 days to 19 days.[119] In turn, aggregate hospital charges for NAS increased from 732 million to 15 billion, 81% attributed to state Medicaid programs.[92,95,119] The National Institute of Drug Abuse 2017 "Monitoring the Future" study showed that past-year misuse of prescription opioids over the last 15 years (2002 to 2017) among 12th graders is declining (Vicodin dropped from 9.6% to 2%).[82] Across all grades, past-year use in 2017 of heroin, methamphetamine, synthetic cannabinoids, and cigarettes are at their lowest.[19,82]

Providers must recognize these data as a snapshot of these young people and that these behaviors can change. **The sequelae of both licit and illicit substance use by the mother during pregnancy must be recognized and addressed to provide optimal medical care of the neonate.** Stereotypic biases should not interfere with the diagnosis or treatment. Therefore, **health care providers must consider drug exposure in any neonate who is exhibiting symptoms at birth suggestive of withdrawal from or exposure to illicit or prescribed drugs.**

Opioid use by a mother during pregnancy has been studied in detail for decades in terms of its effects on the woman, the fetus, and the developing child.[27,33,46,51,65] **An *opioid* is defined as any natural or synthetic drug that has pharmacologic properties similar to those of opium.**[27,32,46] An opiate is derived from opium or contains opium. The diagnosis of "opioid use disorder" was introduced in the *Diagnostic and Statistical Manual of Mental Disorders*

BLUE type highlights content that is particularly applicable to clinical settings.

(DSM 5) in 2013 and combined the two previous diagnoses: opioid dependence and opioid abuse. The diagnosis incorporates a wide range of illicit and prescribed drugs of the opioid class. Because time, circumstances, and knowledge have changed, other factors now should be considered in treating neonates. **Diagnostic data can no longer be gathered on the assumption that one drug or substance was used. Poly-drug use (the concurrent use of two or more drugs) is now the norm and not the exception. Poly-drug use also can be the combination of illicit substances with those that are legal or found over the counter. The effect on the fetus and neonate is not necessarily minimized by the legality of the substance.** Patterns of abuse, purity of the illicit drug, and sometimes potent or poisonous additions to them also may cause catastrophic sequelae in newborns.

Iatrogenic physical dependence has been documented in infants given intravenous fentanyl or morphine to maintain continuous analgesia and/or sedation during extracorporeal membrane oxygenation (ECMO) and mechanical ventilation.[118] The signs of withdrawal are much like those reported in infants born to opioid-dependent mothers. Fifty percent to 84% of neonates removed from fentanyl within a 24-hour period exhibited withdrawal symptoms, and 48% exhibited signs and symptoms with morphine withdrawal.[118] **Regardless of the agent(s) used for sedation, once the decision is made to start weaning the medication, careful observation of the infant is crucial to monitor for signs and symptoms of withdrawal.**[14,118] A review of the literature points out the importance of initiatives for adequate analgesia in neonates, the development of formal policies concerning intensive care sedation, and the treatment of the withdrawal.[8,114,118]

Several authors have described the use of specific tools for documentation of the manifestations of withdrawal including: the Lipsitz Tool (1975), the Finnegan Scoring System (1975), and the Neonatal Withdrawal Inventory by Zahorodny (1998).[74,80,88] The literature cites various pharmacologic agents that have been used to alleviate the symptoms of opioid withdrawal with methadone, buprenorphine, oral morphine sulfate, and others.[33,45,58,64,68]

Advances in neonatology have continued to broaden the period of viability as many more premature infants are surviving. **What appears to be decreased severity of abstinence in preterm infants may be related to developmental immaturity of the central nervous system (CNS) or to differences in total drug exposure.** This proves to be a problem in evaluating the severity of abstinence signs in a smaller preterm infant because scoring tools were developed largely for use with term or near-term infants.[5,46,78]

This chapter presents current information about treatment issues surrounding drug-exposed neonates, with the main focus on opioid withdrawal. The effects of other substances such as stimulants, hallucinogens, selective serotonin reuptake inhibitors (SSRIs), nonopioid CNS depressants, tobacco, methamphetamines, and alcohol are addressed when symptoms deviate from those of NAS.

PHYSIOLOGY

Because of their low molecular weight and lipid solubility, all drugs of abuse reach the fetal circulation by crossing the placenta, causing direct toxic effects on the fetus.[15,24,48,56]

Although certain drugs may produce specific effects, many abused drugs produce similar manifestations of fetal and neonatal disease. In addition, the effects of legal drugs such as tobacco, caffeine, and alcohol may confound simple drug-effect relationships.[5,13,46,75,93] **A hostile intrauterine environment may also be caused by adverse effects of the mother's drug use and must be considered when diagnosing the neonate's problems.** Examples of factors that could affect neonatal outcome include lifestyle, homelessness, physical or sexual abuse, prostitution, poverty, poor or no prenatal care, poly-drug abuse, intravenous drug abuse, binge and withdrawal cycles, anorexia, poor maternal nutrition, pica, dehydration, alcoholism, sexually transmitted diseases, dental abscesses, preexisting medical conditions requiring pharmacologic therapy, human immunodeficiency virus (HIV)–positive status or acquired immunodeficiency syndrome (AIDS), and hepatitis B and hepatitis C.[5,24,52]

ETIOLOGY OF NEONATAL ABSTINENCE SYNDROME

Neonatal abstinence is described as a generalized disorder characterized by CNS hyperirritability, gastrointestinal dysfunction, respiratory distress,

and autonomic dysfunction manifesting as vague symptoms such as yawning, hiccups, sneezing, mottled skin color, and fever.[27,33,46,64,65,122] NAS occurs in two ways as listed in Box 11.1. Infants exposed in utero and born to mothers using potent narcotics; morphine derivatives, heroin, methadone, or buprenorphine have a high incidence of NAS (60% to 90%).[30] Less potent opioids or opioid-like agents have also been implicated in the development of NAS. Box 11.2 **gives a complete list of drugs associated with NAS.**

When narcotics cross the placenta, equilibrium is established between maternal and fetal circulations. Before birth, the drug is cleared from the fetal circulation primarily by the placenta and maternal excretory and metabolic mechanisms.[46] Multiple investigators have described the potential genetic contributors to variability in fetal opiate exposure, NAS severity, and response to treatment.[21,67] A multicenter cohort study examined the association of *OPRMI* and *COMT* single-nucleotide polymorphisms on NAS, the infant's length of stay, and need for pharmacologic treatment. This study concluded that infants with the *OPRMI* gene had a length of stay 8.5 days less than those without the variation and a better chance of not needing pharmacologic treatment. Neonates with the *COMT* gene variation were in the hospital 10.8 fewer days and had less treatment.[121]

The onset of withdrawal symptoms varies from hours after birth to 2 weeks of age, but the majority of symptoms appear within 72 hours. Many factors influence the onset of NAS (Boxes 11.3 and 11.4).

Once the umbilical cord has been cut, the **neonate is no longer exposed to the drug, and monitoring of symptoms of withdrawal should commence within 2 to 4 hours. Any symptoms occurring before this point are likely "drug effect" (symptoms of the drug expressing themselves in the newborn, which is the drug toxic profile or toxidrome). These symptoms will**

BOX 11.1 ETIOLOGY OF NEONATAL ABSTINENCE SYNDROME

- Passive exposure to opiates/opioids in utero
  - Use of illegal drugs (e.g., heroin) or use of legal medications that are not prescribed to the user (e.g., "off the street" codeine, hydrocodone, oxycodone, methadone, buprenorphine)
  - Use of medications that are prescribed, but not as part of a structured treatment program (e.g., short-acting narcotics for pain)
  - Use of medications that are prescribed as part of a structured treatment program (methadone or buprenorphine).
- Iatrogenically, by the administration of opiates/opioids such as fentanyl, morphine, hydromorphone, or methadone to the neonate for analgesia and sedation.

BOX 11.2 DRUGS ASSOCIATED WITH NEONATAL ABSTINENCE SYNDROME

Opioids
- Heroin
- Fentanyl
- Methadone/buprenorphine
- Morphine
- Meperidine (Demerol)

Less Potent Opioids and Opioid-like Agents
- Propoxyphene hydrochloride
- Codeine
- Pentazocine (Talwin)
- Tramadol
- Dextropropoxyphene

BOX 11.3 FACTORS INFLUENCING THE ONSET OF IN-UTERO ACQUIRED NEONATAL ABSTINENCE SYNDROME

- Drugs used by the mother (mono- or poly-medication/drug use, nicotine exposure)
- Possible gene variations of the *OPRM1* gene or *COMT* gene (currently under investigation)

BOX 11.4 FACTORS INFLUENCING THE ONSET OF IATROGENIC NEONATAL ABSTINENCE SYNDROME

- Prolonged opiate sedation for mechanical ventilation
- Duration of opioid analgesia use during extracorporeal membrane oxygenation
- Type of opiate used
- Maturity and presence of intrinsic disease in the neonate

decrease as the drug is cleared from the newborn's system as opposed to worsening as is seen with true withdrawal.[46]

Neonatal withdrawal from psychoactive substances that the fetus is exposed to occurs in varying degrees. Because most opioids are short-acting and not stored by the fetus in appreciable amounts, **neonatal abstinence is usually apparent within the first 24 to 72 hours of life. The onset of clinical NAS symptoms depends on which opioids the pregnant woman used.** For example, with heroin, NAS may occur in the first 24 hours, whereas with methadone, it may not develop until after 2 to 5 days.[27,46,61,74] **Symptoms of NAS in heroin-exposed infants occur earlier than in infants of methadone-maintained mothers because of heroin's shorter half-life.**

Withdrawal may be mild, transient, and delayed in onset, or it may increase stepwise in severity. **Symptoms may be present intermittently or follow a biphasic course characterized by acute NAS signs, followed by improvement, and then the onset of a subacute withdrawal reaction.**[33,46]

Whether drug dose and period of exposure influence the degree of withdrawal seen in affected neonates is unclear. While some researchers report that NAS is more severe in infants whose mothers have taken large amounts of drugs for an extended period, other researchers have not confirmed this finding.[46,74,122]

Usually the origin of NAS lies in the abnormal intrauterine environment. A series of steps appear to be necessary for the onset of NAS and thus the recovery of the infant. The growth and ongoing survival of the fetus are threatened by the continuing or episodic transfer of noxious substances from the maternal to the fetal circulation. During this time, the fetus goes through a biochemical adaptation to the abnormal element. **At delivery, abrupt removal of the drug is the catalyst needed to start the onset of symptoms.** The newborn continues to metabolize and excrete the substance, so that withdrawal signs occur when critically low tissue levels have been reached. **Recovery from NAS is gradual and occurs as the infant's metabolism is reorganized to adjust to the absence of the offending drug.**[33,46]

Studies of the relationship between maternal dose of methadone and severity of NAS have yielded inconsistent results: 50% of the studies find a relationship, whereas 50% find no relationship.[11,30,33,46,108] Use of adequate maternal methadone for therapeutic effect may decrease concomitant drug use and fetal risk; there is no compelling evidence to reduce maternal dosing to avoid NAS.[4,30] **Box 11.5 outlines the effect of maternal methadone maintenance on mother and newborn.**

Neonates experience a physiologic tolerance and withdrawal from medications and drugs they are exposed to in utero, but do not experience "addiction," and cannot be classified as "addicts." Addiction implies a psychological component of dependence that is not part of the newborn experience.

BOX 11.5 EFFECT OF MATERNAL METHADONE MAINTENANCE ON THE MOTHER AND CHILD

- Reduces illegal opiate use and use of other drugs, diminishing the risk for hepatitis, HIV/AIDS, and other sexually transmitted diseases
- Helps remove the opiate-dependent woman from the drug-seeking environment
- Eliminates illegal behavior, including prostitution
- Prevents fluctuation of the maternal drug level that may occur throughout the day
- Decreases mortality and severe maternal morbidity
- Permits a more stable intrauterine environment for the fetus, decreasing chances of hypoxia; increases birth weight
- Increases retention in substance abuse treatment
- Stabilized mothers on methadone more likely to retain custody of their children
- Children can be monitored by methadone clinic staff
- Provides opportunity for parenting education and other life skills
- No association between neonatal abstinence syndrome severity and the following:
  - Maternal methadone dose
  - Trimester of methadone initiation
  - Duration and amount of methadone exposure
  - Duration of maternal drug use before pregnancy

Modified from Substance Abuse and Mental Health Services Administration (SAMHSA). Pregnant, Substance-Using Women (TIP2) BKD127 Guideline 4. U.S. Department of Health and Human Services; 1995.

Maternal Exposure to Opioid Substances

When drugs such as heroin, methadone, morphine, buprenorphine, and meperidine cross the placenta, the fetus may become passively dependent.

Morphine, the major metabolite of heroin, methadone, as well as buprenorphine and its metabolite have been identified and measured in amniotic fluid, cord blood, breast milk,[1,35,38] neonatal urine, and meconium.[46,55,68,79] Non-opioid CNS depressants (e.g., benzodiazepines, barbiturates) and the other opiates/opioids (e.g., codeine, hydrocodone, oxycodone, hydromorphone, pentazocine, propoxyphene) all have been identified in neonatal urine and meconium.[46,73] Ethanol and its primary metabolite, acetaldehyde, have been identified in placental tissue and amniotic fluid.[22,46,74]

Human and animal studies have shown that **use of opioids during pregnancy directly affects fetal growth.** Heroin is associated with intrauterine growth restriction (IUGR), with only a slight reduction in gestational length, although the mechanism through which heroin inhibits growth is not known.[29] Early speculation reported that maternal heroin use during pregnancy accelerated fetal lung maturity, but this has not been borne out when formally studied. Additionally, no plausible mechanism through which heroin exposure resulted in this has been elucidated, although the associated growth restriction and chronic stress has been suggested.[43]

Older studies comparing methadone-exposed with non-exposed infants have found that methadone-exposed infants had lower birth weights. However, **infants born to methadone-maintained women have been reported to have higher birth weights than those born to women using heroin,** while decreased head circumference has been an inconsistent finding. A meta-analysis of illicit drug use and neonatal outcomes found birth weights of newborns born to mothers using heroin were lower than those of newborns whose mothers used methadone alone, and those of newborns whose mothers used both heroin and methadone during their pregnancy.[106] A mean reduction of 483 g (about 1 pound) in birth weight and a relative risk for low birth weight were associated with any opiate use during pregnancy. **Uncertainty remains regarding the teratogenicity of opioids. One systematic review found some association with oral clefts, ventricular septal defects/atrial septal defects, and clubfoot with prenatal opioid use.**[68]

Methadone maintenance had been an accepted treatment strategy for opioid dependence for more than 40 years. Beginning in 2010, reports were published using buprenorphine for the treatment of maternal opioid use and opioid use disorder as well the effect on NAS.*

Buprenorphine in Comparison to Methadone

Buprenorphine and methadone both act on the μ-opioid receptor; however, each has a unique pharmacology. **Whereas methadone has approximately 90% oral bioavailability, buprenorphine has approximately 50% oral bioavailability.** This is because methadone is a full μ-agonist and buprenorphine is a partial μ-agonist and κ-agonist. Buprenorphine has higher receptor affinity and a longer duration of action than methadone.[51,53]

The MOTHER Study, an eight-site, international, double-blind, double-dummy, flexible-dosing trial compared buprenorphine and methadone in a comprehensive care environment, enrolling 175 opioid-dependent pregnant women, of whom 131 delivered while on the study. Among the women who completed the study, there were **no significant differences between the buprenorphine and methadone groups with respect to any baseline characteristics.** There also were no significant differences between the groups in primary outcomes (i.e., percentage of neonates requiring NAS treatment, peak NAS scores, and head circumference). **However, there were significant differences in two primary outcome measures: (1) the total amount of morphine needed for NAS treatment (mean dose 1.1 mg vs. 10.4 mg) and (2) the length of hospital stay (4.1 days vs. 9.9 days). On average, the buprenorphine-exposed neonates required 89% less morphine and spent 43% less time in the hospital than those exposed to methadone.**[51,53]

Table 11.1 compares methadone and buprenorphine **for the management of women with opioid use and opioid use disorder in pregnancy**. Since the MOTHER study, investigators continue to compare the effects of methadone versus buprenorphine for maternal treatment in regard to infant outcomes. In a study environment, or retrospective review, methadone and buprenorphine are likely comparable, but there are some possible advantages to buprenorphine.[59,83,89,124] However, concerns remain regarding confounders in these evaluations, as well as the structure in which buprenorphine is used in the natural environment.[18,50,66,89]

*References 36,46,48,51,53,54,106,124.

TABLE 11.1 A COMPARISON OF METHADONE AND BUPRENORPHINE FOR THE MANAGEMENT OF WOMEN WITH OPIOID USE AND OPIOID USE DISORDER IN PREGNANCY

	METHADONE	BUPRENORPHINE
Issue	**Only available through tightly regulated programs**	**Available through registered individual providers**
Risks	Stigma attached to the program. Limited number of programs, many exclude pregnancy, difficult for women to access on short notice because of waiting lists	Not carefully regulated[50]
Benefits	Carefully regulated with psychosocial supports and wraparound services; higher rates of retention in some populations	More easily available to more people More private and less stigma
Issue	**Dose given either daily or at tightly regulated time only through the program**	**Prescription given, often for months at a time with multiple doses dispensed**
Risks	Difficult for low-resource or gainfully employed women to get to the clinic daily	Patients can vary their dosing as desired (which may contribute to increased NAS). Patients can share or sell dosing and take less or more as desired.
Benefits	Dosing controlled; patient unable to vary dosing. Unable to sell doses and/or take more or less than prescribed	Patients do not have to make a trip for medication at regular intervals
Issue	**Mandated regular drug screening**	**No required drug screening**
Risks	Inability to obtain an accurate specimen. Women fail to come for dosing if worried about other medications/drugs appearing in the drug screen	Patients can use other legal or illegal substances without understanding the consequences of an increase in NAS
Benefits	If patient uses other drugs, her supports can be adjusted to help her maintenance on the program	Less expensive program
Issue	**Psychosocial supports mandated**	**Psychosocial supports often not available**
Risks	Some patients may fail to enroll because of their aversion to group or individual therapy	Addiction not treated as a multifaceted disease; only treats physiologic dependence on drugs/medications. Greater risk of relapse postpartally because the underlying disease is not treated.
Benefits	Addiction is treated as a multifaceted disease, not just a physiologic dependence on drugs/medications	Patients who would not enroll in a methadone program will seek a provider for buprenorphine and regulate the exposure of the substance to the fetus, which has the potential to increase the risk of NAS (from erratic dosing of other substances) if taken as prescribed without continued use of other drugs/medications.
Issue	**Payment for program: some are state subsidized, in over one-half of the states. Medicaid or private insurance provides coverage. More likely to receive the medication covered by insurance because it is dispensed as part of the program.**[87,89,93,112]	**Payment for program and medication: often not paid for by private insurance or Medicaid because the drug is dispensed by an "outside pharmacy." Many providers have a "cash-and-carry" model and will not bill insurance.**

Maternal Exposure to Nonopioid Substances

COCAINE

Although still controversial, the neonatal effects of maternal cocaine use, especially on fetal growth, is consistently observed. Researchers hypothesize that **cocaine reduces fetal growth through maternal vasoconstriction, reduced uteroplacental transfer, and direct effect on fetal metabolism interfering with fat deposition.**[105] Cocaine crosses the placenta by simple diffusion. This occurs because of its high lipid solubility, low molecular weight, and low ionization at physiologic pH. In addition, the low level of plasma esterases in the fetus and the relatively low pH of fetal blood (cocaine is a weak base) enhance the accumulation of cocaine in fetal compartments.[79] Taking advantage of the fact that cocaine and its metabolite *benzoylecgonine (BE)* accumulate and can be detected months after exposure in maternal and neonatal hair, an analytic test for cocaine and BE has been developed. The investigators looked at the characteristics of maternal and neonatal hair cocaine as biomarkers of fetal exposure.[37] Cocaine in hair and BE concentrations are not normally distributed, and there was no correlation between maternal hair cocaine concentration and the baby-to-mother cocaine ratio, which ruled out a dose-dependent mechanism. **However, the positive correlation between cocaine concentrations in maternal and neonates' hair corroborates previous reports showing transplacental transfer of cocaine.[37,79] Cocaine has a significant vasoconstrictive property, which decreases blood flow to the placenta and fetus, contributing to IUGR and hypoxia.**[37]

Accumulated evidence from well-designed prospective investigations has revealed less severe sequelae in the majority of infants exposed to cocaine than originally anticipated. Unlike opioids, which may produce NAS and neurobehavioral deficits, **cocaine exposure appears to be associated with significant but subtle decrements in neurobehavioral, cognitive, and language function.**[8]

Maternal cocaine abuse has been shown to produce infants of lower birth weight and birth length, and infants who were significantly more likely to require medical support or resuscitation.[34] Another study revealed children with intrauterine exposure to cocaine had lower mean cortical gray matter, lower total parenchymal brain volumes, and smaller mean head circumferences than comparison children.[100] The most important central action of cocaine is its stimulation of the CNS by inhibiting the reuptake of norepinephrine, serotonin, and dopamine. In the neonatal period, cocaine, unlike opiates, does not produce an abstinence syndrome.

As part of the Maternal Lifestyle Study, Bada et al. used multivariate regression models with more than 11,000 mother-infant dyads to try to estimate the effects of cocaine exposure on intrauterine growth and to investigate when fetal growth deviation would manifest itself in the woman's gestation.[7] After controlling for confounders, at 40 weeks of gestation, cocaine exposure was estimated to be associated with decreases of 151 g in birth weight, 0.71 cm in length, and 0.43 cm in head circumference. **Investigators concluded that in utero cocaine exposure was associated with growth deceleration that becomes more pronounced as gestation advances.**[7]

ALCOHOL

Alcohol is the most common teratogen that fetuses are exposed to in Western societies, and unlike other teratogens, ethanol has no receptor but affects cellular activity.[110] In both recent prospective and retrospective studies of animals and mammals, ethanol has been shown to cause multiple problems during gastrulation and organogenesis that includes cellular growth, differentiation, and migration.[110,120] These cellular effects can be seen with both ethanol and acetaldehyde and are instrumental in inducing fetal malformations.

Early exposure to alcohol, whose effects are globally referred to as fetal alcohol spectrum disorders (FASD) are well-known causes of mental deficit.[120] *FASD* is an umbrella term describing the range of effects that can occur in an individual who was prenatally exposed to alcohol. These effects may include physical, mental, behavioral, and/or learning disabilities with lifelong implications. FASD is not a diagnostic term. It refers to specific conditions, such as fetal alcohol syndrome (FAS), alcohol-related neurodevelopmental disorder (ARND), and alcohol-related birth defects (ARBDs).[111] **Research documenting deleterious outcomes for children prenatally exposed to even small amounts of alcohol (0.5 drink per day) has led to a realization that a threshold (or critical dose effect) has not been identified.**

Current research has also found a genomic effect that is different in all individuals.[110] When ethanol exposure is held constant, genetic factors modulate the risk for cardiac, craniofacial, skeletal, and central nervous system defects in the developing fetus.[110] In light of these facts, **health care professionals should counsel all women not to drink any alcohol while pregnant.**[97,98]

When women consume cocaine and alcohol together, they compound the danger. Researchers have found that the human liver combines cocaine and alcohol to produce a unique metabolite, cocaethylene, which intensifies cocaine's euphoric effects. Cocaethylene is associated with a greater risk for sudden death than cocaine alone.[81] **Discussions in the 1990s surrounding the use of cocaine and alcohol together suggested that cocaethylene was reported to be 10 times more potent than cocaine alone and more toxic to the growing fetus.** No current studies further our understanding of this toxic metabolite.

AMPHETAMINES

Amphetamines and methamphetamines known as *crystal, ice,* or *crank* are abused by pregnant women in many geographic areas in the United States with the same frequency as cocaine. Like cocaine and "crack," the amphetamines are potent stimulants, and effects on the fetus and neonate are similar; also like cocaine the preponderance of available data would suggest little or no effect of amphetamine on organogenesis.[44] Early research has shown how in utero amphetamine exposure can lead to congenital brain lesions, including hemorrhage, infarction, or cavitary lesions. Investigators also described the sites of these lesions as frontal lobes, basal ganglia, posterior fossa, or generalized atrophy; the effects of the lesions are not exhibited until the child is older. In the neonatal period, neurologic abnormalities including decreased arousal, poor state control, difficulty with habituation, tremors, hyperactive neonatal reflexes, abnormal cry, increased stress, drowsiness, poor feeding, and seizures have been reported.[109] Outcome effects of prenatal exposure to amphetamines have yet to be isolated from the effects of alcohol and nicotine, the two drugs most often used with the methamphetamines.[81]

A review of the literature documents lack of prenatal care as the hallmark of maternal cocaine and amphetamine use with an increase in maternal morbidity and mortality as its consequence.[46,106] **The use of these stimulants is reported to be toxic to the fetal brain, and there may be an increase in sudden infant death syndrome (SIDS). Stimulants (amphetamines and cocaine) have been found in breast milk in extremely high levels, and may produce an acute neurotoxic syndrome with hypertonia, tremors, apnea, and seizures.**[7,37,46,105,109]

MARIJUANA

Marijuana, one of the most popular illicit drugs used by pregnant women,[33] has been studied for many years with conflicting data. Accumulating evidence in animals and humans indicate that prenatal exposure may result in harm to the developing fetus. Cannabinoids mediate their effects through the endocannabinoid receptors, which form very early in fetal life and have critical function in fetal and postnatal brain development, neuronal connectivity, and glial cell differentiation.[16,49,102] In a prospective cross-sectional study that included full-term infants born to adolescent mothers who used marijuana, de Moraes et al. found that marijuana was detected in both the mother's and the infant's hair and that the exposure during pregnancy altered the neurobehavioral performance of the term newborns when assessed with the neonatal intensive care unit (NICU) Network Neurobehavioral Scale (NNNS).[24,46] Other recent studies have highlighted the long-term effects of marijuana use in pregnancy on the neonate and child and reveal conflicting data. While **some studies show a correlation with prenatal marijuana use and increased hyperactivity, impulsivity, inattention symptoms, and delinquency,**[81] **other studies have reported minimal effects on cognition, language, and motor development.**[16,76] There are also conflicting data in regard to fetal growth and birth complications, with few studies citing lower birth weight, others concluding an increase in NICU admissions, and still others reporting an increased risk of neonatal morbidity.[16,76] The only finding that seems consistent across studies is that **marijuana does not cause structural anatomic defects in humans.**[16] In summary, there are no randomized controlled trials on the effect of marijuana use by pregnant and lactating women, and the available longitudinal studies must be viewed with caution given the potential confounding of the effect of marijuana during pregnancy by other licit and illicit substances, as well as

sociodemographic and environmental risk factors. Given that the evidence about the effects of marijuana use during pregnancy and fetal-related complications and child development is inconclusive, **continued counseling to abstain from marijuana use during pregnancy needs to be conveyed.**[102] Further research is critical to understand the specific risks to the developing fetus and growing child.[123]

BENZODIAZEPINES

Benzodiazepines have hypnotic, muscle-relaxant, and anticonvulsant properties. They can be used to treat anxiety, insomnia, panic disorder, seizures, and agitation, and for sedation.

The data regarding the use of the benzodiazepines (including clonazepam, alprazolam, lorazepam, and diazepam) during pregnancy are insufficient. There is some suggestion that there may be an **increased risk of cleft lip and palate associated with first-trimester exposure to these medications.**[85] Risk does not seem to be influenced by the dosage of medication taken by the mother.

There is further concern regarding drug effect (toxidrome) and withdrawal for the baby exposed to benzodiazepines in utero. **Symptoms of toxicity have been reported in newborns, and these include sedation, hypotonia, and breathing problems**, as could be seen in anyone exposed to these medications. **Withdrawal symptoms include irritability, sleep disruption, and, less commonly, seizure.** Onset ranges from 12 hours to days.[3,6,71,115]

BARBITURATES

Barbiturates, a type of sedative-hypnotic, are used to treat anxiety, seizures, and insomnia. **Barbiturates are no longer routinely prescribed for pregnant women because of concern for birth defects, but remain a substance of abuse.** The drug effect or toxidrome of barbiturates is similar to those of benzodiazepines described earlier. **Withdrawal symptoms include irritability, tremors, hyperacusis, excessive crying, vasomotor instability, diarrhea, restlessness, increased tone, hyperphagia, vomiting, and disturbed sleep.** Onset can occur during the first 24 hours, but as late as 10 to 14 days of life.[3,6,115]

INHALANTS

No well-controlled, prospective studies have been done on maternal inhalant use (huffing)—often substances of abuse in poor and underprivileged communities because they are widely available (e.g. acetone), legal, and relatively inexpensive. Organic solvents are chemical compounds used to dissolve substances, and although their chemical structures widely differ, they share some common features: low molecular weight, lipophilia, and volatility at room temperature.[73,107] Inhalants are classified into four groups: volatile solvents, aerosols, gases, and nitrites.[73,75,107]

Inhalants may produce a variety of rapid neuropsychiatric effects with euphoria or drowsiness occurring within seconds to minutes. Case reports and follow-up studies of children of inhalant/solvent-abusing mothers are available. **Inhalant/solvent-abusing mothers give birth to babies who are small for gestational age (SGA) and who have developmental delays, craniofacial deformities, and an alcohol-like withdrawal syndrome.**

ANTIDEPRESSANT USE IN PREGNANT WOMEN AND OCCURRENCE OF NEONATAL ABSTINENCE SYNDROME

Psychopharmacology for pregnant women with coexisting mental health diagnoses are also of concern.[42] **As many as 70% of pregnant women experience some symptoms of depression, with 10% to 16% of pregnant women meeting diagnostic criteria for a major depressive disorder.**[116] The typical or atypical antipsychotic drugs all pass the maternal blood–placenta barrier, with significant difference among compounds.[99] Continuing treatment throughout pregnancy, at the lowest effective dose, may be necessary to prevent relapse and to prevent potential harmful effects on the mother-fetal dyad. Case reports, adverse drug reaction reports, and prospective studies have linked third-trimester use of SSRIs in pregnant women to a **constellation of neonatal signs indicating an altered neonatal adaptation to extrauterine life. These include continuous crying, irritability, jitteriness, and/or restlessness; shivering; fever; tremors; hypertonia or rigidity; tachypnea or respiratory distress; feeding difficulty; sleep disturbance; hypoglycemia; and seizures.** The onset of these signs ranged from several hours to several days after birth and usually resolved within 1 to 2 weeks. **Biochemical studies that correlate serial serum SSRI concentrations and markers of CNS serotonin activity support a drug toxicity phenomena rather than a drug withdrawal state as the cause of the clinical signs.**[46,57,58] A mother on treatment with an

SSRI who desires to breastfeed her infant should be counseled about the benefits of breastfeeding as well as the potential risk that her infant may continue to be exposed to a measurable level of the SSRI with unknown long-term effects.[46] There has been some suggestion of possible link of SSRIs with congenital malformations.[85]

*PREVENTION

Neonatal drug withdrawal is preventable if women do not use dependence-producing substances, licit or illicit, during pregnancy. Through intense educational efforts, the desirability and availability of drugs may be thwarted. Unfortunately, the psychosocial and socioeconomic milieu of modern society continues to propagate dysfunctional families, victimization of women, and an intergenerational cycle of substance abuse.

Therefore, our goals must be to provide prenatal care for the pregnant drug-dependent woman and her fetus to diminish or eliminate the sequelae of NAS. The health care community is challenged to become more astute in its assessment and intervention for the problems of drug-dependent parturients. More treatment options are necessary for women with opioid use disorder and their neonates through inpatient residential care and outpatient interdisciplinary clinics that focus on the elimination, as well as the consequences, of addiction. Despite recent discussion in the press and some literature regarding medically supervised withdrawal during pregnancy, studies continue to demonstrate, and the American College of Obstetricians and Gynecologists (ACOG) states, **"that for women with an opioid use disorder, opioid agonist pharmacotherapy is the recommended therapy."** The ACOG document also states that pharmocotherapy is preferable to medically supervised withdrawal because withdrawal is associated with high relapse rates, which lead to unfavorable outcomes.[4,10,16,40,117] **Additionally, it is now recognized that to achieve lasting results from treatment of opioid use disorder in any population, treatment must be family centered and trauma informed.**[70,90]

For iatrogenic NAS, there is a need for guidelines for effective weaning of neonates from opiate analgesics and sedatives.[8] **Investigators encourage dose reductions of 10% to 20% per day.** For the prevention of iatrogenic NAS, discussions in recent literature include limiting total doses of fentanyl during ECMO therapy by administering morphine boluses or using continuous morphine infusions to replace fentanyl, substituting enteral methadone for morphine, or using sublingual buprenorphine.[64,77]

DIAGNOSIS

History

A comprehensive prenatal medical and drug history, especially with respect to poly-drug abuse, is of prime importance. All pregnant patients who are substance abusers, regardless of the drug used, are considered high risk because of the effects of the drug, as well as complications arising from concomitant infections and lifestyle.[26] Fear of referral to child welfare agencies or the legal system in recent years has prompted women to conceal their drug abuse and/or pregnancy. This fear and denial may prevent the pregnant woman from seeking prenatal care. Thus, she may appear in the emergency department of the hospital either in crisis or ready to deliver. In this instance, a prenatal history is absent, making neonatal assessment more difficult.[4]

Signs and Symptoms of Neonatal Abstinence Syndrome

At birth, most infants exposed to opioids appear physically and behaviorally normal with **symptoms of withdrawal beginning shortly after birth and up to 2 weeks of age, but the majority are exhibited within 72 hours.**[33,46,61] **Acute symptoms may persist for several weeks, whereas subacute symptoms (e.g., irritability, sleep problems, hyperactivity, feeding problems, hypertonia) may persist for 4 to 6 months.**[15]

The most common signs and symptoms of NAS are listed in Box 11.6. A standardized NAS scoring system is recommended for assessing infants.[46] Caregivers should have extensive training on this scoring system with ongoing competencies and second-scorer validation for high scores to ensure as objective a measure as possible. For the convenience of referencing, the signs and symptoms discussed here are in the order in which they appear on the assessment sheet reviewed within this chapter, as shown in Fig. 11.2.

BOX 11.6 CRITICAL FINDINGS[29,32] NEONATAL ABSTINENCE SYNDROME

- Signs and symptoms of neonatal abstinence syndrome may not be exhibited for up to 72 hours.
- Most common signs and symptoms of neonatal abstinence syndrome are central nervous system hyperirritability, gastrointestinal dysfunction, respiratory distress, and autonomic instability.
  - Acute signs and symptoms that may persist for several weeks:
  - Restlessness
  - Tremors (disturbed at first to undisturbed)
  - High-pitched cry
  - Increased muscle tone
  - Irritability and inconsolability
  - Increased deep tendon reflexes
  - Exaggerated Moro reflex
  - Seizures in approximately 1% to 2% of heroin-exposed neonates and approximately 7% of methadone-exposed neonates
- Subacute signs and symptoms that may persist for 4 to 6 months:
  - Irritability
  - Sleep pattern disturbance
  - Hyperactivity
  - Feeding problems
  - Hypertonia

Initially, the infants appear only to be restless. **Tremors develop, which are mild and occur only when the infant is disturbed, but these progress until they occur spontaneously without external stimulation of the infant.** One of the most serious but rare consequences of neonatal opioid abstinence is the development of seizures. No relationship between maternal methadone dosage and the frequency or severity of neonatal seizures has been established. In addition, no significant differences have been found between neonates with seizures and those without seizures in birth weight, gestational age, occurrence of their withdrawal symptoms, day of onset of withdrawal symptoms, or the need for specific pharmacologic treatment.[46] **The short-term prognosis for abstinence-associated seizures is favorable compared with the prognosis after seizures associated with other causes.** This observed improvement in neurologic function may be based on the replenishment of neurotransmitters after transient depletion in the neonatal period.[72,109]

The risk for SIDS should be considered when the neonate has an especially difficult course of NAS, when the mother uses multiple agents (poly-pharmacy: opioids and stimulants such as cocaine or amphetamine, nicotine), and when a combination of therapeutic agents is used for treatment. The rate of SIDS in these infants has been demonstrated to be 5 to 10 times over that in the general population. Research reports that the risk for SIDS is increased in opiate-exposed infants and varies from 2.5% to 4%.[47] Wingkun and other investigators studied carbon dioxide sensitivity in infants of substance-abusing mothers and found that these infants have abnormal sleep ventilatory patterns and "an impaired repertoire" of protective responses to hypoxia and hypercapnia during sleep cycles.[125]

In addition to having disturbed sleep patterns, infants undergoing withdrawal from narcotics exhibit excessive spontaneous generalized sweating. Other autonomic nervous system signs include yawning, elevation of temperature, sneezing, and skin mottling. **The rooting reflex is exaggerated, and these infants frequently suck their fists or thumbs; yet when fed, their suck-and-swallow reflexes are uncoordinated and ineffectual.** Therefore they tend to regurgitate or vomit in a projectile manner. The infant also may develop loose stools and is susceptible to dehydration and electrolyte imbalance.[5,33,46] These symptoms are exhibited as a result of exposure to opioids, as well as to nonopioid CNS depressants. However, with **nonopioid CNS depressant exposure, symptoms tend to begin at a later age, with malnourishment at birth an unusual feature.** Because barbiturate withdrawal may not develop until an infant has been discharged from the nursery, it may not be treated unless suspicion has been aroused by the mother's symptoms or actions. **Furthermore, there is a greater risk for seizure activity in neonates withdrawing from barbiturates than in those withdrawing from opioids.**[5,30,46]

Symptoms exhibited by stimulant-exposed newborns are manifestation of drug toxicity (drug effect or toxidrome) rather than withdrawal.[46] **The symptoms usually decrease with time rather than increase as is seen with true withdrawal.** The literature describes cocaine-exposed infants as tremulous, irritable, lethargic, unable to respond appropriately to stimuli, and having abnormal state control and cry patterns.[5,7,46,61,106]

Also described are abnormalities in orientation, motor ability, state regulation, muscular hypertonia, and abnormal reflexes. Infants may show symptoms of lethargy intermittently with irritability, poor sucking patterns, and sleep disturbances. When cocaine has been the primary drug of abuse, most clinicians have not seen symptoms severe enough to treat the infant pharmacologically.[31,46,61]

Laboratory Data and Differential Diagnosis

Before initiating medication for treatment of NAS, common neonatal metabolic alterations that can mimic or compound withdrawal, such as hypocalcemia, hypomagnesemia, hypoglycemia, and hypothermia must be ruled out. Serum glucose and calcium tests may be indicated. If the mother has had no prenatal care, it would be prudent to thoroughly assess the infant at birth, including testing for occult disease, sepsis, and intracranial bleeding. A urine and meconium test for toxicology should also be obtained. Meconium is more accurate and can detect a longer period of drug exposure. Umbilical cord testing has the benefit of being obtained even before drug exposure is suspected, but may not be as sensitive a test as meconium, and can be logistically more difficult.[20,28,74,121]

TREATMENT AND INTERVENTION

Infants at risk for NAS should be monitored closely for signs and symptoms of withdrawal. The appropriate duration of observation should be dependent on careful assessment of maternal substance history. **Infants born to mothers requiring or taking an opiate with a short half-life (hydrocodone) may be discharged after 72 hours if without signs of withdrawal. Infants exposed to maternal opiates with a long half-life (methadone, buprenorphine) should be monitored for 5 to 7 days.**[46] Fifty-five percent to 94% of infants with maternal opiate exposure will have some signs or symptoms of withdrawal. While there is **clear literature to support nonpharmacologic management as the initial treatment for infants at risk for NAS or experiencing symptoms of NAS, there is no literature-based standard for pharmacologic treatment.**[46] A randomized control trial showed that implementation and adherence to a formalized NAS protocol with set initiation, escalation, and weaning parameters was key to improving pediatric outcomes.[42] **Nonpharmacologic care should be implemented after birth to help abate symptoms of withdrawal and to help control symptoms if pharmacologic treatment becomes necessary.**[41,42,46,121]

To best monitor an infant, each nursery should adopt a protocol for the evaluation and management of NAS. Staff should be trained on the use of an abstinence assessment tool.[46] Institutions may increase the reliability of NAS assessment through competency requirements and second-scorer validation of elevated scores. The most predominantly used assessment tool is the Finnegan Neonatal Abstinence Scoring System (FNASS). The Lipsitz Tool, initially endorsed by the American Academy of Pediatrics in 1998, is still in use in some institutions.[74]

With the increased focus on NAS monitoring and treatment, many centers have moved attention to not only modifying the Finnegan Scoring System, but also creating whole new systems that emphasize physiologic behaviors, comfort care, and team-approach scoring.[39] For example, **the *Eat, Sleep, Console model* is a comprehensive nonpharmacologic approach on which infants are assessed on three key aspects: how well the infant is eating, how well the infant is sleeping, and consolability of the infant.** Pharmacologic treatment is based on infant function and comfort versus reducing all signs of opioid withdrawal. **Medication treatment is initiated only when an infant fails to eat, sleep, or console because of symptoms from NAS after assuring nonpharmacologic treatment has been maximized.** Although this model of care has not been validated, the initial study showed a decreased length of hospitalization in infants with NAS from 22.5 to 5.9 days with the initiation of the Eat, Sleep, Console model's launch in 2011.[39] Presently, further validation and evaluation of this system is taking place.

The FNASS, developed in 1975, is used in 95% of US hospitals, although the tool has been modified frequently. **Centers now allow for comfort care, clustering of care, assessing after feedings, and not waking an infant simply for scoring.**[39]

This system allows for assessment of the onset, progression, and resolution of symptoms, as well as the infant's clinical response to pharmacotherapy for the control of NAS symptoms. Titration of therapeutic agents is thus based on the degree of withdrawal symptoms that correspond to a specific score (Fig. 11.1). **Although a number of scoring tools have been used in both clinical and research settings, the modified 21-item Finnegan neonatal abstinence score has remained useful.** The nurse and multidisciplinary team are vital in the assessment of withdrawal in an infant. It is vital that interrater reliability be developed among all nursing staff and anyone responsible for scoring and assessment of the infant.

The ***Finnegan Abstinence Score*** sheet (see Fig. 11.2) uses a weighted scoring of 21 actual items that are most commonly observed in an opioid-exposed neonate.[31,46,74] **Signs and symptoms are recorded as single entities, or in several categories if they occur in varying degrees of severity.** Each symptom, with its associated degree of severity, has been assigned a score. **Higher scores are assigned to symptoms found in infants with more severe withdrawal. The total score is determined by adding the scores assigned to each symptom observed throughout the entire scoring interval. The scoring system is dynamic rather than static;** all signs and symptoms observed during the 3- to 4-hour intervals at which infant symptoms are monitored are point-totaled for that interval. Most institutions now use intervals from one feeding to the next to ensure the implementation of nonpharmacologic comfort care.

Fig. 11.2 shows the NAS scoring system. Symptoms are listed on the left and scores on the right. Times of each evaluation are listed at the top, and the total score is listed for each evaluation. A new sheet should be started at the beginning of each day. A "Comments" column is provided for nursing and medical staff to record important notes about the infant's progress.

The first score should be recorded approximately 2 to 4 hours after the neonate's admission. This score reflects all infant behaviors from admission to the first point in time when the scoring interval is complete. The times designating the end of the scoring intervals have been left blank to permit the health care team or nursing staff to choose appropriate times for scoring. **Most institutions now center scoring around or after feedings.**

The need for medication is indicated when the total score is 8 or higher for three consecutive scorings (e.g., 9, 8, 10). Medication treatment is also warranted when the infant's total is 12 or higher for two consecutive intervals.

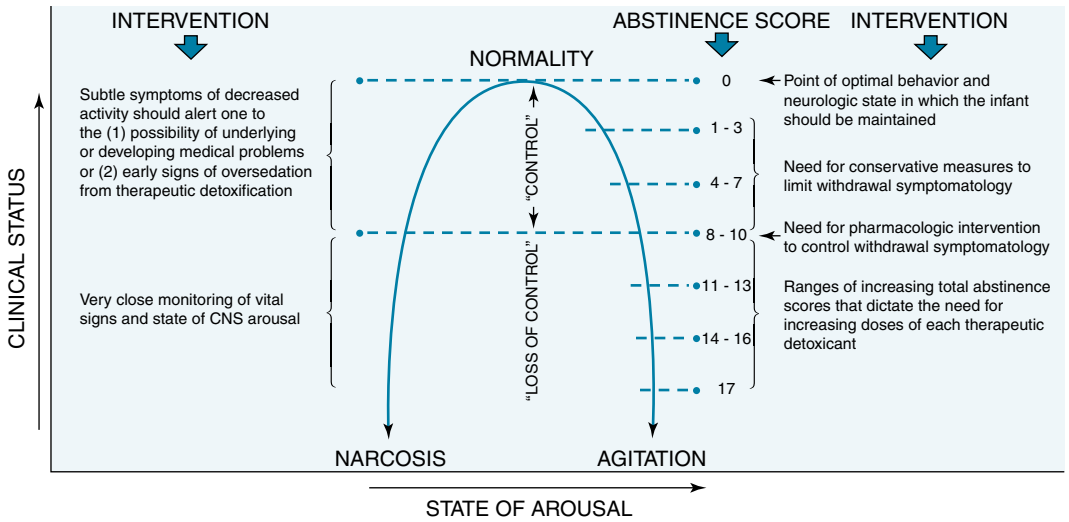

FIGURE 11.1 Management of neonatal abstinence syndrome. *CNS,* Central nervous system. (From Finnegan LP. Neonatal abstinence syndrome. In: Nelson N, ed. *Current Therapy in Neonatal-Perinatal Medicine.* 2nd ed. Ontario: Decker; 1990.)

NEONATAL ABSTINENCE SCORE

Date:_____ Weight: _____

System	Signs and Symptoms	Score	Time AM / PM	Comments
Central nervous system disturbances	Excessive high-pitched cry	2		
	Continuous high-pitched cry	3		
	Sleeps <1 hour after feeding	3		
	Sleeps <2 hours after feeding	2		
	Sleeps <3 hours after feeding	1		
	Hyperactive Moro reflex	2		
	Markedly hyperactive Moro reflex	3		
	Mild tremors when disturbed	1		
	Moderate - severe tremors disturbed	2		
	Mild tremors when undisturbed	3		
	Moderate - severe tremors undisturbed	4		
	Increased muscle tone	2		
	Excoriation (specific area)	1		
	Myoclonic jerks	3		
	Generalized convulsions	5		
Metabolic/vasomotor/ respiratory disturbances	Sweating	1		
	Fever <101° F (37.2° - 38.2° C)	1		
	Fever 38.4° C and higher	2		
	Frequent yawning (>3 - 4 times/interval)	1		
	Mottling	1		
	Nasal stuffiness	1		
	Sneezing (>3 - 4 times/interval)	1		
	Nasal flaring	2		
	Respiratory rate >60/min	1		
	Respiratory rate >60/min with retractions	2		
Gastrointestinal disturbances	Excessive sucking	1		
	Poor feeding	2		
	Regurgitation	2		
	Projectile vomiting	3		
	Loose stools	2		
	Watery stools	3		
	TOTAL SCORE			
	Initials of Scorer			

FIGURE 11.2 Neonatal abstinence score sheet. Check sign or symptom observed at various time intervals, and add scores for a total at each evaluation. (Modified from Finnegan LP, Kaltenbach K. The assessment and management of neonatal abstinence syndrome. In Hoekelman RA, Nelson N, eds. *Primary Pediatric Care*. 3rd ed. St Louis, MO: Mosby; 1992.)

Some simply refer to the threshold for medical treatment as the "rule of 24." **When two to three consecutive scores add up to 24 or greater, then pharmacologic treatment should be considered. Once an infant's score is 8 or higher, one must ensure nonpharmacologic measures (comfort measures) are maximized, and scoring intervals should be changed to hourly to closely monitor the infant's symptoms, the efficacy of the comfort measures employed, and the potential need for pharmacologic treatment.** Many centers now use a second scorer to validate ("second-scorer validation") scores greater than 8 to allow more objectivity in scoring. This is important because the decision to treat medically relies on this measure. Table 11.2 describes the symptoms of withdrawal, appropriate observations, and nonpharmacologic interventions (comfort care).

Pharmacologic Treatment of Neonatal Abstinence Syndrome

Even though there is a plethora of evidence to support nonpharmacologic (comfort) approaches for NAS, no single evidence-based best practice concerning pharmacologic treatment exists.[45,46,94,121] Many pharmacologic approaches, all varying in choice of drug and dose, as well as approaches to escalation of dosing and weaning have been suggested.[46,60,61,74,121] **In the past decade and in the latest study of 199 US NICUs in the Vermont Oxford Network,**[96] **morphine is the most commonly used medication for pharmacologic treatment of NAS. However, in recent years there is increasing research about the use of methadone or buprenorphine.**[23,46,61,96,121] Table 11.3 lists

TABLE 11.2 CREATING A SUPPORTIVE ENVIRONMENT FOR THE DRUG-EXPOSED NEONATE

INFANT BEHAVIOR	OBSERVATIONS	INTERVENTIONS (COMFORT CARE)
High-pitched cry	Note onset. Note length of time the cry persists: Is it continuous? Is it high pitched and piercing as though infant were in pain?	Nonnutritive sucking Swaddle infant Soothe with slow, rhythmic swaying Skin-to-skin contact with parent Feed on demand Decrease environmental stimuli (low noise, low light, limit visitors) Organize care to minimize handling
Inability to sleep	Note how long infant sleeps after feeding. Note general sleep-wake patterns. If drug therapy has been initiated, note changes in sleep patterns, ability to rest, and any decreased activity indicative of drug overdose.	Decrease environmental stimuli (low noise, low light, limit visitors) Feed on demand, or small amounts at frequent intervals Organize care to minimize handling Swaddle infant Skin-to-skin contact with parent Soothe with slow, rhythmic swaying
Frantic sucking of fists	Note onset and amount of fist sucking.	Use infant shirts with sewn-in sleeves for mitts to prevent skin trauma Offer pacifier for nonnutritive sucking
Yawning	Note onset and frequency.	None
Sneezing	Note onset and frequency.	Wipe secretions with cloth
Nasal stuffiness	Note severity of nasal stuffiness, and determine whether it hinders breathing and feeding.	Allow more time for feeding with rest between sucking Check rate and character of respirations frequently
Poor feeding	Note sucking pattern: Is infant uncoordinated in attempt to suck, swallow, and breathe?	Weigh daily Decrease environmental stimuli (low lights, low noise, limit visitors) Feed small amounts at close intervals Swaddle infant Maintain fluid and caloric intake required for infant's weight Feed on demand Use alternative feeding methods (e.g., gavage) Consider higher-calorie formula Organize care to minimize handling to ensure adequate rest between feedings
Regurgitation	Note when regurgitation or vomiting occurs: Is there a precipitating factor (e.g., medication, handling, manipulation, position)?	Measure intake and output closely Burp infant each time he or she has a long pause in sucking during a feeding Hold infant upright for 15–20 minutes after feeding Monitor weight closely Feed small amounts at close intervals
Hyperactive Moro reflex	Is reflex moderately or markedly exaggerated? If drug therapy has been started, is Moro reflex diminished or absent?	None

Continued

TABLE 11.2 CREATING A SUPPORTIVE ENVIRONMENT FOR THE DRUG-EXPOSED NEONATE—CONT'D

INFANT BEHAVIOR	OBSERVATIONS	INTERVENTIONS (COMFORT CARE)
Hypertonicity	Note degree (mild, moderate, or severe) of increased muscle tone by: • Attempting to straighten arms and legs and recording degree of resistance • Picking up infant by hands and noting body rigidity with degree of head lag (a withdrawing infant often exhibits trunk rigidity and holds the head on a plane with the body for a prolonged time) • Raising infant by arms and letting baby stand (a withdrawing neonate exhibits marked leg rigidity and can support body weight for considerable periods)	Swaddle infant Skin-to-skin contact with parent Decrease environmental stimuli (low lights, low noise, limit visitors) Organize care to minimize handling Avoid overdressing or overswaddling because of the risk for increased body temperature with hypertonicity
Tremors	Note whether tremors occur when infant is disturbed or undisturbed. Note location of tremors: • Note whether degree of tremors is mild, moderate, or severe.	Decrease environmental stimuli (low lights, low noise, limit visitors) Organize care to decrease handling Support movements during caregiving Swaddle infant as much as possible during caregiving Swaddle when sleeping in crib
Seizures	Observe for seizures; if they occur, note onset, length, origin, body involvement, type (tonic, clonic, or both), eye deviation, and infant's color.	Monitor respiratory rate, heart rate (sign of apnea or bradycardia) Initiate resuscitation as indicated

Modified from Finnegan LP, MacNew BA. Care of the addicted infant. *Am J Nurs.* 1974;74:685.

first-line and adjunctive pharmacologic treatment for NAS. Although preliminary data suggest methadone and buprenorphine are both viable options in the pharmacologic treatment of NAS, there are presently no neonatal formulations of these medications commercially available for use, and studies have used formulations specifically designed for the study.[23] Additionally, in former eras of NAS care, the longer-acting opioid choices had fallen out of favor because of a prolonged half-life and difficultly weaning effectively in a short period. **Both phenobarbital and clonidine are used for adjunct therapy when first-line treatment does not control symptoms.**[46,96,121] Although continued data are needed to support a specific treatment drug choice or protocol, standardized, evidence-based practice is essential. Within a specific unit or system, the following must be clearly defined: (1) medication to be used, (2) initial dosing (can be symptom based, weight based, or both), (3) parameters for escalation of dosing, (4) parameters for weaning of dosing, and (5) second-line therapy with all of the previously mentioned specifications. The development and use of a standardized NAS treatment protocol has been shown to improve neonatal response and decrease length of stay.[17,41] **Although a standard pharmacologic approach to NAS is important, expert clinical judgment is also necessary to individualize care when necessary.** If there are some unappreciated clinical findings that seem to confound scoring, this must be fully examined before starting treatment "per protocol." Likewise, if an infant becomes excessively sleepy or less responsive, the dosing protocol must be put on hold while the infant is thoroughly assessed by the provider. Although the standard medication dosing dictated by a protocol may be appropriate for most infants, there may be cases in which the starting dose is in excess of that required by an individual infant so that care individualization is necessary.

TABLE 11.3 PHARMACOLOGIC TREATMENT FOR NEONATAL ABSTINENCE SYNDROME

DRUG	DOSAGE	COMMENTS
Oral buprenorphine[62–64]	Initial dose: 5.3 mcg/kg every 8 hours sublingually; give pacifier and administer under tongue while neonate sucks on pacifier Total dose per day: 15.9 mcg/kg/day divided in three doses	Three RCTs comparing oral buprenorphine and morphine found advantages to buprenorphine use.[62–64] The most recent RCT found fewer days of treatment (15 days vs. 28 days), shorter LOS (21 days vs. 33 days), and fewer babies requiring adjunctive phenobarbital in the buprenorphine-treated group.[62] Longer duration of action than methadone
Oral methadone: used in 20% of participating VON US NICUs[96]	Initial dose: 0.05–0.1mg/kg every 6 hours Increment: 0.05 mg/kg/dose Maximum dose: to effect	Long half-life of 8–59 hours[101]
Oral morphine: used in 80% of participating VON US NICUs[96]	Initial dose: 0.04 mg/kg every 3–4 hours Increment: 0.04 mg/kg/dose Maximum dose: 0.2 mg/kg/dose[46] Use a 0.4-mg/mL dilution: 1 mL of the 4 mg/mL injectable solution added to 9 mL preservative-free normal saline solution. Protect from light; stable for 7 days, refrigerated.	Control is evidenced by an NAS average score <8, rhythmic feeding/sleep cycles, optimal weight gain, same opium dose for 72 hours, and pharmacologic weaning. Continue to score for NAS. Scores must remain <8. Advantages: Diminishes bowel motility and loose stools; 20% to 40% bioavailability when administered orally; lower doses and shorter dosing interval are associated with shorter hospital stay in infants with NAS resulting from maternal methadone treatment. Disadvantages: Respiratory depression, hypotension, delayed gastric emptying, ileus, urine retention.
Adjunctive Pharmacologic Therapy		
Oral clonidine[46]: used in less than 10% of participating VON US NICUs[96]	Initial dose: 0.5–1 mcg/kg every 6 hours Increment: not studied Maximum dose: 1 mcg/kg every 3 hours	Reduces CNS sympathetic outflow and palliates symptoms of autonomic overactivity, such a tachycardia, hypertension, diaphoresis, restlessness, and diarrhea. Cessation of clonidine treatment can result in a rebound of autonomic activity. Reported experience with clonidine as a primary or adjunctive treatment of NAS is limited but promising.[46]
Phenobarbital: used in 24% of participating VON US NICUs[96]	Loading dose: 20 mg/kg to achieve an expected therapeutic level in a single dose. If score is ≥8, give 10 mg/kg every 12 hours until control or signs of toxicity appear. Maintenance dose (once under control): 2–6 mg/kg/day for 3–4 days. Decrease dose to 3 mg/kg/day. Discontinue: serum levels <15 mcg/mL.	Daily serum levels can be obtained. Advantages: Drug of choice for poly-drug use; especially effective in controlling irritability and insomnia; controls symptoms in 50% of infants. Disadvantages: Does not prevent loose stools. Infant should be in a nursery where he or she can be monitored closely.

LOS, Length of stay; *NAS*, neonatal abstinence syndrome; *PO*, by mouth; *RCT*, randomized controlled trial; *VON*, Vermont Oxford Network.

Complications of excessive pharmacologic treatment are listed in Box 11.7. Alternatively, these neonatal symptoms may represent another underlying issue (e.g., hypoglycemia, sepsis, meningitis) unrelated to NAS that requires investigation and treatment. Detection of underlying medical problems may be difficult, because poorly controlled abstinence may mimic and/or disguise many common neonatal conditions.

Breastfeeding the Infant With Neonatal Abstinence Syndrome

All drugs of abuse pass through the breast milk. However, breastfeeding for women in medically supervised treatment programs with nontoxic agents need not be discouraged.[1,30,46,61,84] In contrast, women using stimulants and other potentially toxic drugs, as well as those who are infected with HIV, should be discouraged from breastfeeding because of the potential toxic and negative effects on the neonate.

Both methadone and buprenorphine are found in breast milk. Methadone appears in low levels in breast milk, but absolute levels depends on maternal dosing.[30] **Buprenorphine is excreted into breast milk approximately 2 hours after maternal ingestion.** The concentrations of buprenorphine and norbuprenorphine in breast milk are highly variable because of differences in breast milk protein and fat. However, neither concentrations of buprenorphine and norbuprenorphine exceed plasma concentrations.[51] One study comparing breastfeeding rates and the relationship between breastfeeding and NAS in buprenorphine-exposed neonates found the following:[51]

- 76% or (65 of 85 participants) in the study chose to breastfeed.
- 66% were still breastfeeding at 6 to 8 weeks postpartum.
- **NAS was less severe with the breastfeeding group** (mean peak NAS scores of 8.83 vs. 9.65 on the Finnegan scoring system).
- **Breastfed infants were less likely to require pharmacologic treatment** (23.1% vs. 30%) than infants who were not breastfed.

The Norwegian National Cohort Study of 124 women treated with either methadone or buprenorphine found that 77% of the women chose to breastfeed. **Methadone-exposed infants had a lower incidence of NAS requiring pharmacologic treatment (53% vs. 80%). Breastfed infants exposed to both methadone and buprenorphine needed less medication for a shorter period.**[69]

In summary, the limited published research (barring other complications and contraindications, such as an HIV-positive mother) support **current guidelines that recommend breastfeeding for mothers who are stabilized on either methadone or buprenorphine.**[2,51] **Likewise, it is recommended that women who are stable on any medically supervised opioid agonist treatment program are supported in their breastfeeding efforts.**[4] **Marijuana is the most commonly used recreational drug among breastfeeding women.** Authors of case reports have documented the presence of marijuana metabolites in human milk. Recently, one study measured variable quantities of the primary psychoactive ingredient in marijuana, Δ-9-tetrahydrocannabinol, in human milk up to approximately 6 days after marijuana use.[12] Similar to marijuana use during pregnancy, there are insufficient data to evaluate the effects of marijuana use on infants during lactation and breastfeeding, and in the absence of such data, marijuana use is discouraged.[16]

BOX 11.7 COMPLICATIONS OF EXCESSIVE PHARMACOLOGIC TREATMENT

- Diminished or absent reflexes: Moro, sucking, swallowing, Galant, Perez, tonic neck, corneal, grasp (palmar, plantar)
- Truncal (central) or circumoral cyanosis or persistent mottling not associated with ambient temperature decreases
- Decreased muscle tone with passive resistance to extension of extremities, or decreased neck or trunk tone
- Altered state of arousal (e.g., obtunded, comatose)
- Diminished response to painful stimuli
- Failure of visual following
- Hypothermia
- Altered respirations: irregular (periodic breathing in full-term infants), shallow (decreased air entry), decreased respiratory rate (<20/min), apnea
- Cardiac alterations: irregular rate, distant heart sounds with weak peripheral pulses, heart rate of 80 to 100 beats/min, poor peripheral perfusion (pale, gray, mottled skin), cardiac arrest

Complications

Kocherlakota nicely summarized in a 2014 publication the recommendations for discharge and

follow-up of babies who have exhibited signs and symptoms of NAS[61]:

- **Neurodevelopmental assessments** to identify motor deficits, cognitive delays, or relative microcephaly
- **Psychobehavioral assessments** to identify hyperactivity, impulsivity, and attention-deficit/hyperactivity disorder in preschool-age children, as well as school absences, school failure, and other behavioral problems in school-age children
- **Ophthalmologic assessment** to identify nystagmus, strabismus, refractive errors, and other visual defects
- **Growth and nutritional assessment** to identify failure to thrive and short stature
- **Family support assessments** to exclude continuous maternal substance abuse and child abuse

Depending on the substance to which the fetus was exposed some expected long term effects may include alterations in growth, behavior, cognition/ executive function, language and school achievement.[9] An empiric evaluation of in utero drug exposure and school performance also demonstrated poor and deteriorating school performance in children who were diagnosed with NAS during the neonatal period.[86]

PARENT TEACHING

As soon as it is identified that an infant may be at risk for NAS through maternal use of illicit or prescription drugs, whether in a structured program or prescribed by an individual caregiver, education for the family must begin. The education is best delivered by health care providers who have been educated and are well versed in the issues of NAS. **Best practice is to supply written material that is supportive and nonjudgmental, describing the symptoms of NAS; what families can do before, during, and after birth; comfort measures; expectations regarding time of observation; and details of scoring.** Also essential is a discussion regarding the potential need for treatment and what to expect regarding length of stay and location of care (family room vs. separate location). **When families are prepared with knowledge and expectations before the birth, they are better able to partner in the care of their infant and comply with recommendations.**[46]

It is important for primary caretakers to understand that infants exposed to narcotics through maternal drug use have been found to be more irritable and less cuddly, exhibit more tremors, and have increased tone (Box 11.8). These infants are also less responsive to visual stimulation and are less likely to maintain an alert state. **Some symptoms of withdrawal may persist for 2 to 6 months, and the health care professional should discuss this possibility with the family caregivers well before discharge so they can begin building the skills they will need under the watchful eye of supportive staff.** The infant may continue to feed poorly and regurgitate, yet vigorously suck fists and hands. Mothers and families frequently misread this continued, exaggerated rooting reflex as hunger and therefore may overfeed the infant, contributing to emesis and continued loose stool.

These infants may have hyperacusis or are easily disturbed by normal household sounds and do not sleep well. They sweat more than other infants and, when crying, continue to have a high-pitched cry. They may have poor tolerance of being held or to abrupt changes in position. This, along with

BOX 11.8 PARENT/CAREGIVER TEACHING

CARING FOR AN INFANT EXPOSED TO OPIOIDS

Some symptoms may persist for 2 to 6 months.

- Infants exposed to narcotics in utero are more irritable, less cuddly, and tremulous and have increased tone: Parent(s) may interpret these behaviors as signs of rejection; the infant may not want to be held or cuddled as other babies do.
- Less responsive to visual stimulation
- Less likely to maintain a quiet-alert state: Let parent know symptoms are time-limited.
- Poor feeding habits: Continues to regurgitate yet shows vigorous sucking of fists or pacifier: Constant sucking and exaggerated rooting reflex may lead to overfeeding the infant.
- Continuation of loose stools: Important to stress good diaper hygiene to prevent infection from excoriated skin.
- Infants easily disturbed by sounds: Parent may decrease stimuli in house.
- Sweat more than other newborns: Dress infant appropriately to avoid overheating.
- High-pitched cry: Not easily consoled, parents need someone to share infant care and give them some rest from an irritable infant to prevent neglect or abuse.
- Hypertonia
- Less eye-to-eye contact, which decreases social interaction

hypertonia, may continue, and the mother may interpret this as a sign of rejection. Clinician support (doctors, nurses, and all in contact with the family), including a thorough description of potential symptoms and their management and the fact that they are time-limited, is vital if maternal-infant attachment is to occur and potential neglect and abuse are to be avoided. **Studies continue to demonstrate that drug-dependent mothers and their newborns demonstrated poor performance on a measure of social engagement.** The drug-dependent mothers demonstrated significantly less positive affect and greater detachment, and the drug-exposed infants presented fewer behaviors promoting social involvement. Drug-exposed infants and their mothers experience a difficult early period during which both are less available, less likely to initiate, and less responsive to social involvement.[61]

Therefore, parents of the drug-exposed infant may need assistance in recognizing important symptoms that signal problems and cues necessary for caregiving. A frank discussion must be had regarding the infant's exposure to secondary crack smoke, crystal methamphetamine smoke, marijuana smoke, and tobacco smoke. These can be detrimental to the health of the newborn; therefore, parents should be warned of the consequences of using these substances around their infant.

Parents also need to be educated about sudden infant death syndrome (SIDS) and complications from any perinatal infections. The complexity and challenging nature of the home atmosphere should never be underestimated in these situations. The importance of an optimal home environment for the global development of these children should be emphasized to all parents.[61]

Although much has been learned over the past several decades from research in the field of perinatal substance exposure and abuse, there remains a need for continued evidence-based studies to better determine the intricacies of NAS, effective treatment, and overall immediate and long-term effects.

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12 PAIN AND PAIN RELIEF

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Neonatal pain is a complex phenomenon and at times elusive. **Extremely fragile premature infants experience multiple painful procedures** (e.g., heel sticks, intravenous sticks, intubation, lumbar punctures, introduction of chest tubes, placement of nasogastric tubes) during their stay in the neonatal intensive care unit (NICU). **The number of exposures to these procedural events varies from 0 to 53 per day, and approximately 30% of these neonates fail to receive analgesia.**[21,272] **Rationalization for inadequate treatment of pain has resulted in unnecessary suffering for these fragile infants and the suffering of the neonatal nurses who care for them.**[170] Research has shown that the "unchecked release of stress hormones by untreated pain may exacerbate injury, prevent wound healing, lead to infection, prolong hospitalization, and even [lead] to death."[348] **These fragile neonates are simply too sick to *not* have their pain treated. Health care professionals are responsible for influencing positive change in clinical practice about neonatal pain.***

Several decades ago, neonates did not receive analgesia and/or anesthesia agents for surgery because of the controversy as to whether they feel pain and whether they are physiologically stable enough to tolerate the effects of these drugs. **The rationale for withholding analgesia and/or anesthesia agents included the following beliefs:**

- Neonates have an immature central nervous system (CNS) with nonmyelinated pain fibers and are thus incapable of perceiving pain.
- Neonates have no memory of pain.
- Pain is a highly subjective experience that is difficult to objectively assess in nonverbal neonates.
- Anesthetics and analgesics are dangerous when administered to neonates, and neonates are safer if they are not medicated.

There is increasing evidence from more than 30 years of research that neonates, including preterm infants, have a CNS that is much more mature than previously thought.[11,29] **Pain pathways are myelinated in the fetus during the second and third trimesters and are completely myelinated by 30 to 37 weeks of gestation.** Even thinly myelinated or nonmyelinated fibers carry pain stimuli. Incomplete myelination implies only a slower transmission, which is offset in the neonate by the shorter distance the impulse must travel.[29]

Even though pain is not expressed verbally in semiconscious patients, nonverbal adults (e.g., intubated, mute), or infants, this does not negate their experience of pain. In response to the question of whether the neonate's responses are reflexive or express a perception of pain, research has focused on measuring the infant's pain experience. **The infant's capacity for memory is far greater than was previously thought,**[11,20,21] **and a neuropsychologic complex of altered pain threshold and pain-related behavior has been identified.***

Concern has been expressed that giving potent medications to an already critically ill infant might be dangerous. Local and systemic drugs that are now available, as well as new techniques and devices for monitoring, enable all neonates to be safely anesthetized and provide safe and effective analgesia while maintaining a stable condition.[29]

Neonates exhibit (1) physiologic, (2) hormonal, (3) metabolic, and (4) behavioral responses to invasive procedures that are

*References 2, 11–16, 111, 112, 222, 345, 417.

*References 10, 139, 179, 303, 304, 327, 346, 390, 391, 397.

BLUE type highlights content that is particularly applicable to clinical settings.

similar to, but more intense than, adult responses.[17,18,22,29,96] Exposure to multiple painful procedures may increase the vulnerability of preterm infants to gross neurologic damage (intraventricular hemorrhage, periventricular leukomalacia).[19,21,61,172] **Pain relief benefits the neonate by decreasing physiologic instability, hormonal and metabolic stress, and the behavioral reactions accompanying painful procedures.**★

The Committee on Fetus and Newborn of the **American Academy of Pediatrics (AAP) has recommended the administration of local or systemic drugs for anesthesia or analgesia to neonates undergoing surgical procedures.**[12] The committee further states that any decision to withhold these drugs should not be based solely on the infant's age or perceived degree of cortical maturity but should be based on the same criteria used in older patients.[12,22] The latest version of the AAP guidelines cites that **prolonged exposure to untreated pain increases morbidity and alters subsequent behavioral and physiologic responses to pain.**[13] **National and international associations have promulgated standard-of-care guidelines or position statements about neonatal pain management.**† **The focus of these documents is on the proactive assessment and management of pain in the neonate.** The National Association of Neonatal Nurses (NANN) guidelines outline the following recommendations.[412]

- Parents must be informed of pain relief as an important part of the neonate's health care plan, must be educated by staff about nonpharmacologic measures they can use,[243,323] and should be encouraged to actively participate in their neonate's assessment and management of pain.[40]
- *Every* institution must mandate clinical practice guidelines that ensure access and safe administration of pain control to the neonate. Institutions also should develop guidelines for assessing and monitoring pain management practices that include parental input[40] with the goal of measuring the adequacy of pain relief and control in the neonate.
- Institutions must support interdisciplinary research and ongoing education that includes a description of neonatal pain, accurate pain assessment, interventions to improve patient care and reduce morbidity, and guidelines to ensure adequate use of nonpharmacologic measures,[243] administration of analgesics and sedatives for the neonate, and quality improvement programs to monitor use of guidelines.[76,309]

A national study of experienced, highly educated neonatal nurses who were members of NANN was recently published.[96] **Only 50% of the surveyed nurses felt knowledgeable about pain; some disagreed about the neonate's capacity to feel pain or that there were long-term consequences of unrelieved pain.** Other findings of the survey include the following: (1) 81% used a pain assessment tool; only 65% thought the tool was appropriate for neonates, and 60% thought it was an accurate measure; (2) 83% felt confident in the use of pharmacologic interventions; and (3) 79% felt confident in the use of nonpharmacologic interventions.[96] Only 44% of the respondents reported that neonatal pain was well managed, and only 43% thought that their pain protocols were evidence-based. Barriers to relief of neonatal pain were identified as (1) professional (both nurses and doctors) resistance to change (44%); (2) lack of knowledge (23%); (3) fear of side effects of pain medications and incorrect evaluation of pain symptoms (15%); (4) time delay from pain assessment to receipt of medications (13%); and (5) lack of trust in the assessment tool (13%).[96] In this study, 147 of the total 237 respondents identified the following strategies to improve pain management: (1) education about pain (45%), (2) reading and using research (15%), and (3) more interdisciplinary communication.[96]

All neonatal health care providers have an ethical and legal obligation to practice the standard of care in assessing and intervening to relieve the neonate's pain, and to re-evaluate the safety and efficacy of the pharmacologic and comfort interventions used to treat pain.★

PHYSIOLOGY AND PATHOPHYSIOLOGY

"Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[210] The neonate's expression of pain

★References 17, 18, 30, 31, 179, 303, 423.

†References 2, 11, 16, 246, 345, 417.

★References 2, 11–16, 23, 144, 195, 222, 231, 279, 317, 345.

does not fit the self-report aspect of this definition, which often results in the health care provider's failure to recognize and treat pain. Self-report is absent in the preverbal neonate, therefore, nonverbal behavioral information needs to be assessed and used to determine the treatment options for neonates. **The definition of pain has been amended. "The inability to communicate in no way negates the possibility that an individual is experiencing pain, and is in need of appropriate pain-relieving treatment."**[210] Although we cannot assess the emotional experience associated with pain in these babies, the necessary sensory pathways are now better understood. **Neonates have a developing, incompletely myelinated nervous system at birth; however, all the components of the nociceptive (pain)** pathways are present.[137,182] As background for an understanding of neonatal responses and their differences from adult responses, the basic mechanisms of adult pain transmission are presented in Fig. 12.1.

Types of pain experienced by the neonate have been identified as (1) *physiologic,* caused by tissue injury; (2) *inflammatory,* caused by inflammation of tissues; (3) *neuropathic,* caused by nerve injury/damage; and (4) *visceral,* caused by distention, inflammation, and contraction of viscera.[24,25] The common types of pain experienced by the newborn along with proposed definitions are shown in Table 12.1. **Pain in the neonate needs to be viewed as an *adverse event* and *traumatic event*.**[110,263]

NEUROANATOMY

Peripheral Nervous System

Peripheral nerves can be classified into three broad categories based on fiber diameter and velocity (Table 12.2). Pain receptors (nociceptors) are the A-delta fibers (A-δ) and C fibers that are widely spread in the superficial layers of the skin, periosteum, fascia, peritoneum, joints, muscle, pleura, dura, and tooth pulp. Most visceral tissues have fewer nociceptors, and these transmit to the spinal cord through the sympathetic, parasympathetic, and splanchnic nerves. **Tissue damage and inflammation cause the release of arachidonic acid and**

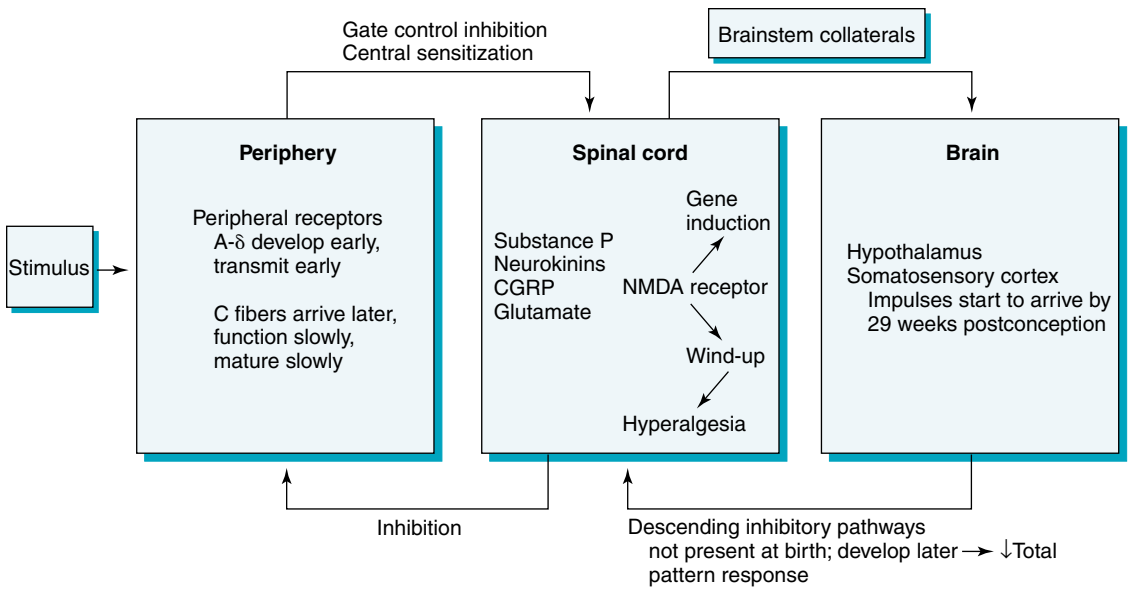


FIGURE 12.1 Schematic representation of transmission of noxious stimuli from the periphery to the brain. *CGRP,* Calcitonin gene–related peptide; *NMDA, N*-methyl-D-aspartate.

TABLE 12.1 SUGGESTED STARTING POINT FOR DEFINING THE PAIN TERMS USED FOR NEONATAL PAIN

PAIN TERM	ONSET	DURATION	CHARACTER *	PRIMARY HYPERALGESIA
Acute episodic	Immediate	0–120† minutes	Sharp, well-located	Present, mild, short-lasting
Acute recurrent	Immediate	Variable	Sharp, well-located	Present, moderate or severe
Prolonged‡	Rapid, may be gradual	1–24 hours†	Sharp, diffusely localized	Present, moderate or severe
Persistent‡	Rapid or gradual, cumulative	1–7 days	Dull/sharp, diffusely localized	Present, moderate or severe
Chronic	Usually gradual	8 days or longer	Dull, diffusely localized	May be present or absent, mild if present

PAIN TERM	SECONDARY HYPERALGESIA	ALLODYNIA	BEHAVIORAL PHENOTYPE	PHYSIOLOGICAL PHENOTYPE
Acute episodic	Probably absent	Probably absent	Strongly reactive and reflexive	High peak, sympathetic activation
Acute recurrent	Present, mild or moderate	Probably absent	Weakly reactive or reflexive	Prolonged peak, sympathetic activation
Prolonged‡	Mild or absent	Probably absent	Strongly reactive on stimulation	High plateau, sympathetic activation
Persistent‡	Present, mild or moderate	May be present, mild/moderate	Hyperactive initially, later hyporeactive	Normal or low sympathetic activation
Chronic	Present, mild or moderate	May be present, moderate/severe	Hyporeactive more often, could also be hyperreactive	Normal or suppressed sympathetic drive

*Based on descriptions in adult patients, but may be discerned by careful physical examination.
†Some infants with increased sensitivity to pain may have a slower decay of the acute pain following an invasive procedure, thus justifying some overlap in the duration of acute episodic pain and prolonged pain.
‡Continuous pain may be characterized as either "prolonged" or "persistent."
From: Anand KJS. Defining pain in newborns: need for uniform taxonomy? *Acta Paediatr.* 2017;106(9):1438.

other chemicals that can sensitize nerve endings and cause vasodilation and plasma extravasation. This causes pain, swelling, and hyperalgesia.[121]

Aδ fibers are myelinated and therefore capable of fast impulse conduction. These nerves are responsible for "fast" or "first" pain. They are also known as *high-threshold mechanoreceptors (HTMs)* because they respond to strong pressure or tissue injury. The C fibers (polymodal nociceptors) are unmyelinated, conduct impulses more slowly, and are the main nociceptors for transmitting chemical, thermal, and mechanical noxious stimuli to the spinal cord.[281] The Aδ fibers develop ahead of the C fibers in the skin and the spinal cord. Aδ fibers are involved in the cutaneous flexion reflex. This reflex is exaggerated in the preterm infant. Thresholds to mechanical skin stimulation (which may or may not be perceived as pain in a newborn) are lower, and responses last longer. **Complete myelination occurs during the second and third trimesters. Lack of myelination had been thought to indicate the inability of a neonate to perceive pain; however, incomplete myelination leads only to slower conduction, which is offset by the shorter distances traversed in the infant.**[29,182]

Reflex responses to somatic stimuli begin at 7.5 weeks postconceptual age (PCA) in the perioral skin and continue to develop in the palms of the hands before finally reaching the hind limbs by 13 to 14 weeks. **Peripheral pain receptors are in place throughout the body by 20 weeks of gestation.**[373] It is likely that both Aδ fibers (touching) and Aδ fibers (pinching) transmit painful stimuli in the human fetus. In rat pups, the C fibers reach the

TABLE 12.2 CLASSIFICATION AND CHARACTERISTICS OF PERIPHERAL NERVES

NAME/CHARACTERISTICS	FUNCTION
A-alpha (A-α) d: 10–20 μ v: 70–120 m/sec myelinated	Innervate skeletal muscle
A-beta (A-β) d: 12–20 μ v: 30–70 m/sec myelinated	Light touch or pressure may be involved in peripheral sensitization and allodynia; in the premature and newborn infant, may be involved in the transmission of noxious stimuli
A-gamma (A-γ) d: 3–6 μ v: 15–30 m/sec myelinated	Muscle tone
A-delta (A-δ) d: 2–5 μ v: 12–30 m/sec myelinated	Fast, well-localized pain; high threshold mechanoreceptors
B d: 3 μ v: 3–15 m/sec myelinated	Preganglionic autonomic fibers may be involved in sensory or sympathetic coupling
C d: 0.4–1.2 μ v: 0.5–2 m/sec unmyelinated	Slow pain, touch, temperature, postganglionic sympathetic fibers, polymodal nociceptors

d, Nerve diameter; *v*, nerve velocity.

spinal cord but do not start to stimulate dorsal horn cells until the end of the first postnatal week. They subsequently continue to mature for several weeks. This slow maturation in rats may be caused by low levels of neuropeptides such as substance P (SP), neurotransmitters, or immature receptor sites. These changes in rat pups appear to correlate with the third trimester and the early neonatal period in humans.[137]

Spinal Cord

The pain transmission system begins with the peripheral pain receptors (nociceptors). Once a noxious stimulus is detected by the nociceptors, the signal is transmitted via the primary afferents to the dorsal root ganglia and from there to the dorsal horn of the spinal cord.[44,80] **Neurotransmitters and their receptors amplify or attenuate the signal in the dorsal horn before sending the signal to the brain.**

Excitatory neurotransmitters such as SP and other neurokinins are increased after acute inflammation and may be necessary for the transmission of painful stimuli to the brain.[215] Glutamate and aspartate are amino acids that appear to be involved in central hypersensitivity and wind-up.[28] ***Wind-up* is a phenomenon in which repetition of the same noxious stimulus leads to an exaggerated response. This response continues even after the noxious stimulus ceases.** Wind-up also may be responsible for converting a low-level, pain-related activity to a high-level, pain-related activity.[44,121,392] **The preterm infant experiences increased stress and activity in the nociceptive pathways after prolonged periods of exposure to painful stimuli.** A recent study showed that neonates with high levels of physiologic stress have larger amplitude of cortical nociceptive responses not reflected in their behavior.[222] During a heel lance, brain activity in infants with underlying stress is enhanced but not reflected in their behavioral response to the noxious stimuli. **After prolonged exposure, the preterm infant exhibits similar pain responses when exposed to other caregiving activities** (e.g., handling, suctioning the endotracheal tube, positioning).[132]

An additional factor in the development of **hypersensitivity (e.g., decreased pain threshold) and hyperalgesia** is the presence of nociceptive-specific receptors,[182] which respond only to pain. In the presence of peripheral inflammation, the threshold of these receptors is decreased so that they are capable of responding to other nonnoxious stimuli.[121] **For example, an infant whose heel has been repeatedly stuck for blood samples may demonstrate pain behavior, even when the heel is merely touched. Many of these responses can be blocked by low doses of opioids. However, once these responses are established, a 10-fold increased dose of opioids may be necessary to reverse them.**[138,418]

The spinal cord also contains inhibitory neurotransmitters (γ-aminobutyric acid [GABA], glycine), which are activated by descending neural pathways (from the brain to the spinal cord) and decrease the intensity of pain transmission. This results in modulation of pain transmission from the spinal cord to the cortex. Descending inhibition is necessary to modulate the pain response and yet allow for specific pain responses (e.g., withdrawal from a needle stick). **Delayed maturation of the**

descending inhibitory fibers results in a *higher pain threshold* in the upper extremities and a lower threshold in the lower extremities, resulting in more pain sensitivity in the lower extremities.[23] Lack of inhibition produces exaggerated, generalized, but definite responses to pain such as body wriggling, facial grimacing, and excessive crying. These pathways, in contrast with the excitatory ones, are not fully developed at birth in "rat pups and probably in preterm infants"[182] therefore, the neonatal spinal cord is more excitable.[137] **The pain transmission system of the premature infant (<36 weeks) is more developed than the pain modulation system; therefore preterm infants are *more* sensitive to pain than are term or older infants.**[182,373]

Neurotransmitters in the developing nervous system may be expressed early but are not necessarily located in areas normally found in an adult. This is particularly true of SP and glutamate, which may contribute to the unorganized responses noted with pain stimuli in the newborn (e.g., the whole body moves when an intravenous [IV] line is started).

Brain

Much less is known about the development of the pathways to the higher brain centers, such as the hypothalamus and cortex. **Once again, there is evidence of immaturity of the inhibitory pathways.**[137] Development in the human cortex continues for many years after birth. **Contrary to previous beliefs that newborns do not feel pain, it appears that, in fact, cutaneous responses are exaggerated and occur at much lower thresholds, and reflex muscle contractions last longer in newborns than in mature individuals.** Using real-time near-infrared spectroscopy (NIRS) in 18 preterm infants (25 to 45 weeks' postmenstrual age [PMA]), an increase in cerebral oxygenation over the contralateral somatosensory cortex was measured in response to heel stick blood draws[367] and in response to venipuncture in another study.[45] From these findings, researchers concluded that **pain is transmitted to the cerebral cortex of preterm infants from 25 weeks' PMA.**[367] Other recent research has found that low biobehavioral responsiveness to pain at 32 weeks' PCA is associated with poorer quality of motor function at 8 months' PCA; therefore pain reactivity in the NICU may be a marker of neuromotor development in later infancy.[180] In summary, **the newborn's nervous system, although still developing, is fully capable of transmitting, perceiving, responding to, and probably remembering noxious stimuli.**

PHYSIOLOGIC RESPONSES

Acute pain in adults is associated with increased sympathetic stimulation, heart rate, respiratory rate, blood pressure, cardiac output, myocardial oxygen consumption, peripheral resistance, anxiety, emotional distress, and hormonal imbalance, and greater morbidity and mortality. **Numerous studies have shown that both premature and full-term infants express the same physiologic responses to pain and noxious stimuli (e.g., intubation) as adults do (Box 12.1).**[12,29,96,420] Despite research on infants' pain response to circumcision and recommendations to use anesthetics or analgesics during circumcision, a survey in a large academic medical center showed that only 30% of infants being circumcised by obstetricians received any pain relief, and there was no documentation of discussion with parents about pain management.[236]

Pain reactivity varies by prior experience with pain.[96,351,386] Studies on pain reactivity in very-low-birth-weight (VLBW) infants at 32 weeks' PCA found that **younger gestational ages (GAs) and increased number of invasive procedures at birth resulted in a "dampening" of normal pain reactions** (e.g., delayed or fewer facial changes; lower pain scale scores)[96,220] and cortisol response.[174] These infants had higher baseline heart rates, which may have indicated that they were in a perpetual state of stress or pain. Previous exposure to morphine was associated with a "normalization" of responses to painful stimuli. More recent studies of the pain response in extremely low-birth-weight (ELBW) preterm infants (<27 weeks' GA) found (1) similar responses to older infants but also "dampened" responses[154,155,420] (i.e. discrete reactions such as eye movements, changes in respiratory pattern, and slight increase in pulse oximetry oxygenation value)[269] and (2) lower cortisol levels representing downregulation of the hypothalamic-pituitary-adrenal axis that is not counteracted by morphine use.[174] **These lower salivary levels are directly related to the number of painful procedures and have recently**

BOX 12.1 CRITICAL FINDINGS
NEONATAL PAIN RESPONSE*

Physiologic

- Increase in
  - Heart rate
  - Blood pressure (also fluctuations)
  - Intracranial pressure/cerebral blood flow,[266] which leads to higher risk for intraventricular hemorrhage
  - Respiratory rate
  - Mean airway pressure
  - Muscle tension
  - Carbon dioxide (↑$TcPco_2$; Pco_2)
  - Pulmonary vascular tone
  - Oxygen consumption
- Decrease in
  - Depth of respiration (shallow)
  - Oxygenation (↓Po_2; Sao_2), which leads to apnea or bradycardia
  - Vagal tone and peripheral blood flow
  - Cerebral oxygenation with vigorous crying
- Pallor or flushing
- Diaphoresis or palmar sweating
- Dilated pupils
- Nausea, vomiting, gagging, and hiccoughing

Behavioral

- Vocalizations
  - Crying (higher pitched, tense, and harsh)
  - Inaudible crying
  - Whimpering
  - Moaning
- Facial expressions
  - Grimacing
  - Furrowing or bulging of the brow
  - Quivering chin
  - Eye squeeze
  - Nasal flaring
  - Curling/curving of the tongue
  - Facial twitching
  - Lips open and pursed
- Body movements
  - General diffuse body activity (flexing/extending extremities; extending legs; finger splay, fisting, hand on face)
  - Limb withdrawal, swiping, thrashing
- Changes in tone
  - Hypertonicity, rigidity, fist clenching
  - Hypotonicity, flaccidity
- Touch aversion
- States
  - Sleep-wake cycle changes, wakefulness
  - Activity level changes: increased fussiness, irritability, listlessness, lethargy
  - Feeding difficulties
  - More difficult to comfort, soothe, quiet
  - Disruption of interactive ability with parents

Hormonal/Catabolic Stress Response

- Increase in
  - Plasma rennin activity
  - Catecholamine levels (epinephrine and norepinephrine)
  - Cortisol levels (serum and hair)
  - Nitrogen excretion/protein catabolism
  - Release of
    - Growth hormone
    - Glucagons
    - Aldosterone
  - Biomarkers of oxidative stress: Advanced oxidation protein products and total hydroperoxides[317]
  - Serum levels of
    - Glucose
    - Lactate
    - Pyruvate
    - Ketones
    - Nonesterified fatty acids
- Decrease in
  - Insulin secretion
  - Prolactin
  - Immune responses

* References 17, 18, 30, 97, 99, 159, 177, 181, 195, 293, 302, 381, 387, 418, 421.

been shown to still be present in 3-month-old (former) very preterm infants when reacting to a socioemotional stressor.[328] Two other studies have compared the biobehavioral pain responses of ELBW infants with term controls. The studies found that (1) at 4 months' corrected age, behavioral and cardiac autonomic responses were similar, with less parasympathetic withdrawal and more sustained sympathetic response during recovery in the ELBW group,[300] and (2) at 8 months' corrected age, behavioral response was similar to that in term infants but less sustained (i.e., faster dampening); baseline heart

rate was significantly higher in ELBW neonates.[178] **The number of previous painful experiences in the NICU was significantly related to subsequent pain reactivity in the ELBW infants,** and the ELBW infants who were exposed to higher doses of morphine had heart rate recovery more similar to that of the term infants.[178] **Higher numbers of invasive procedures are significantly associated with brain structure alterations, specifically reduced white matter and subcortical gray matter maturation in preterm infants.**[61]

ETIOLOGY

Invasive Procedures

Pain is produced with any invasive procedure (**Box 12.2**).[22,363] Two studies of the first 14 days in the NICU found (1) an average of 196 procedures per neonate with 14 invasive procedures per day per infant[363] and (2) a median of 115 procedures per neonate with 16 invasive procedures per day per infant.[74] In a more recent study, one-third of the

BOX 12.2 SELECTED COMMON CAUSES OF PAIN IN NEONATES

INVASIVE PROCEDURES	SURGICAL PROCEDURES	OTHERS
Intravenous cannulation	Central line placement	Clavicle, rib fracture
Venipuncture	PDA ligation	Extremity fracture
Heel stick	TEF repair	Chest pain
Intramuscular injection	Gastroschisis repair	Central pain syndrome (i.e., pain derived from CNS damage)
Arterial line, blood gas	Omphalocele repair	Echocardiogram[3]
Umbilical catheterization	CDH repair	Spasticity
Chest tube insertion or removal	Inguinal hernia repair	Abdominal pain resulting from short gut syndrome, multiple abdominal surgeries; visceral hyperalgesia[38]
Bone marrow aspiration	Cardiac surgery	Necrotizing enterocolitis
Lumbar puncture	Circumcision	Bowel obstruction
Paracentesis	Broviac catheter insertion or removal	Prolonged and/or improper positioning
Endotracheal intubation/removal	ECMO catheter insertion or removal	Position changes
Endotracheal or nasal288 suction		NG tube placement
Laryngoscopy for less invasive surfactant administration[56]		Flushing lines
Mechanical ventilation		Dressing changes
NCPAP		Eye examination for ROP
Bladder catheterization		IV administration of medications
Suprapubic aspiration		Addition/withdrawal of fluid from umbilical catheter
Ventricular tap		Transient mechanical birth trauma (e.g., cephalic hematoma, molding, bruising, forceps marks, petechiae)
Endoscopy		Cryo/laser surgery for ROP
Bronchoscopy		Chest physiotherapy
PICC line insertion/removal		Changing tape/suture removal
Cutdown (arterial/venous) for access		Therapeutic hypothermia[195]

CDH, Congenital diaphragmatic hernia; *CNS,* central nervous system; *ECMO,* extracorporeal membrane oxygenation; *IV,* intravenous; *NCPAP,* nasal continuous positive airway pressure; *NG,* nasogastric; *PDA,* patent ductus arteriosus; *PICC,* peripherally inserted central catheter; *ROP,* retinopathy of prematurity; *TEF,* tracheoesophageal fistula.

Data from Anand KJ and the International Evidence-Based Group for Neonatal Pain. Consensus statement for the prevention and management of pain in the newborn. *Arch Pediatr Adolesc Med.* 2001;155:173; Barker D, Rutter N. Exposure to invasive procedures in neonatal intensive care unit admissions. *Arch Dis Child Fetal Neonatal Ed.* 1995;72:F47; Bauchner H, May A, Coates E. Use of analgesic agents for invasive medical procedures in pediatric and neonatal intensive care units. *J Pediatr.* 1992;4:647; Belda S, Pallas C, Dela Cruz J, et al. Screening for retinopathy of prematurity: is it painful? *Biol Neonate.* 2004;86:195; Evans JC, Vogelpohl DG, Bourguignon CM, et al. Pain behaviors in LBW infants accompany some "nonpainful" caregiving procedures. *Neonatal Netw.* 1997;16:33.

infants received treatment for painful procedures, which included the following[74]:

1. Pharmacologic-only therapy (2.1%)
2. Nonpharmacologic-only therapy (18.2%)
3. Combination therapy (both No. 1 and No. 2) (20.8%)
4. No specific analgesia (79.2%)
5. Concurrent analgesia/anesthesia for other purposes (34.2%)

A recent systematic analysis of 18 observational studies found an average of 7.5 to 17.3 painful procedures per NICU infant per day, with the most frequent procedures being heel lance, suctioning, venipuncture, and peripheral intravenous (PIV) line insertion.[108] Another study showed that neonates in their first 7 days in the NICU underwent a mean of 6.6 invasive procedures per day, with only 32.5 % of them receiving pharmacologic or nonpharmacologic interventions for pain.[372] The Epidemiology of Procedural Pain in Neonates (EPIPPAIN) study looked at pain and pain management (for heel stick and venipuncture) in 16 NICUs in Paris, France[106,107] from birth to the first 2 weeks of life. The mean number of heel sticks per neonate was 16,[107] and the mean number of venipunctures per neonate was 3.8 for infants with a mean gestational age of 33.3 weeks and 4.1 for neonates less than 33 weeks.[107] Although 75.2% of heel sticks were performed with either continuous analgesia or specific pre-procedural analgesia, the use of analgesia was not systematic.[106] In this study, 76% of venipunctures were performed with pre-procedural analgesia, and 23.2% were done while the infant was receiving continuous analgesia.[106] These researchers recommend strategies to decrease the number of PIV attempts (38.3% required more than one attempt) and promotion of parental presence—both associated with lower pain scores.[106]

A study of neonates at increased risk for neurologic impairment found that these infants had the highest number of invasive procedures but received the least amount of analgesic on the first day of life.[378] Despite how these studies indicate an improvement in the use of pain relief for invasive procedures, **considerable work is needed to educate practitioners about the safety, efficacy, and benefits of appropriate pain management in neonates. Use of "better practices" strategies, clinical practice guidelines, and proven quality improvement methods has resulted in better pain management for neonates in the NICU.**[116,241,244,251]

Endotracheal intubation is associated with hypoxia, bradycardia, catabolism, increased intracranial pressure, increased systemic and pulmonary hypertension, and release of stress hormones.[236] **Recent research has shown that use of premedication for elective, nonurgent intubations is safer and more effective than awake intubations (see the Endotracheal Intubation section in** Chapter 23**). Unmedicated endotracheal intubation in the neonate should be reserved for emergency resuscitation in the delivery room.**[236] There is currently no validated scoring system to assess the level of sedation before elective intubation.[115]

No consensus exists about pain relief in the mechanically ventilated neonate, and clinical practice varies widely.[71,184,226,277,424] A recent survey of the use of sedatives and analgesics among a large group of ventilated preterm infants found that the use of opioids increased from 5% to 32%, and the use of sedatives increased from 5% to 24% from 1997 to 2012.[424] **Benefits of pain management in the ventilated neonate include (1) improved ventilator synchrony; (2) improved pulmonary function; (3) less neuroendocrine (cortisol, beta-endorphins, catecholamine) response; (4) better oxygenation; and (5) potentially ameliorated adverse effects of mechanical ventilation (Fig. 12.2) in the preterm infant.**[184,277] Two approaches to pain management in ventilated neonates are commonly used: (1) preemptive, continuous opioid infusion and (2) as-needed (PRN) intermittent bolus administration of opioids.[34,109,226,278] The NOPAIN pilot study found poor neurologic outcomes in only 4% of the ventilated preterm infants receiving continuous morphine sulfate (MS) for pain compared with 24% in the placebo group and 32% in the midazolam group.[27] In this study, the MS-treated preterm infants were the only group with significantly lower pain scores.[27]

The European Pain Audit in Neonates (EUROPAIN) study evaluated the use of sedatives and analgesics in the NICUs of 18 European countries.[71] **Tracheal ventilation and noninvasive ventilation resulted in administration of sedatives (midazolam) and analgesics (opiates) in 82% and 18% of the neonates, respectively, given by a continuous IV dose, intermittent doses, or both. Use of sedatives and analgesics**

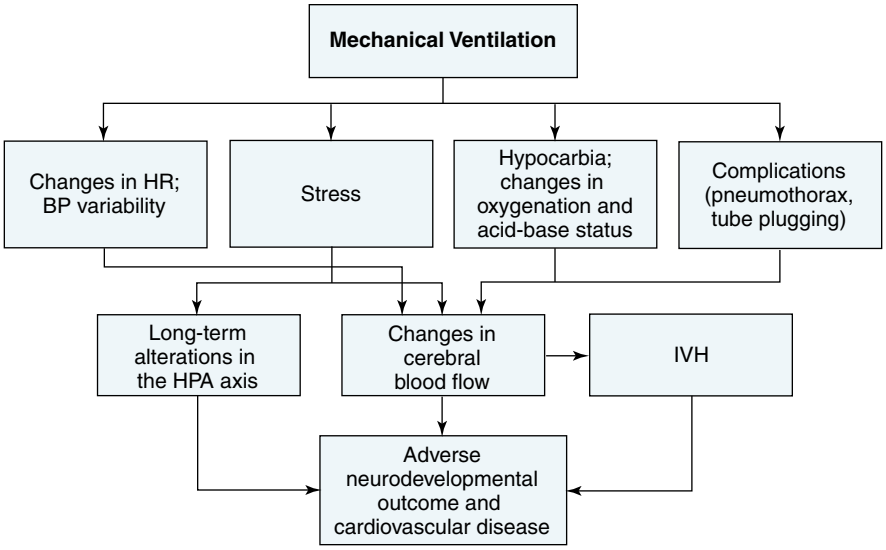


FIGURE 12.2 Potential mechanisms leading to adverse effects from mechanical ventilation in preterm neonates. *BP,* Blood pressure; *HPA,* hypothalamic-pituitary-adrenal; *HR,* heart rate; *IVH,* intraventricular hemorrhage. (Modified from Hall RW, Boyle E, Young T. Do ventilated neonates require pain management? *Semin Perinatol.* 2007;31:289.)

in the intubated neonates resulted in longer mechanical ventilation.[71] Using the same database, assessment for continuous pain only occurred in less than one-third of NICU admissions and daily in only 10% of neonates. The presence of pain guidelines, preterm infants less than 32 weeks of gestation, nursing champions, surgical admissions, mechanical ventilation, and use of opiates, sedatives, and general anesthesia resulted in more frequent assessments for continuous pain.[33] An analysis of the Italian data from the EUROPAIN study also found wide variation in the use of analgesia and sedatives and pain assessment among Italian NICUs.[242]

The NEOPAIN double-blind, randomized controlled trial (RCT), conducted in 12 American and 4 European NICUs, studied whether preemptive morphine analgesia would decrease early neurologic injury in 898 ventilated preterm infants less than 32 weeks of gestation.[28] There was a higher incidence of severe intraventricular hemorrhage (IVH) in the morphine-treated group of 27 to 29 weeks of gestation, possibly resulting from higher MS infusion rates or less MS clearance in hypotensive infants.[28] Further analysis of cohorts from the NEOPAIN study found the following: (1) MS-treated preterm infants had significantly longer ventilation, as well as more air leaks and supplemental oxygen use in preterm infants who received additional intermittent boluses of MS[53]; (2) MS delays the start of and the full attainment of enteral feedings but does not increase gastrointestinal complications[280]; (3) both preemptive and additional MS and lower GA are associated with hypotension[185]; (4) IVH (i.e., any and severe) and death are associated with preexisting hypotension, but morphine therapy did not contribute to these outcomes[185]; and (5) although MS infusions cause hypotension, they can safely be used for most preterm neonates.[185] **Use MS cautiously for 23- to 26-week preterm infants and those with preexisting hypotension.**[185] Another randomized, double-blind, placebo-controlled trial of morphine infusion for ventilated preterm infants showed that (1) the analgesic effect was similar between the treated and placebo group, (2) routine morphine infusion decreased the incidence of IVH but did not influence poor neurologic outcome, (3) routine use of MS infusions is not supported by the lack of analgesic effect and the absence of any beneficial effect, and (4) the long-term effects of MS on the neurologic outcomes of preterm infants need study.[364]

Studies have also compared fentanyl with morphine and fentanyl with sufentanil for analgesia during mechanical ventilation in neonates.[345,350] Fentanyl was equianalgesic with morphine, sufentanil

was equianalgesic to fentanyl, and sufentanil did not reduce the weaning period for ventilated (term) infants.[345,350] Continuous fentanyl infusion (plus open-label PRN boluses of fentanyl) for very preterm ventilated infants has been shown to reduce acute, but not prolonged, pain with more side effects (longer ventilation and delayed meconium passage) than use of PRN fentanyl boluses alone.[34] A recent follow-up of very preterm ventilated infants who received continuous fentanyl and open-label boluses found significantly poorer eye-hand coordination at 24 months' corrected age in the IV infusion group.[35] **Morphine, fentanyl, and sufentanil reduce the pain and stress of preterm infants being mechanically ventilated but may prolong the duration of ventilation.**[34] Only two studies have investigated the effect of fentanyl analgesia on acute brain outcomes, and no difference was found in the incidence of IVH, PVL, or mortality.[240,345]

Dexmedetomidine hydrochloride, an α-adrenergic receptor agonist, provides analgesia, anesthesia, and sedation for mechanically ventilated neonates.[277,302] Advantages include (1) less adjunctive sedation needed, compared with fentanyl; (2) minimal effect on blood pressure, heart and respiratory rates, oxygen saturation, and gastric motility; and (3) its safety and effectiveness for short-term pain relief during invasive procedures in ventilated and nonventilated neonates.[277,302] Only one study of the effect of dexmedetomidine on brain injury has been conducted. In a comparison of dexmedetomidine versus fentanyl used for sedation in mechanically ventilated preterm infants, there was no difference in the incidence of severe IVH or PVL between the two groups.[397] An RCT of the safety and efficacy of dexmedetomidine hydrochloride and the short- and long-term neurologic outcomes are needed.[88]

Although use of analgesia in ventilated infants is recommended,[13,21] **a meta-analysis concludes that there is insufficient evidence for "routine use" of opioids during mechanical ventilation.**[51] **The meta-analysis states that opioids should be selectively used for individual neonates based on clinical judgment and pain assessment.**[51] Long-term neurologic outcomes of MS analgesia for ventilated preterm infants are being studied. A recent pilot study of 5- to 7-year-olds from the NEOPAIN cohort of ventilated preterm infants who had received preemptive MS found that they were 7% smaller in head circumference; were 4% less in body weight; took longer and completed fewer (27%) short-term memory tasks; and had more social problems, specifically with creating and maintaining friendships.[136] This same cohort was again studied at 8 to 9 years of age and found to have significantly better executive function as evaluated by parents and teachers.[114] The method of pharmacologic pain relief, the appropriate drug to use, the use of preemptive or bolus infusion based on pain scores, and minimizing long-term adverse outcomes remain clinical and research challenges.

Surgery

Painful stimuli, surgery, and traumatic injuries have been shown in adults to trigger the "stress response," which causes the release of a variety of hormones, including epinephrine, norepinephrine, corticosteroids, glucagon, and growth hormones. These hormones prepare the body for a *fight-or-flight response* and cause, among other things, an increase in heart rate, respiratory rate, glucose production, and muscle and fat breakdown. This response allows the body to deal with an insult in the short term. **If the insult continues or is untreated, the ongoing catabolic stress response may become deleterious to the body's well-being by promoting more tissue breakdown and preventing growth and tissue repair. During the period of rapid brain growth and development, the immature brain of the preterm infant has heightened vulnerability to pain.** The first study to link cumulative neonatal pain stress to alteration in brain function in extremely low-gestation (≤28 weeks) preterm infants has recently been published. This study found **an association between cumulative neonatal pain-related stress and alteration in cortical function resulting in visual-perceptual difficulties at school age in this vulnerable population.**[124]

Both premature and full-term infants have a decreased stress response with the use of appropriate analgesia both during and immediately after surgery. Physiologic indicators (e.g., heart/respiratory rate, blood pressure) of postoperative pain may be unreliable or confounded by illness severity and use of analgesics and neuromuscular blocking agents★. **Use of adequate operative anesthesia**[12,13] **and postoperative analgesia is mandatory, even if its use might prolong postoperative ventilatory support.**

★References 16, 18, 23, 28, 30, 31, 67, 142.

A special example of untreated operative pain is newborn circumcision. In addition to the previously mentioned short-term effects of not treating the pain associated with circumcision, **male infants who have undergone circumcision without analgesia have an increased pain response to vaccination** at 4 to 6 months of age.[385,387] When these infants were pretreated for their immunizations with a topical anesthetic, their pain response was lessened.[387] Another study of 14- and 45-month-old children who had major surgery with appropriate analgesia (in their first 3 months of life) found that their biobehavioral pain response to immunizations was not altered compared with a matched group of toddlers who had not had surgery.[318] However, **prolonged exposure to early hospitalization did contribute to an altered pain response (in areas of prior tissue damage)** that "recovered" over time.[318,319] **Although early painful memories may not be consciously recalled, experiences of pain are "remembered" by the developing nervous system.**[19,20,32,319] Newborns have a much greater capacity for memory than was previously thought.

Other Causes

Rib, clavicular, and extremity fractures are not uncommon and should be considered in the presence of prolonged crying and failure to move the affected extremity.

Bronchopulmonary dysplasia (BPD) is a common problem in infants who were premature and may cause chest pain, a syndrome known to occur in some older patients with chronic lung disease. Neurologic dysfunction can leave patients with ongoing pain from central pain syndrome or excessive spasticity. One study showed that 27% of former ELBW infants who were now teenagers had neurosensory impairment, and 9% reported moderate or severe pain.[346]

PREVENTION

Prevention of pain in the neonate and preterm infant begins with a proactive plan of care aimed at preventing the pain cycle. The key approaches in this plan include (1) anticipation; (2) comprehensive and ongoing assessment of the variables; (3) distinguishing agitation and irritability from pain expressions and responses of the preterm infant; (4) ongoing communication among health care providers, using input from the parents; (5) advocating and implementing timely and effective treatment for irritability, agitation, and pain (e.g., pharmacologic and comfort measures); (6) reducing the number of painful procedures[74,123,291,410]; and (7) ongoing reevaluation of this proactive plan of care.[2] **Different types of common procedures in the NICU can be anticipated to be painful.** *Diagnostic procedures* include arterial puncture, heel stick, lumbar puncture, and retinopathy of prematurity (ROP) examination. *Therapeutic procedures* include tracheal intubation and extubation, tracheal suctioning,[118] surfactant administration with laryngoscopy,[56] chest tube insertion, mechanical ventilation, suture removal, therapeutic hypothermia,[195] and removal of adhesive tape. Some of the *common surgical procedures* are circumcision, patent ductus arteriosus (PDA) ligation, insertion of central venous catheters, and laser therapy for ROP. **Anticipation and prevention of pain during such procedures can markedly affect the success of the procedure and the condition of the infant. Preventing, reducing, and relieving neonatal pain constitute an essential health care provider goal to maintain the sick neonate's behavioral, physiologic, and biochemical homeostasis.**[22,349]

Individualized behavioral and developmental care is another important area in preventing stress and sensory overload, which often contribute to an ongoing pain cycle.[105,287,349,365] These approaches help prevent disorganization in the neonate. Several studies have shown that clustering care, a common practice in the NICU (see Chapter 13), actually results in an increase in behavioral responses and cortisol secretion for preterm infants of younger GA when exposed to a painful procedure.[197,198,201] **To facilitate stability and self-regulation before and during an invasive painful procedure, (1) do not cluster care, and provide a period of rest before the procedure; (2) assess the infant's state, and facilitate a change to an alert state; (3) contain extremities (see Chapter 13); (4) provide a pacifier and an opportunity to grasp (a finger, hand, or blanket); and (5) use another person (e.g., parent, caregiver) to support, contain, and observe for stress. After the procedure, provide support, comfort, and slow withdrawal so that the infant remains calm.**

The suffering of neonates can be avoided. Needless suffering is prevented by an established plan of care for assessment, management, and evaluation of pain and attempts to relieve pain. **Neonates depend on the skilled observations, assessments, and interventions of care providers for *prompt, safe,* and *effective* relief. A cooperative effort among health care providers and parents in the form of pain management teams[273] and well-established pain protocols[116,349] prevents unnecessary suffering of both neonates and their families.[230]** Controlling environmental stimuli (e.g., dimming lights, controlling noise level, speaking softly, performing rounds outside of the unit), although often difficult in the NICU, is crucial for decreasing stress and preventing unnecessary agitation. **Use of an individualized, developmentally appropriate plan of care reduces the need for sedation in severely ill, VLBW neonates.[17,365] Quieting techniques are also a useful way to help control pain response in the neonate; these include nonnutritive sucking (NNS), containment interventions, and rocking** (see Chapter 13).

DATA COLLECTION

History

Neonates experiencing procedural, surgical, and/or chronic pain must be provided measures to alleviate pain. Neonatal irritability and agitation (Box 12.3) secondary to chronic conditions (e.g., BPD, necrotizing enterocolitis, short bowel syndrome, neurologic deficits) **and/or environmental overstimulation may also require a combination of environmental interventions and sedation.[13]**

Assessment of pain in neonates is often challenging because they cannot verbalize their subjective

BOX 12.3 CRITICAL FINDINGS
INDICATORS OF IRRITABILITY AND AGITATION

Physiologic

- Increase in
  - Heart rate and blood pressure only with activity
  - Oxygenation ($\uparrow TcPco_2$; Po_2; Sao_2)
  - Respiratory rate and effort
- Decrease in
  - Oxygenation ($\downarrow Po_2$; Sao_2) after prolonged agitation
  - Heart rate (bradycardia)
  - Respirations (apnea)
- Alterations in skin color: cyanosis, mottling, duskiness, pallor
- Diaphoresis
- Vomiting
- Poor pattern of weight gain

Behavioral

- Vocalizations
  - Whining cry
  - Intense, urgent cry
  - High-pitched cry
  - Resumes fussiness when consolation ceases
- Facial expressions
  - Frowning
  - Worried facies
  - Gaze aversion
  - Closes eyes to tune out
- Body movements
  - Random movements of head and body
  - Hypertonic, rigid posturing; arching; hyperextended neck
  - Flailing, thrashing, frantic activity of extremities during fuss or cry
  - Decreased activity
  - Tremulousness
- States
  - Hyperalert—easily aroused from sleep; startles easily
  - Rapid and frequent state changes to fuss or cry
  - Unpredictable sleep-wake cycles
  - Feeding difficulties
  - Difficult to console, soothe
  - High level of persistence
  - Needs environmental structure to fall asleep; takes a long time to fall asleep
  - Ineffective self-consoling; requires vestibular stimulation or body containment to console; responds inconsistently to consolation
  - Noncuddly

Modified from Broome ME, Tanzillo H. Differentiating between pain and agitation in premature neonates. *J Perinat Neonat Nurs.* 1990;4:53; Burdeau G, Kleiber C. Clinical indicators of infant irritability. *Neonat Netw.* 1991;9:23; Franck LS. A national survey of the assessment and treatment of pain and agitation in the NICU. *J Obstet Gynecol Neonat Nurs.* 1987;16:387.

BOX 12.4 GUIDELINES FOR ASSESSING PAIN

- Assess and document pain, with vital signs every 4 to 6 hours or as indicated by pain scores and/or the clinical condition of the neonate.
- Use standardized pain assessment tools and methods with evidence of validity, reliability, and clinical utility.
- Use pain assessment tools that are sensitive and specific for infants of different gestational ages and/or with acute, chronic, or continuous pain (e.g., postoperative pain, inflammatory conditions).
- Use pain assessment tools that are comprehensive and multidimensional (e.g., measure behavioral, physiologic, and hormonal/biochemical indicators of pain) within the context of pain experience.
- Assess the neonate's pain after each potentially painful clinical intervention.
- Reassess and re-evaluate the neonate's pain to assess the efficacy of pharmacologic, behavioral, and environmental interventions.

Modified from Anand KJ and the International Evidence-Based Group for Neonatal Pain. Consensus statement for the prevention and management of pain in the newborn. *Arch Pediatr Adolesc Med.* 2001;155:173; Prince W, Horns K, Latta T, et al. Treatment of neonatal pain without a gold standard: the case for caregiving interventions and sucrose administration. *Neonatal Netw.* 2004;23:33.

experience.[21] The four objectives in the assessment of pain are (1) detecting the presence of pain, (2) assessing its effect, (3) providing pain-relieving interventions, and (4) evaluating the effectiveness of interventions.[97] **Guidelines for the assessment of pain are listed in** Box 12.4. **Expression of pain through behavior is one of the neonate's only means of communicating about pain.** Behavioral cues may include diffuse or localized motor activity, facial grimacing, crying, agitation, and change in level of activity (see Box 12.3). Female infants, both preterm and term, show more facial expressions of pain compared with male infants.[374] In an analysis of the responses of 149 infants to a painful event, facial actions were found 40% of the time to account for pain indicators in vulnerable neonates.[374]

Assessment of pain in the neonate is complicated by the infant's level of neural development and maturation.★ Infants of younger GA have limited autonomic and self-regulatory abilities. **Developmental immaturity also results in disorganized, ineffective responses to stimuli and makes it more difficult for these immature preterm infants to communicate pain.** Fewer facial changes related to painful stimuli have been observed in young preterm infants.[155] However, **crying, change in arousal state, and facial grimacing have been found to be the most robust pain behaviors.**[420] Another study showed a change in facial expression with heel lance in preterm infants as young as 25 weeks of gestation.[368] However, in this study, preterm infants less than 32 weeks' PMA took a significantly longer time to change their facial expression than did older infants.★

A more immature, fragile neonate may manifest alterations in sleep-wake cycles and habituate to the overwhelming stimuli of the NICU (see Chapter 13) and thus cannot exhibit any response to pain. Illness severity as an influence on pain response has shown contradictory findings in research studies. Some studies show altered pain response in more severely ill neonates, whereas others show no alteration in the most severely ill.[96,376]

Behavioral expressions of pain by the neonate are further hampered by intubation, use of restraints, and neuromuscular blockers.[299] Similarly, **chronically ill infants who have been exposed to repeated painful procedures have difficulty generating a pain response and exhibit a "dampened" pain response.**[98,154,155,174] Recent research shows that several body movements (e.g., fisting, flexing/extending extremities, finger splay, hand on the face) commonly assessed in the Newborn Individualized Care and Assessment Program (NIDCAP) for developmental care (see Chapter 13) are associated with acute pain response in preterm infants[290] (see Box 12.1). Preterm infants who have experienced more invasive procedures, who are lower in GA at birth, and who have spent more days on ventilators have a diminished behavioral and cardiac autonomic pain response to acute pain at 32 weeks' PCA.[172,175] Another study indicates that both term and preterm neonates who undergo handling and immobilization may exhibit exaggerated behavioral and physiologic response to later painful procedures.[184] Other studies have demonstrated no difference in biobehavioral response to pain in preterm infants with neurologic injury.[298,368,420]

Physiologic parameters also may indicate pain (e.g., increased heart and respiratory rates, elevated blood pressure, desaturation, apnea, palmar sweating). These symptoms are the result of sympathetic nervous system activation (see Box 12.1). One study found that some physiologic responses to pain (e.g., facial activity and state) moderately correlated to

★References 180, 199, 221, 272, 293, 336, 425.

★References 180, 199, 221, 293, 336, 372, 425.

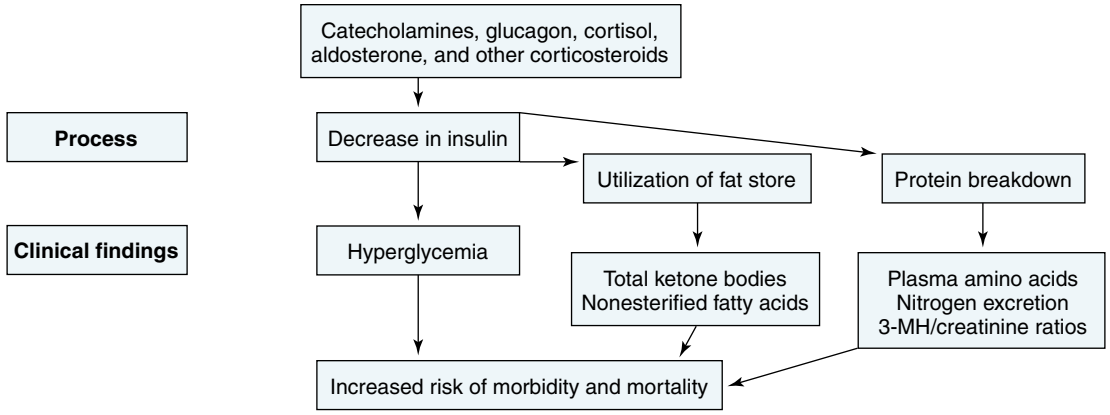


FIGURE 12.3 Hormonal response to pain in infants. *3-MH,* 3-Methylhistidine. (From Johnston C, Stevens B. Pain in infants. In: Watt-Watson J, Donovan M, eds. *Pain Management: Nursing Perspective.* St Louis, MO: Mosby; 1992.)

heart rate changes, whereas other behavioral expressions (e.g., finger splay) did not correlate with any autonomic changes.[289] However, in the same study, specific measures of cardiac autonomic modulation did not correlate with behavioral changes, suggesting that cardiac alterations are influenced by a multitude of factors[299] and may be independent measures of pain in the preterm infant.[289] A more recent study found higher physiologic reactivity (i.e., heart rate changes) in male preterm infants, but the evidence was insufficient to confirm a gender difference in pain responsivity.[400] **Some preterm infants respond to pain with more behavioral changes, whereas others respond with more physiologic changes.[377] In the first week of life, all infants of different GAs (e.g., <28 to 36 weeks) can differentiate between mild and more invasive procedures.[325]** At 36 weeks, these same infants exhibited differing physiologic pain responses based on their GA at birth. (e.g., infants born closer to term had lower increases in heart rate than those born at a younger GA).[325,420]

When pain is repetitive or persists for hours or days, there is a *decompensatory* response, resulting in hormonal and metabolic alterations (Fig. 12.3; see Box 12.1). The fight-or-flight mechanism of the sympathetic nervous system can no longer compensate, so **an adaptation syndrome begins with a return to baseline physiologic parameters.** The return of the heart rate, respirations, and blood pressure to baseline parameters makes assessment of the infant's pain more difficult and does not mean that the infant has "adjusted" to or is no longer experiencing pain.[66]

The lack of an expression of pain through physiologic and behavioral responses also does not mean that the neonate is not experiencing pain.[210] Pain responses may be delayed, cumulative, or absent. In the preterm infant, sustained elevations in vital signs and decreased oxygenation confirm the persistence of physiologic alterations after painful stimuli.[376] **Critically ill neonates and immature preterm infants may be so weak and overwhelmed that they have completely exhausted their energy and cannot respond.[177]** A recent study showed that only 65% of healthy newborns (>37 weeks and <42 weeks of gestation) cried after heel stick, although 100% of them showed a cortical peak response measured by electroencephalography (EEG) to the heel stick.[267] **The incidence of crying in response to painful or noxious stimuli is less than 50% in the preterm infant.[376]** Depending on GA, a preterm infant's behavioral responses to pain are similar to those of the term infant.[19,177,376] **A prospective cohort study comparing full-term infants (e.g., of diabetic mothers who were exposed to repeated heel sticks in the first 1 to 2 days of life) showed that these infants learned by conditioning to anticipate pain after their heel was swabbed with alcohol and exhibited a more intense pain response to a later venipuncture than infants who had not been exposed to repeated painful procedures.[393]**

Pain responses of the neonate are also influenced by the number and timing of painful procedures, the technique used, and the degree

of professional expertise.[13,98,393] Lack of a response to a painful stimulus occurs more frequently in younger newborns (both GA and PCA) who are asleep and who have recently undergone another painful procedure.[220,299,325] **Pain scores may be lower in preterm infants with higher severity of illness and higher number of previous invasive procedures,**[165] **whereas there is a larger heart rate response to repeated pain.**[322] **Mechanical lancets are preferred over manual devices for capillary blood draws.** A recent comparison of five automatic lancets found that the Tenderfoot device (Accriva Diagnostics, San Diego, CA) evoked the least pain and was most effective in obtaining adequate blood with a single lance.[371] **Venipuncture has been shown to be associated with less pain in the neonate than heel stick,**[303,356] and a new blood glucose device using the forearm has been found to be less painful for term infants than heel sticks.[347]

Assessment of neonatal pain is influenced by the attitudes and beliefs of care providers; amount of time spent observing for and having knowledge of pain responses; discrepancy between attitudes and practice, knowledge, and education of parents and professionals about pain; prioritization of pain recognition and relief in the NICU; interdisciplinary communication and collaboration; and the social community. If professionals (1) deny that newborns experience pain, (2) become desensitized to newborns' pain experience, (3) rationalize reasons for not assessing or treating pain, and (4) do not take responsibility for inflicting pain, there can be no improvement in neonatal pain management.[21,249,276]

A qualitative study of the responses of neonatal nurses to "inflicting pain" on extremely premature neonates found three subthemes: (1) "when caring and torture are the same thing," (2) "why are we doing this!" and (3) "comfort for baby and nurse."[170] In this study, the Australian neonatal nurses are passionate about the need for pain relief for neonates. **When these nurses inflicted pain on extremely premature infants, they experienced a profound sense of distress, manifested as existential suffering. Instead of relieving pain, the necessity of inflicting pain results in neonatal nurses questioning their role as compassionate caregivers: "It's agony for us as well."**[170]

Numerous other social factors influencing pain recognition and relief include the following: (1) appearance, behavior, and responsiveness of a sick neonate who varies markedly from the usual expectations about newborns; (2) lack of knowledge about analgesia and belief that pain is secondary in importance to the focus on survival; and (3) lack of knowledge about the effect on morbidity, mortality, and long-term consequences.*

Researchers have examined the beliefs and management techniques of 374 clinicians (both physicians and nurses) about procedural pain in newborn infants. Although the majority of clinicians believe that infants experience pain in the same or greater degree than adults, of 12 commonly performed bedside procedures (e.g., intubation, chest tube insertion, arterial or venous catheter insertion, heel sticks) were rated as "moderately to very painful." Neither pharmacologic nor comfort measures were frequently used.[325] More recent surveys and studies of professional attitudes have found the following: (1) assessment for neonatal pain is based on instinct rather than tested pain tools[4,67,91,104]; (2) there is inadequate staff knowledge and lack of evidence-based guidelines[4,67,91]; (3) level of empathy, secondary trauma, and burnout of the professional caregiver influences caregiving[248]; (4) there is difficulty translating knowledge to clinical practice[4,104,249]; and (5) nurse-physician collaboration is a strong predictor of evidence-based procedural pain control.[22,249,276] A recent qualitative study revealed NICU staff attitudes concerning neonatal pain. **Pain causes unnecessary suffering, and staff members realized how multiple and repeated procedures result in long-term consequences from previous pain experiences.** Second, health care providers realized how approaches to pain relief are based on feeling rather than facts. Furthermore, while comforting the neonate and when suffering is detected, health care providers have doubts and concerns about the use and side effects of drugs for pain relief. Lastly, **staff members felt that the parent's presence and caretaking in the NICU had the potential to decrease the neonate's response to painful stimuli.**[147] **Despite over 40 years of research focusing on pain and pain control in neonates, "clinical use of pain-control measures in neonates undergoing invasive procedures remains sporadic and suboptimal."**[31]

IRRITABILITY AND AGITATION

Differentiation between pain and irritability or agitation is a challenge (Fig. 12.4). **Agitation is a**

*References 23, 147, 187, 225, 251, 279, 307, 379.

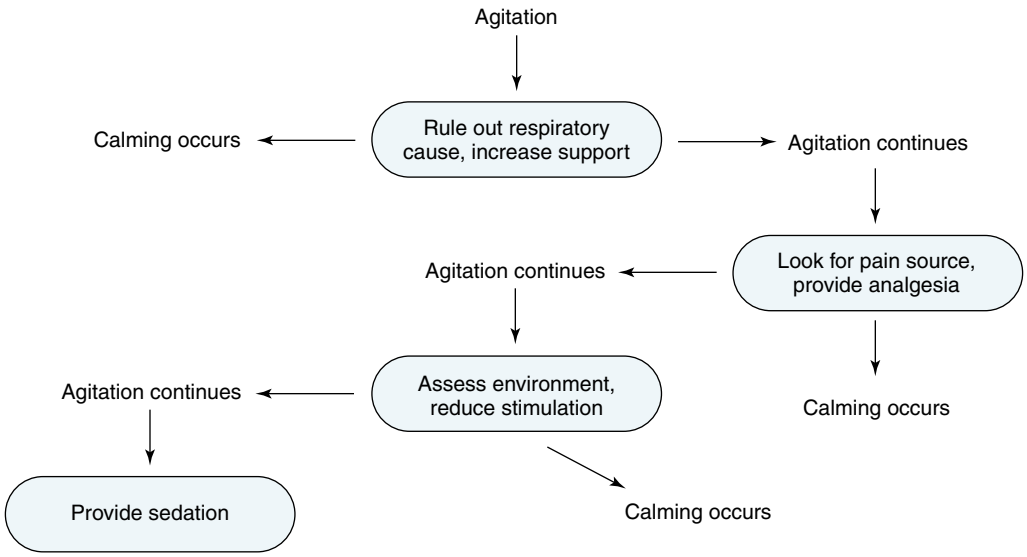


FIGURE 12.4 Decision tree for assessing and managing pain and/or agitation. (From Gordin P. Assessing and managing agitation in the critically ill infant. *Matern Child Nurs.* 1990;15:26.)

behavioral symptom of many problems, including environmental overstimulation, respiratory insufficiency, neurologic irritability, and pain. Factors influencing chronic irritability and agitation in neonates in the NICU are shown in Fig. 12.5. **Causes of agitation other than pain should be eliminated before pain management and/or sedation is initiated.** Assessment of environmental stimuli should be a routine part of the neonate's care. The neonate may associate certain stimuli with unpleasant events over time, and repeated exposure (e.g., ventilator alarms, placement of heel warmer, the odor of an alcohol wipe) may trigger agitation. Although these stimuli are inevitable, identifying, avoiding, or limiting them will help prevent anticipatory decompensation in these fragile infants.[411]

Strategies to prevent and intervene with irritable or agitated infants include the following:

- Minimize caregivers, and provide consistency in care by staff and family.
- Determine whether there is a "locus of pain" (e.g., pain-related irritability).
- Determine whether physiologic instability (e.g., needs suction/position change; hypoxemia) is the cause or the result of irritable behaviors.
- Use developmental care (see Chapter 13).
- Use sedatives judiciously.[411]
- Use individualized, developmental care to significantly reduce the need for sedatives in VLBW infants.[411]

Pain-related irritability must be treated by alleviating pain with the use of opioids and comfort measures. Use of sedatives *alone* for pain-related irritability suppresses behavioral expression of pain, has no analgesic effects, and may *increase* pain. Sedatives should be used only when pain has been ruled out as the source of the irritability or agitation. Although no research documents the safety or efficacy of combining sedatives and analgesics for the treatment of neonatal pain, sedatives are used with opioids to wean infants who have developed tolerance from prolonged opioid therapy.[411]

Assessment Tools

To quantify and objectify a neonate's pain experience and to facilitate health care professionals' recognition of the presence and severity of pain in neonates, research has resulted in the development of over 40 infant pain assessment tools.[98] Both the AAP[13] and the International Evidence-Based Group for Neonatal Pain strongly recommend use of neonatal pain assessment tools.[12,23] **The Joint Commission requires the selection and use of**

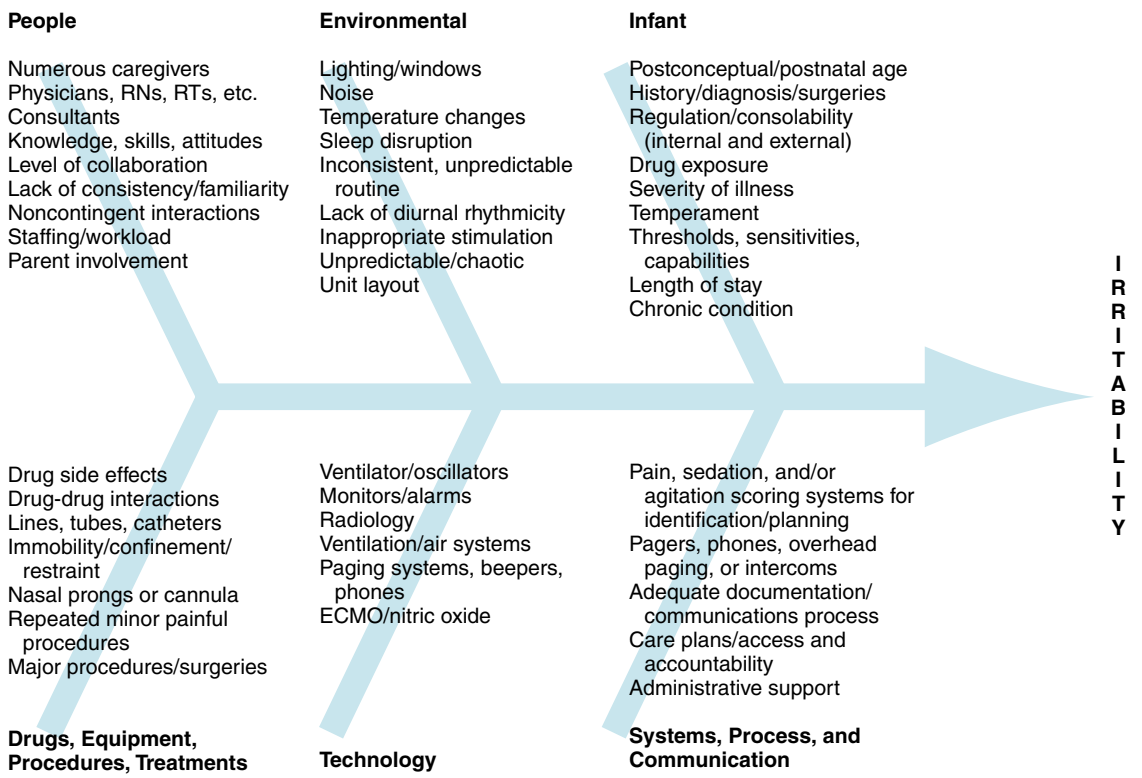


FIGURE 12.5 Fishbone diagram of factors influencing irritability. *ECMO,* Extracorporeal membrane oxygenation; *RNs,* registered nurses; *RT,* respiratory therapist. (From Walden M, Carrier C. Sleeping beauties: the impact of sedation on neonatal development, *J Obstet Gynecol Neonatal Nurs.* 2003;32:393.)

a valid, reliable pain assessment tool; however, there is no "gold standard" neonatal pain assessment tool.[23,98,221]

Of the myriad neonatal pain assessment tools, the Premature Infant Pain Profile (PIPP); and Neonatal Pain, Agitation, and Sedation Scale (N-PASS), Neonatal Facial Coding System, the Behavioral Infant Pain Profile, and the Echelle Douleur Inconfort Nouveau-Ne (EDIN) scale have been extensively tested and their validity and reliability established.[13]

The PIPP (Table 12.3) **is a multidimensional (physiologic and behavioral) assessment tool intended for use within clinical practice.**[377] The PIPP is a seven-item, four-point scale; its maximum score depends on the infant's GA and behavioral state of the premature infant at baseline. The PIPP has been validated with both full-term and preterm neonates and can distinguish between procedural and postoperative pain and nonpain (e.g., noxious) events. The revised PIPP (PIPP-R) has recently been validated in full-term neonates and preterm infants greater than 26 weeks' GA, it is easy to use, and higher pain scores require effective interventions.[156] Lower pain scores in the PIPP-R indicate that pain intervention strategy is efficacious.[156] The PIPP has not been validated for assessment of the efficacy of analgesia nor for its usefulness in the assessment of continuous pain.

The N-PASS (Table 12.4) **is an easily used clinical scale to assess, document, and manage pain and sedation.**[117,119,204,207–205] NICU infants being mechanically ventilated or in the immediate postoperative period were assessed with the N-PASS before and after pharmacologic intervention. **N-PASS measures acute, prolonged, and chronic pain, as well as the level of sedation.**[98,117,119,208] The N-PASS is a reliable and valid assessment tool for

TABLE 12.3 PREMATURE INFANT PAIN PROFILE (PIPP)

Infant Study Number: _____

Date/Time: _____

Event: _____

PROCESS	INDICATOR	0	1	2	3	SCORE
Chart	Gestational age	36 wk and more	32–35 wk, 6 days	28–31 wk, 6 days	Less than 28 wk	
Observe infant 15 seconds	Behavioral state	Active/awake; eyes open; facial movements	Quiet/awake; eyes closed; no facial movement	Active/asleep; eyes closed; facial movement	Quiet/asleep; eyes closed; no facial movements	
Observe baseline heart rate oxygen saturation						
Observe infant 30 seconds	Heart rate (max)	0–4 beats/min increase	5–14 beats/min increase	5–24 beats/min increase	25 beats/min or more increase	
	Oxygen saturation (min)	0%–2.4% decrease	2.5%–4.9% decrease	5.0%–7.4% decrease	7.5% or more decrease	
	Brow bulge	None 0%–9% of time	Minimum 10%–39% of time	Moderate 40%–69% of time	Maximum 70% of time or more	
	Eye squeeze	None 0%–9% of time	Minimum 10%–39% of time	Moderate 40%–69% of time	Maximum 70% of time or more	
	Nasolabial	None 0%–9% of time	Minimum 10%–39% of time	Moderate 40%–69% of time	Maximum 70% of time or more	

Scoring method for the PIPP:

1 Familiarize yourself with each indicator and how it is to be scored by looking at the measure.
2 Score gestational age (from the chart) before you begin.
3 Score behavioral state by observing the infant for 15 seconds immediately before the event.
4 Record baseline heart rate and oxygen saturation.
5 Observe the infant for 30 seconds immediately after the event. You will have to look back and forth from the monitor to the infant's face. Score physiologic and facial action changes seen during that time, and record immediately after the observation period.
6 Calculate the final score.

min, Minimum; *max,* maximum; *wk,* weeks.

From Stevens B, Johnston C, Petroshen P, et al. Premature Infant Pain Profile: development and initial validation. *Clin J Pain.* 1996;12:13.

pain/agitation and sedation in postoperative and/or ventilated neonates (0 to 100 days of age) at 23 or more weeks of gestation.[119,204,207,209]

The Neonatal Facial Coding System (Table 12.5) is an assessment tool based on nine facial expressions of term newborns in four sleep-wake states while experiencing the discomfort of heel rub and the pain of heel lance. Quiet, awake neonates demonstrate the most facial activity, whereas those in quiet sleep demonstrate the

TABLE 12.4 NEONATAL PAIN, AGITATION, AND SEDATION SCALE (N-PASS)

ASSESSMENT CRITERIA	SEDATION		SEDATION/PAIN	PAIN/AGITATION	
	–2	–1	0/0	+1	+2
Crying Irritability	No cry with painful stimuli	Moans or cries minimally with painful stimuli	No sedation/No pain signs	Irritable or crying at intervals Consolable	High-pitched or silent, continuous cry Inconsolable
Behavior state	No arousal to any stimuli No spontaneous movement	Arouses minimally to stimuli Little spontaneous movement	No sedation/No pain signs	Restless, squirming Awakens frequently	Arching, kicking Constantly awake *or* Arouses minimally/ no movement (not sedated)
Facial expression	Mouth is lax No expression	Minimal expression with stimuli	No sedation/No pain signs	Any pain expression intermittent	Any pain expression continual
Extremities Tone	No grasp reflex Flaccid tone	Weak grasp reflex ↓ muscle tone	No sedation/No pain signs	Intermittent clenching toes, fists, or finger splay Body is not tense	Continual clenched toes, fists, or finger splay Body is tense
Vital signs: HR, RR, BP, Sao_2	No variability with stimuli Hypoventilation or apnea	<10% variability from baseline with stimuli	No sedation/No pain signs	↑↓ 10%–20% from baseline Sao_2 76%–85% with stimulation, quick recovery	↑↓ >20% from baseline Sao_2 ≤75% with stimulation, slow recovery Out of sync with vent

ASSESSMENT OF SEDATION

- Sedation is scored in addition to pain for each behavioral and physiologic criterion to assess the infant's response to stimuli.
- Sedation does not need to be assessed/scored with every pain assessment/score.
- Sedation is scored 0 → –2 for each behavioral and physiologic criterion, then summed and noted as a negative score (0 → –10).
  - A score of 0 is given if the infant has no signs of sedation, does not underreact.
- Desired levels of sedation vary according to the situation:
  - "Deep sedation" → goal score of –10 to –5
  - "Light sedation" → goal score of –5 to –2
  - Deep sedation is not recommended unless an infant is receiving ventilatory support, related to the high potential for hypoventilation and apnea.
- A negative score without the administration of opioids/sedatives may indicate the following:
  - The premature infant's response to prolonged or persistent pain/stress
  - Neurologic depression, sepsis, or other pathology

ASSESSMENT OF PAIN/AGITATION

- Pain assessment is the fifth vital sign. Assessment for pain should be included in every vital sign assessment.
- Pain is scored from 0 → +2 for each behavioral and physiologic criterion and then summed:
  - Points are added to the premature infant's pain score based on his or her gestational age to compensate for his or her limited ability to behaviorally communicate pain.
  - Total pain score is documented as a positive number (0 → +11).
- Treatment/interventions are indicated for scores >3.
  - Interventions for known pain/painful stimuli are indicated before the score reaches 3.
- The goal of pain treatment/intervention is a score ≤3.
- More frequent pain assessment indications:
  - Indwelling tubes or lines that may cause pain, especially with movement (e.g., chest tubes) → at least every 2–4 hours
  - Receiving analgesics and/or sedatives → at least every 2–4 hours
  - 30–60 minutes after an analgesic is given for pain behaviors to assess response to medication
  - Postoperative → at least every 2 hours for 24–48 hours and then every 4 hours until off medications

TABLE 12.4 NEONATAL PAIN, AGITATION, AND SEDATION SCALE (N-PASS)—CONT'D

PARALYSIS/NEUROMUSCULAR BLOCKADE

- It is impossible to behaviorally evaluate a paralyzed infant for pain.
- Increases in heart rate and blood pressure at rest or with stimulation may be the only indicator of a need for more analgesia.
- Analgesics should be administered continuously by drip or around-the-clock dosing.
  - Higher, more frequent doses may be required if the infant is postoperative, has a chest tube, or has other pathology (e.g., NEC) that would normally cause pain.

SCORING CRITERIA

CRYING/IRRITABILITY

−2 → No response to painful stimuli:
- No cry with needle sticks
- No reaction to ETT or nares suctioning
- No response to caregiving

−1 → Moans, sighs, or cries (audible or silent) minimally to painful stimuli (e.g., needle sticks, ETT, or nares suctioning, caregiving)

0 → No sedation signs or No pain/agitation signs

+1 → Infant is irritable/crying at intervals but can be consoled
- If intubated, intermittent silent cry

+2 → Any of the following:
- Cry is high pitched
- Infant cries inconsolably
- If intubated, silent continuous cry

BEHAVIOR/STATE

−2 → Does not arouse or react to any stimuli:
- Eyes continually shut or open
- No spontaneous movement

−1 → Little spontaneous movement; arouses briefly and/or minimally to any stimuli:
- Opens eyes briefly
- Reacts to suctioning
- Withdraws to pain

0 → No sedation signs or No pain/agitation signs

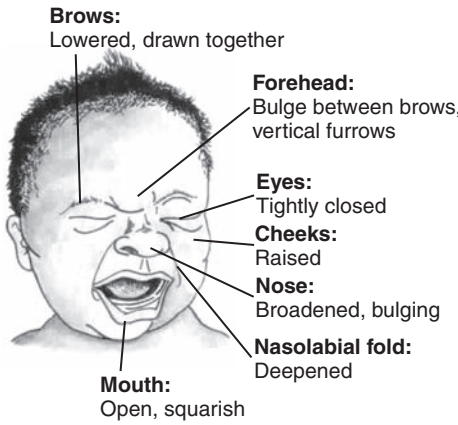
+1 → Any of the following:
- Restless, squirming
- Awakens frequently/easily with minimal or no stimuli

+2 → Any of the following:
- Kicking
- Arching
- Constantly awake
- No movement or minimal arousal with stimulation (not sedated, inappropriate for gestational age or clinical situation)

Continued

TABLE 12.4 NEONATAL PAIN, AGITATION, AND SEDATION SCALE (N-PASS)—CONT'D

FACIAL EXPRESSION



Facial expression of physical distress and pain in the infant

−2 → Any of the following:
- Mouth is lax
- Drooling
- No facial expression at rest or with stimuli

−1 → Minimal facial expression with stimuli
0 → No sedation signs or No pain/agitation signs
+1 → Any pain face expression observed intermittently
+2 → Any pain face expression is continual

EXTREMITIES/TONE

−2 → Any of the following:
- No palmar or plantar grasp can be elicited
- Flaccid tone

−1 → Any of the following:
- Weak palmar or planter grasp can be elicited
- Decreased tone

0 → No sedation signs or No pain/agitation signs
+1 → Intermittent (<30 seconds' duration) observation of toes and/or hands as clenched or fingers splayed
- Body is *not* tense

+2 → Any of the following:
- Frequent (≥30 seconds' duration) observation of toes and/or hands as clenched or fingers splayed
- Body is tense and stiff

TABLE 12.4 NEONATAL PAIN, AGITATION, AND SEDATION SCALE (N-PASS)—CONT'D

VITAL SIGNS: HR, BP, RR, AND O_2 SATURATIONS

−2 → Any of the following:
- No variability in vital signs with stimuli
- Hypoventilation
- Apnea
- Ventilated infant—no spontaneous respiratory effort

−1 → Vital signs show little variability with stimuli—less than 10% from baseline

0 → No sedation signs or No pain/agitation signs

+1 → Any of the following:
- HR, RR, and/or BP are 10%–20% above baseline
- With care/stimuli, infant desaturates minimally to moderately (Sao_2 76%–85%) and recovers quickly (within 2 minutes)

+2 → Any of the following:
- HR, RR, and/or BP are >20% above baseline
- With care/stimuli, infant desaturates severely (Sao_2 <75%) and recovers slowly (>2 minutes)
- Out of sync/fighting ventilator

BP, Blood pressure, *ETT,* endotracheal tube; *HR,* heart rate; *NEC,* necrotizing enterocolitis; *RR,* respiratory rate; *Sao*2, oxygen saturation.

TABLE 12.5 NEONATAL FACIAL CODING SYSTEM

ACTION	DESCRIPTION
Brow bulge	Bulging, creasing, and vertical furrows above and between brows occurring as a result of the lowering and drawing together of the eyebrows
Eye squeeze	Identified by the squeezing or bulging of the eyelids; bulging of the fatty pads about the infant's eyes is pronounced
Nasolabial furrow	Primarily manifested by the pulling upward and deepening of the nasolabial furrow (a line or wrinkle that begins adjacent to the nostril wings and runs downward and outward beyond the lip corners)
Open lips	Any separation of the lips
Stretch mouth (vertical)	Characterized by a tautness of the lip corners coupled with a pronounced downward pull on the jaw; seen when an already wide-open mouth is opened a fraction further by an extra pull at the jaw
Stretch mouth (horizontal)	Appears as a distinct horizontal pull at the corners of the mouth
Lip purse	Lips appear as if an "oo" sound is being pronounced
Taut tongue	Characterized by a raised, cupped tongue with sharp tense edges; the first occurrence of taut tongue usually is easy to see, often occurring with a wide-open mouth; after this first occurrence, the mouth may close slightly; taut tongue is still scorable on the basis of the still visible tongue edges
Chin quiver	An obvious high-frequency up-down motion of the lower jaw

Data from Grunau RVE, Craig KD. Pain expression in neonates: facial action and cry. *Pain.* 1987;28:399; Grunau R, Craig K. Facial activity as a measure of neonatal pain expression. In Tyler DC, Krane EJ, eds. *Advances in Pain, Research and Therapy.* Vol 15. New York, NY: Raven; 1990.

least.[176,180] **Facial activity also increases with GA, so both infant state and GA must be considered when using this scale.** Despite the fact that the Behavioral Infant Pain Profile (discussed next) is a one-dimensional pain assessment tool, both tools have been found to be more sensitive in detecting behavioral pain cues in term newborns than the PIPP tool.[37] This tool is sensitive to changes in pain intensity and useful for evaluating the effectiveness of interventions. There is evidence of reliable clinical use of this tool in term and preterm infants for acute and prolonged pain as well as postoperative pain.[177]

The Behavioral Infant Pain Profile (BIIP)[196] (Table 12.6) is a behavioral assessment tool that combines sleep/wake states, facial responses, and two-hand movements by term and preterm infants responding to procedural (any skin-breaking procedure) pain. Through psychometric testing, the BIIP is a valid and reliable tool with high internal consistency for assessing acute procedural pain in preterm infants. Additionally, the BIIP is a practical clinical tool because it is easily scored by both experienced and inexperienced observers with very high inter-rater reliability.

The Neonatal Infant Pain Scale (NIPS) (Table 12.7) is a behavioral assessment tool for preterm and term neonates responding to a needle puncture. The NIPS provides a measurement of intensity of infant responses to a painful procedure during and after the event (Fig. 12.6).[250] NIPS scores have been correlated with GA and Apgar scores. The NIPS provides an objective measure of pain-relieving interventions and their effectiveness.[250] The NIPS is objective and nonintrusive and assesses only behavioral response to pain; compared with other pain scales, it has been found to be easy and quick to use.[250] Flow sheets have also been designed to facilitate the documentation of pain scores and behaviors.[250]

The EDIN scale consists of five items (facial activity, body movements, quality of sleep, quality of contact with nurses, and consolability) and is meant to assess prolonged, chronic pain. However, because there is no accounting for the developmental immaturity of preterm infants, a modified EDIN score (adding a sixth item, postmenstrual age) has been created and tested. **The EDIN6 scale (Table 12.8) was tested against the EDIN scale and found to be more sensitive in assessing (and thus intervening in) prolonged pain in preterm infants of various gestational ages in one NICU.[332] Cumulative scores on the EDIN6 of greater than 6 are considered pain expressions that require intervention.** This study also

TABLE 12.6 BEHAVIORAL INDICATORS OF INFANT PAIN (BIPP) SCORING SHEET: PRETERM AND FULL TERM

	TIME SITUATION (E.G., POST-OP; PROCEDURE (E.G., SUCTION, BLOOD WORK, IV START)
SCORE	STATE
0	Deep Sleep
0	Active Sleep
0	Quiet Awake
1	Active Awake
2	Agitated/Crying
	FACE
1	Brow bulge
1	Eye squeeze
1	Naso-labial furrow
1	Horizontal mouth stretch
1	Taut tongue
	HAND
1	Finger splay
1	Fisting
	TOTAL SCORE
NOTES	
Hear rate (no change; increase; decrease)	
Oxygen saturation (no change; increase; decrease)	
Environmental Support	
Analgesia	
Sedation Given	

From Holsti L, Grunau RE. Initial validation of the Behavioral Indicators of Infant Pain (BIIP). *Pain* 2007;132:264. Used with permission.

TABLE 12.7 NEONATAL INFANT PAIN SCALE (NIPS) OPERATIONAL DEFINITIONS

FACIAL EXPRESSION	
0—Relaxed muscles	Restful face, neutral expression
1—Grimace	Tight facial muscles; furrowed brow, chin, jaw (negative facial expression—nose, mouth, and brow)
CRY	
0—No cry	Quiet, not crying
1—Whimper	Mild moaning, intermittent
2—Vigorous cry	Loud scream; rising, shrill, continuous (*Note:* Silent cry may be scored if baby is intubated as evidenced by obvious mouth and facial movement)
BREATHING PATTERNS	
0—Relaxed	Usual pattern for this infant
1—Change in breathing	Indrawing, irregular, faster than usual; gagging; breath holding
ARMS	
0—Relaxed/restrained	No muscular rigidity; occasional random movements of arms
1—Flexed/extended	Tense, straight arms; rigid and/or rapid extension, flexion
LEGS	
0—Relaxed/restrained	No muscular rigidity; occasional random leg movement
1—Flexed/extended	Tense, straight legs; rigid and/or rapid extension, flexion
STATE OF AROUSAL	
0—Sleeping/awake	Quiet, peaceful sleeping or alert and settled
1—Fussy	Alert, restless, and thrashing

From Lawrence J, Alcock D, McGrath P, et al. Children's Hospital of Eastern Ontario; 1993.

surveyed 70 NICU nurses who were educated about neonatal pain, but of varying clinical experience, about their evaluation of the EDIN6 tool. In addition to the objective evaluation, the NICU nursing staff also perceived the EDIN6 to be better suited for the assessment of pain in more immature preterm infants.[332]

The National Practice Guidelines provide a list of assessment questions to ask when assessing pain management in the neonate (Box 12.5). Lack of validated assessment tools may leave health care providers wondering if behaviors are indicators or responses to pain. The Acute Pain Management Guideline suggests that "if care providers are unsure whether a behavior indicates pain, and if there is reason to suspect pain, an analgesic trial can be diagnostic, as well as therapeutic."[2]

Assessment of pain and delivery of effective pain-relieving interventions in daily clinical practice must *not* be delayed while adequate, objective assessment tools are developed.[98,375]

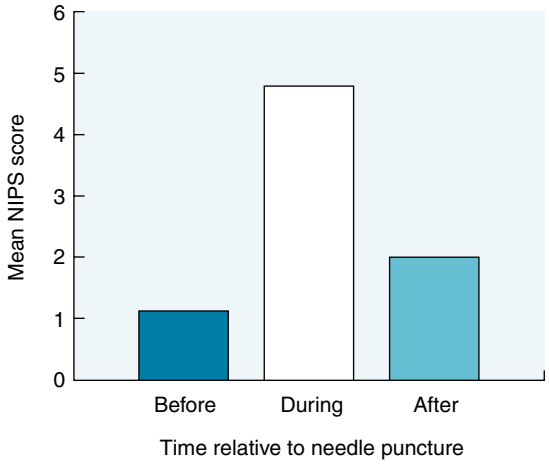


FIGURE 12.6 Mean Neonatal Infant Pain Scale (NIPS) scores over time in 22 infants. (From Lawrence J, Alcock D, McGrath P, et al. The development of a tool to assess neonatal pain. *Neonat Netw.* 1993;12:62.)

The usefulness of pain scores was recently assessed in 196 ventilated premature infant patient-days.[340] Although only 2% of pain scores suggested the presence of pain and only 0.1% of the pain scores resulted in analgesic use, these ventilated infants were obviously exposed to multiple pain-related procedures. In this study, regular reassessment and assignment of a pain score was poorly correlated with exposure to painful procedures.[340] All health care providers must use their highly developed assessment skills, along with input from the parents, to gather information about infant behavioral, physiologic, and hormonal or catabolic stress responses before, during, and after painful stimuli.[98] These same assessment skills enable care providers and parents to evaluate the effectiveness of pharmacologic and comfort interventions and institute more and/or different interventions as necessary to relieve pain and suffering.

TABLE 12.8 EDIN6 SCALE* INTEGRATED BY GESTATIONAL AGE AS A SIXTH ITEM

ITEM	DESCRIPTION	SCORE
Facial activity	Relaxed facial activity	0
	Transient grimaces with frowning, lip purse, and chin quiver	1
	Frequent grimaces, lasting grimaces	2
	Permanent grimaces resembling crying or blank face	3
Body movements	Relaxed body movements	0
	Transient agitation, often quiet	1
	Frequent agitation but can be calmed down	2
	Permanent agitation with contraction of fingers and toes and hypertonia of limbs or infrequent, slow movements and prostration	3
Quality of sleep	Falls asleep easily	0
	Falls asleep with difficulty	1
	Frequent spontaneous arousals, independent of nursing, restless sleep	2
	Sleepless	3
Quality of contact with nurses	Smiles, attentive to voice	0
	Transient apprehension during interactions with nurses	1
	Difficulty communicating with nurses. Cries in response to minor stimulation	2
	Refuses to communicate with nurses. No interpersonal rapport. Moans without stimulation	3
Consolability	Quiet, total relaxation	0
	Calms down quickly in response to stroking or voice or with sucking	1
	Calms down with difficulty	2
	Disconsolate. Sucks desperately	3
Postmenstrual age	Gestational age >37 weeks	0
	Gestational age 33–37 weeks	1
	Gestational age <33 weeks	2

*Modified by Debillion 2001: Echelle Douler Inconfort Nouveau-Ne. From: Raffaeli G, Cristofori G, Befani B, et al. EDN scale implemented by gestational age for pain assessment in preterms: a prospective study. *BioMed Res Int.* 2017;2017:9253710.

BOX 12.5 CRITICAL QUESTIONS TO ASK ABOUT PAIN MANAGEMENT IN NEONATES

- Is the infant being adequately assessed at appropriate intervals?
- Are analgesics ordered for prevention and relief of pain?
- Is the analgesic strong enough for the pain expected or the pain being experienced?
- Is the timing of the drug administration appropriate for the pain expected or being experienced?
- Is the route of administration appropriate (preferably oral or intravenous) for the infant?
- Is the infant adequately monitored for side effects?
- Are side effects appropriately managed?
- Has the analgesic regimen provided adequate comfort and satisfaction from the family's perspective?

Questions to Consider About Nonpharmacologic Strategies

- Is the strategy appropriate for the infant's developmental level, condition, and type of pain?
- Is the timing of the strategy sufficient to optimize its effects?
- Is the strategy adequately effective in preventing or alleviating the infant's pain?
- Is the family satisfied with the strategy for prevention or relief of pain?

From Agency for Health Care Policy and Research, Public Health Service. Acute Pain Management Guideline Panel. *Acute Pain Management: Operative or Medical Procedures and Trauma—Clinical Practice Guideline.* AHCPR Pub No 92-0032. Rockville, MD: U.S. Department of Health and Human Services; 1992.

Laboratory Data

Hormonal and metabolic changes are listed in Box 12.1. Serum glucose levels and reagent test strips monitor for hyperglycemia, which may result in increased serum osmolality and increase the risk for IVH. Glucosuria, ketonuria, and proteinuria result in elevated specific gravity. Metabolic acidosis may result from increased serum levels of lactate, pyruvate, ketones, and nonesterified fatty acids. These data also may be indicative of other serious neonatal problems (e.g., sepsis, acute tubular necrosis).

In the search of more objective measures of pain assessment, use of heart rate variability (HRV), skin conductance (SC) measurements, and brain-oriented techniques such as NIRS, EEG, and magnetic resonance imaging (MRI) are being investigated. Although HRV is a reliable measure of the neonate's response to acute and prolonged pain,[135,155] lack of availability of monitoring devices may preclude its use clinically.[98] SC, which measures stress-induced sweating in the palms and soles of the feet, has shown conflicting results in research, especially in preterm infants.[206,292,381,402] This requires further investigation in the preterm infant before it will be ready for clinical use.[403]

After heel lance, there is an increase of skin blood flow as measured by laser Doppler imaging that correlates to NIPS scores. In a randomized placebo-controlled trial, **use of sucrose before heel lance resulted in decreased NIPS scores that correlated with lower skin blood flow.** The researchers concluded that laser Doppler imaging is potentially a useful method for assessing neonatal procedural pain.[398]

Current and future research is focused on brain-oriented approaches (e.g., NIRS, EEG, and MRI) instead of pain-assessment tools. Painful stimuli cause hemodynamic changes in the brains of preterm and term infants.[45,366,367] As early as 25 weeks of gestation, preterm infants have increased oxygenated hemoglobin in response to a heel stick.[367] Cerebral changes are dependent on GA and sleep-wake state; less robust changes are seen in the younger GA infant and while asleep compared with the awake infant.[367] The first study to assess the correlation between cortical hemodynamic activity (by NIRS) during a heel stick in 25- to 43-week PMA neonates and the PIPP score found significant correlation between the NIRS and the pain score.[366] Use of the NIRS remains clinically challenging because multiple factors (i.e., movement, external stimuli, birth weight, medications, ventilator settings, infection, PDA) alter results.[199]

EEG changes in the frontal lobes of the brain during noxious and painful stimuli have been researched in preterm and full-term infants. Developmental maturation in response to touch and pain has been found in the neonate: (1) before 35 weeks of gestation, nonspecific neuronal bursts to both touch and pain were the dominant response, and (2) after 35 to 37 weeks of gestation, specific responses to touch versus pain were present.[133] Using EEG, a template of neonatal brain activity during a nociceptive procedure (heel stick) has been developed, provides an objective assessment of neonatal pain, and is sensitive to the administration of analgesia for pain relief.[192] Another study of EEG changes in infants greater than 37 weeks and less than 42 weeks of gestation who were presented

with light touch, cold, and a heel stick found significant differences in the cortical peak responses to each stimuli.[267] The researchers also found that only 65% of these newborns cried with heel stick, but all of them had EEG changes with the painful stimuli.[267] **MRI has documented procedural, pain-related stress to alterations in brain maturation in preterm infants in an NICU.**[61] Research into the use of EEG and MRI for pain assessment, especially technical challenges such as movement artifact, is in its infancy.[96,199]

Future assessment of neonatal pain may combine validated and reliable tools as well as laboratory data collected at the point-of-care. One such study used a multimodal approach to measure pain: (1) electromyography (EMG), EEG, and NIRS; (2) video-recording of behavioral responses; and (3) EEG to monitor autonomic responses (i.e., heart and respiratory rates, oxygen saturation with pulse oximetry, and cardiovascular activity).[421] In more than 100 test occasions, this multimodal system is precise, accurate, and 100% sensitive and specific in detecting touch versus a heel stick.[421] Simultaneous use of NIRS and EEG on 30 newborn infants who were exposed to innocuous tactile stimuli and noxious (heel lance) stimuli showed that both technologies recorded quantifiable and distinct activity to each of the stimuli in group analysis, with individual variation among newborns within the group.[407] The heel lance resulted in a peak hemodynamic change on the NIRS that was 10-fold larger than the cortical response to touch. However, this study also found that hemodynamic and electrophysiologic responses do not always occur together in an individual newborn, but when they do occur together (in 64% of heel lances), the responses are significantly correlated in their magnitude.[407]

TREATMENT

The neonate relies on the skilled observations, assessment, and interventions of care providers for prompt, safe, and effective relief of pain. Pain management is an interactive, relationship-based process that comprises (1) the environment of pain management, (2) preparation of the newborn for a procedure, (3) pain relief during a procedure, and (4) restoring safety and security to the infant after a procedure.[47] Barriers in providing adequate analgesia in these patients include an unfamiliarity with medication doses and with regional techniques and concern over increased drug sensitivity in neonates. Because routine care can be irritating to newborns, differentiating between agitation, which may respond well to comfort measures, and pain, which will not, is mandatory. **Opioids are the mainstay of pharmacologic treatment; however, other useful medications and techniques may be used for pain relief.**[13] **Guidelines for managing pain in the neonate are listed in** Box 12.6. **Tables** 12.9 **and** 12.10 **present evidence-based pain management strategies for commonly performed painful procedures and surgical interventions.**

Pharmacologic Measures

Absorption, metabolism, distribution, and clearance of drugs in the neonate differ from those in the older child and adult (see Chapter 10). These differences are summarized in Table 12.11.

OPIOIDS AND BENZODIAZEPINES

Opioids have their primary effect on the μ-receptor in the brain and spinal cord. High-affinity μ-receptors are associated with analgesia, and low-affinity μ-receptors are associated with respiratory depression. **There may be fewer high-affinity μ-receptors in the newborn that are less sensitive to the analgesic effects of opioids. Higher initial doses of opioids may therefore be necessary for effect, which may in turn increase the risk for respiratory depression.** A randomized, double-blind study of postoperative (e.g., thoracic or abdominal surgery) pain relief in full-term newborns receiving either continuous or intermittent morphine found an age-related difference in morphine requirements and metabolism.[57,58] Younger infants (e.g., 7 days or younger) needed less morphine postoperatively (e.g., loading dose [50 mcg/kg], continuous dose [5 to 10 mcg/kg/hr], and need for additional "breakthrough" doses) than neonates older than 7 days (e.g., loading dose [100 mcg/kg] and continuous dose [10 mcg/kg/hr]). This study also found that neonates being mechanically ventilated had slower morphine metabolism and clearance.[57] A retrospective analysis of the postoperative use of morphine in 82

BOX 12.6 GUIDELINES FOR PAIN MANAGEMENT IN THE NEONATE

- Use strategies to prevent pain (e.g., avoid recurrent painful stimuli).
- Use developmental care and environmental interventions to reduce noxious stimuli and stress in the NICU[287] (see Chapter 13).
- Use comfort measures (e.g., breast milk/sucrose/glucose, nonnutritive sucking, containment with swaddling or facilitated tucking).
- Sucrose administration recommendations:
  - Preterm infants: 0.1–0.4 mL; dipping a pacifier into sucrose results in 0.1-mL intake
  - Term infants: 2 mL
  - Administer 2 minutes before a painful procedure*
  - Analgesic effect lasts about 5 minutes
- Use pharmacologic therapy for preemptive analgesia (see Table 12.13).
- Use pharmacologic therapy for ongoing pain.
- Use of a combination of pain interventions (e.g., sucking, containment, medication) may have an additive or synergistic clinical effect.[255]

*Recent research found that waiting 2 minutes before starting a procedure after sucrose administration is not necessary.[279]

Modified from Anand KJ and the International Evidence-Based Group for Neonatal Pain: Consensus statement for the prevention and management of pain in the newborn. *Arch Pediatr Adolesc Med.* 2001;155:173; Prince W, Horns K, Latta T, et al. Treatment of neonatal pain without a gold standard: the case for caregiving interventions and sucrose administration. *Neonatal Netw.* 2004;23:33.

full-term neonates after thoracic and/or abdominal surgery[129] found that both dosage and duration of infusion prolonged mechanical ventilation. After extubation, no apnea or hypotension was associated with morphine use.

Decreased protein binding, drug metabolism, and drug clearance may contribute to higher plasma and CNS concentrations and prolonged drug effect. Effective drug doses and metabolism by the individual neonate depend on weight, GA, postnatal age, genetic variation, and the corresponding pharmacokinetics and pharmacodynamics, which may change in the first days of life.[384,397] All doses must be titrated to the individual neonate's needs and current clinical circumstances.[397]

All of the opioids have similar mechanisms of action; however, there are a few important differences in side effects (see Table 12.13). Morphine is the most commonly used opioid and may cause hypotension in dehydrated patients or when used in high doses; it provides more sedation than fentanyl. Recent research on the blood pressure effects of morphine administration showed (1) no hypotensive effects on ventilated newborns[344] or on preterm infants[405] given analgesic doses[20] and (2) occurrence of hypotensive effects with loading and higher dosages.[28,405] **However, morphine should be used with caution in preterm infants of 23 to 26 weeks of gestation and those with preexisting hypotension.**[185] For acute procedural pain (e.g., heel stick), a loading dose of morphine followed by continuous IV infusion does not provide adequate analgesia for invasive procedures in ventilated preterm infants.[73]

Fentanyl is the preferred drug in many NICUs because of its cardiovascular stability and its ability to decrease pulmonary vascular resistance. It can, however, cause chest wall rigidity and decreased lung compliance if administered too quickly. Neuromuscular blocking agents or slow administration of the drug will prevent this problem. Fentanyl is also commonly used in patients on extracorporeal membrane oxygenation (ECMO) to provide sedation and analgesia and to prevent increases in pulmonary vascular resistance and pressure.[254] Fentanyl is also used for artificial ventilation, persistent pulmonary hypertension of the newborn (PPHN), diaphragmatic hernia, and postoperative pain.[397] Because of its rapid onset and short duration, fentanyl relieves procedural pain.[397] **Sufentanil is 10 times more potent than fentanyl** and significantly more expensive. It is shorter acting and can have even greater effects on lung and chest wall compliance. Hydromorphone and methadone have also been used, particularly in the postoperative period and for infants on long term-opioids.

Administering drugs on a PRN schedule results in peaks and valleys of pain relief and increases in side effects. Because an analgesic is most effective if given before the peak of pain (wind-up), continuous infusions or regular administration can help prevent undue neonatal suffering.[13,384]

Benzodiazepines are commonly used in the NICU for sedation. Midazolam (Versed) has been increasingly used to provide sedation in mechanically ventilated neonates. **A meta-analysis of the research on midazolam concluded that there are significant adverse effects and no clinical benefit to the use of midazolam; there is insufficient evidence to justify the use of midazolam for ventilated neonates in the**

TABLE 12.9 NURSE-DIRECTED/PERFORMED PROCEDURES AND EVIDENCE-BASED NEONATAL PAIN RELIEF

NURSING CARE STRATEGIES[#]	SKIN-TO-SKIN/ KANGAROO CARE	BREAST-FEEDING	MASSAGE	ORAL: NONNUTRITIVE SUCKING *OR* SUCROSE/ GLUCOSE	TACTILE: SWADDLING/ CONTAINMENT/ FACILITATED TUCKING/ HOLDING OR ROCKING	MEDICATIONS: TOPICAL EMLA	REGIONAL INFILTRATION WITH LIDOCAINE	OPIOIDS	NONOPIOID ANALGESIA *OR* GENERAL ANESTHESIA
Heel lance	X	X	X	X					
Venipuncture	X	X	X	X	X	X		X	
Arterial stick				X	X	X	X		
Gavage tube insertion	X	X		X	X				
IM injection	X	X		X	X	X			
ETT or nasal suction	X*			X	X				
Catheterization of bladder	X†	X†		X	X				Nonopioid analgesia†
Dressing changes/tape removal/suture removal	X*	X*		X	X				Nonopioid analgesia†

[#]Using a combination of nonpharmacologic comfort strategies potentiate their pain-relieving effects as does combining comfort measures and pharmacologic measures.
*If already kangaroo caring.
†Postprocedure.
ETT, Endotracheal tube; *IM,* intramuscular injection.
Modified from Gardner SL. Clinical practice tool: nurse-directed/performed procedures and nurse assisted procedures: evidence-based neonatal pain relief; 2008. Used with permission.

TABLE 12.10 NURSE-ASSISTED PROCEDURES AND EVIDENCE-BASED NEONATAL PAIN RELIEF*

NURSING CARE STRATEGIES	SKIN-TO-SKIN/ KANGAROO CARE	BREAST-FEEDING	ORAL: NONNUTRITIVE SUCKING OR SUCROSE/GLUCOSE PACIFIER	TACTILE: SWADDLING/ CONTAINMENT/ FACILITATED TUCKING/HOLDING AND ROCKING	MEDICATIONS: TOPICAL: EMLA CREAM, AMETHOCAINE GEL	REGIONAL INFILTRATION WITH LIDOCAINE	OPIOIDS	NONOPIOID ANALGESIA OR GENERAL ANESTHESIA
PICC line insertion/removal			X	X	X		X	
Taps: lumbar, suprapubic, ventricular, paracentesis, bone marrow			X		X	X	X	
Line placement/removal: (CVP; Broviac); ECMO; arterial/venous cutdowns			X	X	X	X	X	Consider general anesthesia Nonopioid analgesia†
Chest tube insertion/ removal			X	X		X	X†	Nonopioid analgesia†
ETT intubation, NCPAP, ventilation	X‡		X‡	X			X	Nonopioid analgesia†
Circumcision			X		X	X		Nonopioid analgesia†
Scopes: endoscopybronchoscopy			X (pre-procedure)	X			X	Nonopioid analgesia†
Eye examination for ROP	X†	X†	X	X			X	Nonopioid analgesia†
Any surgical procedure: PDA ligation; TEF/gastroschisis repair/omphalocele/ CDH/inguinal hernia; CHD repair/shunt placement			X†	X†			X†	Nonopioid analgesia†
Diagnostic procedures such as echocardiography, ultrasonography, x-ray examination		X	X				X	
Manipulative procedures such as casting for clubfeet			X	X				

*Using a combination of nonpharmacologic, comfort strategies potentiates their pain relieving effects as does combining comfort measures and pharmacologic measures.

†Postprocedure.

‡With NCPAP/ventilation.

CDH, Congenital diaphragmatic hernia; *CHD,* congenital heart disease; CVP, central venous pressure; *ECMO,* extracorporeal membrane oxygenation; *ETT,* endotracheal tube; *PDA,* patent ductus arteriosus; *PICC,* peripherally inserted central catheter; *ROP,* retinopathy of prematurity; *TEF,* tracheoesophageal fistula.

Modified from: Gardner SL: Clinical practice tool: nurse assisted procedures: evidence-based neonatal pain relief, 2008. Used with permission.

TABLE 12.11 PHARMACOLOGIC DIFFERENCES BETWEEN NEWBORNS AND ADULTS

DIFFERENCES	CAUSE	EFFECTS
Altered gastric activity	Presence of alkaline amniotic fluids at birth Immature gastric mucosa Consumption of alkaline milk	Variable drug absorption
Decreased gastric emptying time		Increased absorption of some drugs
Decreased protein binding	Lower levels of albumin, α-acid glycoprotein Increased competition for binding sites by endogenous substances (bilirubin)	Increased levels of free drug (opioids, local anesthetics)
Increased volume of distribution	Larger volume of body water in the newborn	Larger initial dose may be needed for effect (e.g., neuromuscular blocking agents, local anesthetics)
Decreased drug metabolism	Immature liver enzyme systems	Prolonged effect of some medications (e.g., morphine, fentanyl, neuromuscular blockers)
Decreased drug clearance	Immature renal system and decreased glomerular filtration rate	Prolonged effect of some medications (morphine)

From Rovee-Collier C, Hayne H. Reactivation of infant memory: implications for cognitive development. *Adv Child Dev.* 1987;10:185.

NICU (see Table 12.13).[295] Benzodiazepines potentiate the effects of opiates.[373] Therefore, when they are used in combination (e.g., fentanyl and midazolam), lower doses of each medication may be used to gain the same effect as would be attained if either one was used separately. There is increasing concern regarding the neurotoxicity of midazolam[258] (see Table 12.13). It is important to note that although benzodiazepines provide sedation, they have no analgesic effect.[373]

The long-term effects of analgesic use on the developing brain are poorly understood because of a paucity of data on neurodevelopmental outcomes. Several researchers have found a protective effect of analgesic use on neurodevelopmental outcomes, perhaps because of decreased fluctuation in blood pressure, cerebral blood flow, oxygenation, respiratory synchrony with ventilation, and stress hormones.[19,27,32,240,266]

More recent studies on the long-term neurologic effects of morphine analgesia in ventilated preterm infants caution against the lack of protective effects and have documented (1) an increase in severe IVH,[28] (2) a decrease in the incidence of IVH that did not influence poor neurologic outcomes,[364] and (3) subtle neurobehavioral differences in preterm infants exposed to morphine analgesia.[335]

LOCAL ANESTHETICS

Local anesthetics have a variety of uses and provide analgesia by preventing the transmission of noxious stimuli at either the peripheral receptor site or the spinal cord. Bupivacaine, ropivacaine, and lidocaine are the most commonly used local anesthetics (see Table 12.12). A recent study showed that bupivacaine confers better analgesia for neonatal circumcision than that achieved with lidocaine.[380]

Bupivacaine is longer acting but more cardiotoxic than lidocaine. Both are more toxic in neonates than in adults because of increased organ sensitivity and free fraction of drug. The cardiovascular toxicity may be enhanced if epinephrine-containing local anesthetics are used. The long-acting local anesthetics *levobupivacaine* (available in Europe) and *ropivacaine* are as effective as bupivacaine but less cardiotoxic.[419] Procainamide is used as a continuous infusion in many centers because of its rapid ester metabolism and decreased toxicity.

Regional Technique. Regional techniques provide adequate analgesia, thus reducing the need for higher doses of opioids (Table 12.13). Advantages include the following[120]:

- Stress responses are significantly decreased.

TABLE 12.12 TYPES OF REGIONAL BLOCKADE
Potential Uses

BLOCK	POTENTIAL USES	COMPLICATIONS
Spinal	In place of general anesthesia for surgery below the umbilicus; decreased incidence of postoperative apnea	Inability to access space; incomplete block or inadequate duration of anesthesia
Caudal/ epidural	Intraoperative and postoperative analgesia for thoracic, abdominal, perineal, and lower extremity surgery	Inadequate block; local or opioid-related toxicity; nerve damage, paralysis
Dorsal penile nerve/ring block	Circumcision, analgesia for any penile surgery	Hematoma formation; end-organ damage if epinephrine-containing solutions are used
Intercostal nerve block	Rib fracture, thoracic surgery	Pneumothorax; local anesthetic toxicity (highest rate of absorption)

- Normal respiratory patterns return more quickly.
- The need for postoperative ventilation may be avoided or shortened.
- Intestinal motility recovers more quickly.
- Morbidity decreases, particularly with the use of epidural blocks.

Dorsal Penile Nerve/Ring Block.[231] **The dorsal penile nerve block is extremely easy to perform with a high degree of success that can provide surgical anesthesia for circumcision.**[231] The block is performed by injecting 1% lidocaine 3 to 5 mm below the skin at the 2 o'clock and 10 o'clock positions on the dorsum of the penis (Fig. 12.7). In a full-term neonate, 0.5 mL/side is used, and 0.2 mL/kg/side is used in premature infants. An alternative technique less likely to cause hematoma is to inject a subcutaneous ring of 0.5% or 1% lidocaine around the base of the penis. **All solutions should be without epinephrine, and a "wait time" of 5 to 8 minutes is necessary to achieve adequate anesthesia.**[252]

Several studies of pain responses to circumcision with a combination of pharmacologic and nonpharmacologic interventions for neonatal pain have been published. Use of a dorsal penile nerve block/ring block and oral sucrose solution found that infants receiving the combination of a block and oral sucrose had lower pain scores than those who received a ring block or sucrose alone.[341] A more recent study of **ring block, oral sucrose, and eutectic mixture of lidocaine and prilocaine (EMLA) cream found better pain relief with use of all of these methods together.**[358] Dorsal penile block, sucrose, and EMLA cream were not as effective as the ring block, oral sucrose, and EMLA. When only EMLA and sucrose were used, there was a significant increase in heart rate and duration of crying time.[358]

Liposomal lidocaine was compared with EMLA and dorsal penile block in a study of 54 full-term infants being circumcised; liposomal lidocaine was found to be a safe and effective topical anesthetic.[252] A video study found that the dorsal penile nerve block was significantly more effective for pain relief during circumcision than use of topical EMLA cream.[152] A recent meta-analysis of 14 studies of infant circumcision found that pain was dramatically decreased with the combined use of dorsal penile block, acetaminophen, oral sucrose, and topical analgesic cream.[48] However, the addition of liposomal lidocaine to sucrose did not further decrease the pain of venipuncture in healthy term newborns.[394]

Epidural Block. The epidural space is an area surrounding the dura of the spinal cord. This space can be accessed from the caudal, lumbar, or thoracic region. An epidural block is performed by a skilled pediatric anesthesiologist, often with the patient under general anesthesia.[275] A small catheter can be left in the space, or a one-time dose of medication can be given. Local anesthetics act by anesthetizing either the local nerve roots or the spinal tracts at the level of the spinal cord where they are placed. The most commonly used medications in neonates are the local anesthetics *procainamide, ropivacaine,* or *bupivacaine.* They are often used in combination with low doses of opioids and/or clonidine, which have both local and systemic action. **The major advantages of these techniques include their ability to provide continuous pain relief and the potential to minimize respiratory depression, facilitate extubation, and hasten recovery.**

TABLE 12.13 ANALGESICS, SEDATIVES, AND REVERSAL AGENTS FOR THE NEONATE

DRUG	DOSAGE	COMMENTS
	OPIOIDS	
Morphine	0.05–0.1 mg/kg/dose q 4–6 hr PRN IV, IM, or sub-Q Continuous IV infusion: 10–15 mcg/kg/hr (up to 30–40 mcg/kg for ventilator therapy and major surgery) Mean onset of action: 5 min Peak effect: 15 min Duration: 4–5 hr	CNS and respiratory depressant; bronchospasms; peripheral vasodilation with hypovolemic infants; hypotension, decreased gastric/intestinal motility; intestinal obstruction; risk for NEC; increased intracranial pressure; seizures; urinary retention. Easily reversed with naloxone; slower onset but longer duration than for fentanyl; withdrawal symptoms may occur. Ceiling effect (after reaching a therapeutic level, higher doses result in more adverse rather than analgesic effects) reached by using doses up to 0.5 mg/kg.[24] Sleep-wake cycling, measured by EEG, resumed soon after surgery in neonates ≥32 weeks of gestation who received high doses of morphine and midazolam.[306] Does not alter the physiologic response to ETT suctioning.[26] As premedication for ETT intubation: use only if other opioids not available; must wait at least 5 minutes for onset of action.[237]
Fentanyl (Sublimaze)	0.3–2 mcg/kg/dose q 1–2 hr PRN IV or sub-Q Continuous IV infusion: 0.3–5 mcg/kg/hr Onset of action: 2–3 min Peak effect: 3–4 min Duration: 30–60 min	Same as for morphine. Eighty to 100 times more potent than morphine. Rapid onset of action; decreases motor activity; does not increase intracranial pressure in the absence of respiratory depression. Easily reversed with naloxone; short duration of action; may cause bradycardia, hypotension, apnea, seizures, or rigidity if given too rapidly; hypothermia. Less hypotension, urinary retention, GI motility effects than with morphine.[345] Withdrawal symptoms occur with prolonged use (>5 days). Drug of choice for premedication for ETT intubation[237]; safe for PICC line insertion in nonintubated infants.[227]
Sufentanil citrate (Sufenta)	0.5–1 mcg/kg/dose q 30 min to 1 hr Peak effect: 5–6 min Duration: 30 min	Ten times more potent than fentanyl; has a quicker onset and shorter duration of action than fentanyl. Use with caution in neonates with intraventricular hemorrhage, hepatic or renal impairment, or pulmonary disease. Same side effects as for fentanyl. Bolus and continuous infusion affects EEG results in VLBW/ELBW infants; use of sufentanil must be considered in EEG interpretation.[297]
Remifentanil	1–3 mcg/kg/dose IV Repeat in 2–3 min PRN Onset of action: within 1 min of administration[8] Duration: 3–10 min	Same as for fentanyl. Easily reversed with naloxone. Short duration of action. Limited experience in neonates.[237] Premedication for ETT intubation, PICC line insertion, and laser surgery for ROP: acceptable analgesic.[8,39]
Meperidine (Demerol)		*Not recommended* in preterm or term infants. The active metabolite normeperidine accumulates in tissues and causes CNS stimulation (e.g., tremors, muscle twitching, hyperactive reflexes, dilated pupils) and also lowers the seizure threshold level.[13]

TABLE 12.13 ANALGESICS, SEDATIVES, AND REVERSAL AGENTS FOR THE NEONATE—CONT'D

NONOPIOIDS		
Acetaminophen/ paracetamol (Tylenol)	Oral loading dose[310]: 20 mg/kg PO; then 10 mg/kg PO q 6 hr in term infants and q 8 hr in preterm infants <32 weeks of gestation IV loading dose[310]: 20 mg/kg; then 10 mg/kg IV q 6 hr for term infants and q 8 hr for preterm infants <32 weeks of gestation Rectal loading dose[310]: 30–40 mg/kg; then 1–18 mg/kg q 6 hr for term infants and q 8 hr for preterm infants <32 weeks of gestation	Used for mild to moderately severe pain[8]: given alone does *not* relieve surgical pain, heel lance pain, or pain of eye examination[305] Potentiates the effects and significantly reduces the need for opioids after major surgery.[189,305] *Do not use* in patients with G6PD deficiency. May cause hepatotoxicity in overdose .
Ibuprofen (Advil, Motrin)	4–10 mg/kg/dose q 6–8 hr PO	Gastric irritant—administer with or after feeding; use with caution in neonates with necrotizing enterocolitis, impaired renal function, hypertension, compromised cardiac function, or pulmonary hypertension.
LOCAL ANESTHETICS		
Lidocaine	0.5%–1% solution (to avoid systemic toxicity, volume should be less than 0.5 mL/kg of 1% lidocaine solution—5 mg/kg)	Local infiltration anesthesia for invasive procedures; use solution *without epinephrine* to avoid vasoconstriction. Use topical creams (EMLA/amethocaine) before needle insertion; warm solution to body temperature; inject slowly to reduce the pain of injection.[253] One case report of a term newborn developing methemoglobinemia after circumcision with lidocaine and topical EMLA cream.[235]
Bupivacaine Levobupivacaine Ropivacaine	2.5 mg/kg one-time epidural dose Continuous IV infusion: 0.2 mg/kg/hr (maximum dose)	Monitor for CNS (e.g., seizures, irritability) and cardiotoxic (e.g., ventricular dysrhythmias) side effects. Monitor catheter integrity. Epidural infusion is titrated to effect but *must not* exceed maximum dose. Levobupivacaine and ropivacaine are less cardiotoxic than bupivacaine.
EMLA (lidocaine and prilocaine)	2.5–5 g to site for at least 60 min Peak effect: 2–3 hr Duration: 1–2 hr after removal	Vasoconstriction at the site. Site must be covered with water-impermeable dressing (e.g., Tegaderm). Single doses have not been shown to cause methemoglobinemia in preterm or term neonates.[389] Does not relieve pain of heel lance.[13] The possibility of toxicity is increased when EMLA is applied to (1) open skin and (2) a larger area than recommended by the manufacturer.[312] Cannot be used on abraded skin or mucous membranes.
Amethocaine gel* (4%) liposome-encapsulated tetracaine (Ametrope)	1.5 g to site for 30 min to 1 hr	Site must be covered with water-impermeable dressing (e.g., Tegaderm). Vasodilation at the site—mild transient (~20 min) erythema or blanching.[213,253,301,388] Case report of ELBW preterm infant developing a clinically significant cardiac arrhythmia after topical use for PICC insertion.[271]
Liposomal lidocaine (4%) cream	Onset of action: 20–30 min	Available in the United States without a prescription. Does not cause methemoglobinemia; can be applied without an occlusive dressing and has fewer vasoactive effects. Effective in relieving immunization pain in infants.[391]
SEDATIVE-HYPNOTICS		
Barbiturates		*Do not* provide pain relief; help reduce agitation precipitated by painful events. Frequently produce hyperalgesia and increased reaction to painful stimuli; contraindicated for neonates who have pain and also require sedation.

Continued

TABLE 12.13 ANALGESICS, SEDATIVES, AND REVERSAL AGENTS FOR THE NEONATE—CONT'D

SEDATIVE-HYPNOTICS		
Phenobarbital	Loading: 10–20 mg/kg IV to maximum 40 mg/kg Maintenance: 5–7 mg/kg in two divided doses beginning 12 hr after last loading dose	Prolonged sedation possible once therapeutic levels achieved (20–25 mg/mL); depresses CNS—motor and respiratory; slow onset of action; little or no pain relief; not easily reversed; withdrawal symptoms may occur; incompatible with other drugs in solution.
NONBARBITURATES		
Dexmedetomidine HCl (Precedex)	Bolus for procedural sedation: 1–3 mcg/kg Slow IV infusion: Loading dose: 0.5 mcg/kg over 10 minutes Continuous IV infusion: Maintenance dose: 0.25–0.6 mcg/kg/hr Distribution half-life: 6 min Elimination half-life: 2 hr	Sedative, analgesic, and all anesthetic properties for mechanically ventilated preterm infants and invasive procedures in ventilated and nonventilated neonates. Minimal effect on blood pressure, heart and respiratory rates, oxygen saturation, and gastric motility.[277,302] Wean slowly to avoid withdrawal symptoms. Adverse reactions: hypo/hypertension, tachycardia, hypoxia, acidosis, elevation in temperature and blood sugar, anemia, and oliguria.
Chloral hydrate	25–75 mg/kg/dose q 6 hr PRN, PO, or PR Onset: 10–15 min Duration: 2–4 hr	Gastric irritant—administer with or after feeding; paradoxical excitement; prolonged use associated with direct hyperbilirubinemia;[245] *do not* use for analgesia; respiratory depressant; adverse effects in repeated doses to premature infants: CNS depression, dysrhythmias, and renal failure.[159] For occasional procedural sedation, although *not recommended.* Recovery from chloral hydrate accompanied by a "hangover."
Benzodiazepines		*Do not* provide pain relief. Produce sedation, muscle relaxation, amnesia, anxiolysis, and anticonvulsant effects.
Diazepam (Valium)	0.02–0.3 mg/kg IV, IM, or PO q 6–8 hr	*Do not* dilute injection; venous sclerosing; may displace bilirubin and result in kernicterus; respiratory depression; hypotension; may cause agitation; induces sleep; relaxes muscles; withdrawal symptoms may occur; no analgesic effect. This drug should be used with caution in the neonate because of its long half-life, long-acting metabolites, and preservative (benzyl alcohol).[13]
Lorazepam (Ativan)	0.05–0.1 mg/kg/dose (give over ≥3 min) q 4–8 hr	Respiratory depressant, partial airway obstruction, drowsiness; respiratory depression potentiated when opioids or barbiturates also being given; infuse slowly to avoid apnea, bradycardia, and hypotension. Rhythmic myoclonic jerking in preterm infants.

TABLE 12.13 ANALGESICS, SEDATIVES, AND REVERSAL AGENTS FOR THE NEONATE—CONT'D

NONBARBITURATES		
Midazolam (Versed)	0.05–0.15 mg/kg/dose IV (give over ≥5 min) q 2–4 hr PRN Continuous IV infusion: <32 wk: 0.03 mg/kg/hr or 0.5 mcg/kg/min >32 wk: 0.06 mg/kg/hr or 1 mcg/kg/min PO: 0.25 mg/kg/dose of oral syrup Onset: IV—1–2 min; PO—15–30 min Duration: 1 hr after single IV dose For procedural sedation: Give 0.05 mg/kg IV and repeat ×1 PRN for procedure	Same as for lorazepam; continuous IV infusion enables precise titration until sedative effect is obtained; calms agitated infant on ventilator. Rapid bolus delivery and/or use with fentanyl is associated with (1) myoclonus—rhythmic twitching of all extremities that ceases with discontinuation of drug and does not return, and (2) respiratory depression and hypotension—caution use in hypotensive and hypovolemic neonates.[212,265] A systematic review shows (1) increased incidence of adverse neurologic outcomes (e.g., grade 3–4 IVH; PVL), altered CBF; (2) longer duration of NICU stay with midazolam use; and (3) conclusion that there is insufficient evidence to support IV midazolam use as a sedative for neonates in the NICU.[295] Recent study of very preterm infants who received midazolam in the NICU found decreased hippocampal volume (and associated lower cognitive scores) and increased mean diffusivity.[127]
REVERSAL AGENTS		
Naloxone (Narcan)	0.1 mg/kg	Reverses effects of opioids (both side effects and analgesia).
Flumazenil (Mazicon) 10 mcg/kg	10 mcg/kg	Reverses effects of benzodiazepines (e.g., midazolam, diazepam, lorazepam).

*Not yet approved by the Food and Drug Administration for use in the United States.

CBF, Cerebral blood flow; *CNS,* central nervous system; *EEG,* electroencephalography; *ELBW,* extremely low-birth-weight; *EMLA,* eutectic mixture of lidocaine and prilocaine; *ETT,* endotracheal tube; *G6PD,* glucose-6-phosphate dehydrogenase; *GI,* gastrointestinal; *IM,* intramuscular; *IV,* intravenous; *IVH,* intraventricular hemorrhage; *NEC,* necrotizing enterocolitis; *NICU,* neonatal intensive care unit; *PICC,* percutaneous insertion of central catheter; *PO,* per os; *PR,* per rectum; *PRN,* as needed; *PVL,* periventricular leukomalacia; *ROP,* retinopathy of prematurity; *sub-Q,* subcutaneous; *VLBW,* very-low-birth-weight.

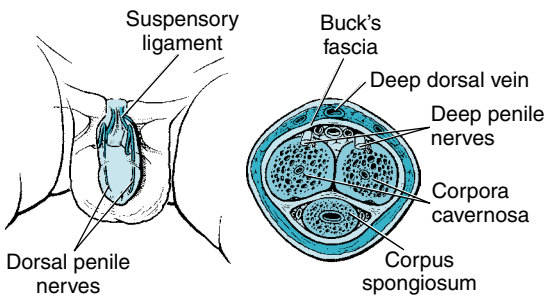


FIGURE 12.7 Anatomic landmarks for placement of a dorsal penile nerve block. (From McClain B, Anand KS. Neonatal pain management. In: Deshpande J, Tobias J, eds. *The Pediatric Pain Handbook.* St Louis, MO: Mosby; 1996.)

Eutectic Mixture of Local Anesthetic and Infiltration. EMLA is a local anesthetic cream that anesthetizes the skin and has been used for a variety of procedures (e.g., lumbar puncture, venipuncture, immunizations).[205,234,416] A study of EMLA, applied 60 to 90 minutes before lumbar puncture, showed a significant decrease in pain response during needle insertion and withdrawal but not during positioning/handling of the newborn.[228] **EMLA has been used for analgesia with circumcisions in newborns and has been shown to be efficacious.[416] However, its analgesic properties are not as effective as those of dorsal penile blocks in relieving postoperative circumcision pain.★**

A meta-analysis of the efficacy of EMLA for a variety of procedures in neonates found that EMLA diminishes pain during circumcision, venipuncture, arterial puncture, and placement of a peripheral/central IV line.[389,416] **For maximum effectiveness, EMLA should be applied and left on for at least 1 to 2 hours before starting an invasive procedure.** Unfortunately, EMLA does not appear to alleviate pain resulting from heel sticks.[142,389,416] **Infiltration of local anesthetic can help decrease pain** for procedures such as placement of percutaneous central lines, removal of Broviac catheters, and circumcision. Methemoglobinemia does not appear to be a problem when single daily doses of 0.5 g EMLA are left in place for 60 minutes,[389] but studies are ongoing to address this issue.

Amethocaine gel (lysosome-encapsulated tetracaine) is a topical local anesthetic preparation that provides more effective superficial analgesia than EMLA in adults. Amethocaine has demonstrated similar efficacy to EMLA when appropriate application times are used and has a more rapid onset and longer duration of action than EMLA.[301] Studies have documented its effectiveness in neonates as follows:

- It relieves pain during venipuncture,[213,260] IV insertion, and injections of vitamin K.[357]
- It does not relieve pain from heel sticks[315] or peripherally inserted central catheter (PICC) insertion, unless combined with morphine use.[388]
- It relieves circumcision pain.[416]
- It does not cause methemoglobinemia.
- It is effective within 30 to 40 minutes of application.

A recent Cochrane review recommends more research into the safety and efficacy of topical anesthetics, especially in the very preterm neonate and for multiple applications.[140]

OTHER MEDICATIONS

Acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs) can be helpful in providing analgesia for mild to moderate pain (see Table 12.13). These medications are more effective when administered on a regular schedule, augment the effects of opioids, and may be delayed in effect because of the rate of gastric emptying.[36,405] **Acetaminophen given 2 hours before circumcision does not reduce pain during the procedure but is effective in postoperative pain relief; repeated doses every 4 to 6 hours for the first 24 hours after circumcision are recommended.** The analgesic effects of IV NSAIDs have not been studied in preterm infants, and the adverse effects of prolonged NSAID use may lead to renal, circulatory, hepatic, gastrointestinal, and hematologic complications.[25,31] Ketorolac in a single dose has been studied in infants as young as 2 months of age and found to be safe and effective at relieving pain.[90,264] Although **use of acetaminophen as a prophylactic for febrile response to immunizations is effective, there is a significantly lower antibody response to vaccine antigen when acetaminophen is used.**[329]

Sedatives can help decrease agitation and improve comfort but do *not* **by themselves provide analgesia. Use of developmental care significantly reduces the need of VLBW infants for sedative drugs.**[411] Sedatives are appropriate to induce sleep for diagnostic procedures (e.g., MRI, computed tomography [CT]), to calm chronically irritable infants whose physiologic stability or ventilatory status is compromised by agitation, and for pain-related agitation.[27,411] Sedatives have potential toxicities, effect behavioral changes, and affect consciousness, which deprive neonates of their ability to communicate and interact with their parents, caregivers, and the environment.[412] Furthermore, the short-term and long-term effects of frequent or continuous use of sedatives on the developing brain are unknown.

Comfort/Nonpharmacologic Measures

Comfort measures alone do not relieve pain; however, their use reduces agitation, which indirectly reduces pain by promoting behavioral organization, relaxation, general comfort, and sleep.[13] Although comfort measures may prevent the intensification of pain (e.g., guarding an abdominal incision by positioning is less painful than four-point restraint), they may not relieve moderate to severe pain. Comfort measures are helpful but inadequate by themselves, considering the intensity of the noxious stimuli causing moderate to severe pain.[13,102]

Provision of nonpharmacologic interventions for neonatal pain is an evidence-based nursing practice that should be initiated by neonatal nurses and parents.[151] A recent survey of NICU nurses found that when rationing of nursing interventions (limiting or omitting interventions to particular patients) occurs, provision of comfort care is "often" and "very often" rationed.[339] Another survey

found that 64% of NICU caregivers used nonpharmacologic interventions for heel sticks or venipunctures.[50] **As partners in care, parents should be encouraged, facilitated, and educated to engage in providing comfort measures for their infants having painful procedures.[68] Nonpharmacologic interventions that have been found to offer the most comfort during a painful intervention include nonnutritive sucking, breastfeeding, skin-to-skin contact (kangaroo care) with the mother or another immediate postpartum mother,[285,293] facilitated tucking, rocking, and holding.* Who better than parents can provide these interventions? Research shows the efficacy of parental involvement.**

Initiation of skin-to-skin contact,[168] taste, and suckling was described in full-term infants receiving heel sticks for genetic screens, who experienced less crying (91%) and grimacing (84%) when being held and breastfed by their mothers.[75,167] **Numerous studies show that very preterm, healthy preterm, and term newborns (between 28 and 36 weeks' PMA) who received heel sticks experienced diminished behavioral and physiologic pain response, less crying, and quicker recovery when being held skin-to-skin (e.g., kangaroo care) by their mothers for 15 to 30 minutes before and during the procedure.** If the preterm infant's mother is not available, does provision of skin-to-skin care by the father or an unrelated woman result in lower pain responses? This question has been researched in two published studies with the following results: (1) fathers were marginally less effective than mothers in decreasing their preterm infant's pain response,[219] (2) unrelated females had a small, although not negligible, decrease in their ability to relieve infant pain, and fathers are more acceptable to the baby's mother than an unrelated female to provide this intimate care.[216] **Animal studies show that the short-term and long-term effects of repeated pain are ameliorated by the presence and ministrations of the mother;[413] perhaps the presence of the human mother or parent provides the same protection for the human neonate.*** One study found concordance between mother and infant cortisol levels during heel lance, which supports the stress regulatory role of maternal skin-to-skin care during painful procedures.[78]

Skin-to-skin care is the most effective nonpharmacologic intervention for neonatal pain,[193,321] and barriers to use need to be identified and addressed. One barrier to using skin-to-skin care and breastfeeding to relieve neonatal pain during invasive procedures such as heel stick and injections is the uncomfortable position of the professional performing the procedure. An ergonomically sound protocol using an adjustable height stool has been developed and tested in the clinical setting.[97] This protocol has resulted in a more comfortable position for the professional and more use of skin-to-skin care and breastfeeding for neonatal pain relief during the procedure.[97]

Developmental care not only prevents pain but also decreases behavioral and physiologic pain scores in preterm infants.[79,365] A recent study of a simple diaper change in VLBW preterm infants showed less physiologic response (e.g., alteration in heart rate, hypoxia, bradycardia, desaturation events) and less pain response (measured with two pain scales) when developmental care was used before and during the procedure.[365] In this study, developmental supports such as opportunities for grasping, hand swaddling, decreasing light and noise, NNS, and body support and containment were used.

NONNUTRITIVE SUCKING

NNS (e.g., the infant's own fingers or hands or a pacifier) soothes by reducing the infant's level of arousal and duration of cry while promoting the quiet alert state.[69] **NNS is effective in reducing pain in preterm infants** during heel stick, circumcision, immunizations, and ROP screening eye examinations.[59] **The effect of NNS is immediate, but the effect ceases immediately on cessation of sucking/removal of the pacifier. Combining NNS and sucrose before and during painful procedures provides a synergistic effect on pain relief for both term and preterm neonates.***

ORAL SUCROSE/GLUCOSE AND BREASTFEEDING

Distressed infants who were offered oral sucrose calmed quickly, stayed calm longer, and spent more time in a quiet alert state than did infants offered only a pacifier.[55] Sucking soothes, reduces

*References 79, 84, 123, 194, 310, 314, 319, 359.

*References 48, 69, 79, 84, 95, 96, 99, 169, 219, 291, 300, 310, 314.

*References 56, 73, 257, 259, 298, 383, 400.

heart and metabolic rates, induces hand-to-mouth behavior, and elevates the pain threshold through opioid and nonopioid systems.[55] **Oral administration of sucrose within 2 to 3 minutes before an invasive procedure (e.g., heel stick/venipuncture, bladder catheterization, ROP examination, insertion of gavage tube, arterial stick, echocardiography, casting) has been shown to decrease crying duration, heart rate, facial activity, and EEG changes associated with pain in full-term and preterm infants.**⋆ However, in the first randomized clinical trial of 40 preterm and term infants receiving oral sucrose (24%) for peripheral intravenous catheter (PIV) placement, no efficacy in relieving the neonate's pain during the procedure was seen.[100] Replication of this study is needed before widespread application of these findings.

In these studies, the amount (0.05 to 2 mL) and concentrations (24% to 50%) of sucrose varied, but even the smallest dose administered once to preterm infants of 26 to 34 weeks of gestation reduced pain behaviors.[379] The small doses of concentrated sucrose solution used to treat neonatal pain have not been shown to cause hyperglycemia in preterm infants.[62] The AAP recommends that oral sucrose/glucose used for pain relief must be ordered and tracked as a medication.[13]

When sucrose is paired with developmental interventions such as rocking, carrying,[162] NNS,[101,422] prone positioning, facilitated tucking,[422] radiant warmth,[166] swaddling[125,128,131] or parental holding,[89,157] sucrose is more effective in decreasing behavioral pain responses. Sensorial saturation (massaging the infant's face, gently talking to the infant, and instilling a sweet solution on the tongue) is effective in newborn pain relief during minor procedures.[49] Sensorial saturation is more effective than oral glucose alone, but use of sensorial saturation without sweet solution is ineffective. A systematic review of sensorial saturation (i.e., oral sucrose, massage, and caregiver's voice) **found that it is more effective in heel stick procedures in preterm and term infants than oral sucrose/glucose alone.**[259] Combining massage and breastfeeding relieves the pain of venipuncture in term and late preterm infants.[425] In healthy full-term neonates, especially males, sensorial saturation reduces pain scores and markers of oxidative stress after heel stick.[317]

Two RCTs of the combination of NNS, oral sucrose, and facilitated tucking during heel stick in preterm infants found reduced arousal during the procedure, less crying and fussing, and better sleep than routine care alone.[422] For intrusive procedures, use of a supportive bundle (i.e., modulating the infant's state, NNS, facilitated tucking, and oral sucrose) increased premature infants' sleep time and efficiency as well as decreased bouts of awakening after the procedure.[246] **In a systematic meta-analysis of 74 studies of sucrose use for analgesia, sucrose was found to be safe, effective, and cost-effective for single painful procedures (e.g., heel stick/venipuncture/intramuscular [IM] injection) for preterm and term neonates.**[379] The addition of liposomal lidocaine to sucrose in one study did not further decrease the pain of venipuncture in healthy term newborns.[394] Despite being aware that sucrose relieves pain, only 10% of surveyed NICUs used sucrose before a heel stick, and only 11% used sucrose before venipuncture.[169] Two other surveys found that (1) only 33% of responding NICUs used sucrose before routine painful procedures, and (2) NICUs in eight European countries found poor compliance with pain management guidelines for heel stick and other invasive procedures.[262] The use of sucrose for neonatal heel lance increased by 84% after an educational intervention for NICU staff.[359]

A systematic review of eight studies for the safety and efficacy of repeated oral sucrose for repeated procedural pain found that (1) different study designs prohibited a meta-analysis; (2) repeated sucrose was effective in decreasing behavioral pain response and composite pain scores; and (3) repeated sucrose had variable efficacy in altering physiologic pain response for preterm (less efficacy in two studies) and term (less variability in one study) infants.[148] **During repeated painful procedures, combining NNS and sucrose provides better pain relief than either intervention used alone,[149] and repeated use of skin-to-skin care continues to provide pain relief for preterm infants.**[150] None of the studies reported adverse outcomes from repeated sucrose use. Neurodevelopmental outcomes were mixed and included: (1) repeated sucrose use for repeated procedural pain would not lead to poor neurologic development (two studies); (2) preterm infants less than 31 weeks' GA who received more than 10 doses of sucrose/24 hours in the first week of life had poorer neurologic outcomes than infants

⋆References 55, 212, 234, 285, 286, 329, 357, 383, 403.

receiving fewer doses; and (3) no study reported long-term neurodevelopmental outcomes. There is limited research supporting the safety and efficacy of repeated sucrose for repeated procedural pain, and multicenter, prospective, large RCTs are needed.[148]

The benefits of sucrose for pain relief have been shown to provide comfort to the infant during subsequent caregiving activities.[393] Two hundred and forty neonates were randomized to a placebo or sucrose-treated group for all needle procedures. After the painful procedure, those infants receiving sucrose reacted to a diaper change with lower pain scores than the infants receiving only a placebo. The comforting benefits of sucrose remained even after the painful procedure was complete.[393]

The Academy of Breastfeeding Medicine supports that when available, breastfeeding should be the first choice to alleviate procedural pain in neonates.[52,337] When possible, breastfeeding throughout the procedure, rather than pumped breast milk, offers more comfort because of the synergism between skin-to-skin contact with the mother, sucking, and reception of breast milk by the infant.[52] An RCT comparing breast milk with sucrose for pain relief in 71 late preterm infants (born at 32 to 37 weeks' PMA) undergoing heel lance was conducted in the Netherlands.[361] Using the PIPP assessment scale, there was no significant difference in pain scores between the preterm infants receiving breast milk (directly breastfed or bottle-fed) and those receiving sucrose. A randomized crossover study comparing expressed breast milk and oral sucrose for relief of pain associated with venipuncture found the same analgesic effect in most preterm infants; however, sucrose had better pain relief in extremely preterm infants.[92] An RCT comparing the analgesic effect of sucrose and breastfeeding during venipuncture in healthy 3-day-old newborns found equal pain relief for both methods as measured by NIRS.[338]

Salivary cortisol levels from birth to 1 year of age are 40% higher in breastfed infants compared with formula-fed infants.[79] The analgesic effect of breast milk may be a result of these higher cortisol levels.[70] **Concerns about breastfeeding as a comfort measure during painful procedures have been raised.** To explore these concerns, a study of 57 preterm infants (30 to 36 weeks' GA) were randomized to be breastfed or given a soother during a blood collection procedure.[200] **Preterm infants with mature breastfeeding skills had lower pain scores during the procedure, all breastfed infants had lower pain scores after the procedure, and use of breastfeeding as a comfort measure did not interfere with the acquisition of breastfeeding skills.**[200] A more recent study comparing breast milk and sucrose for reducing the pain of ROP examination found that preterm infants receiving 1 mL of breast milk recovered more quickly, and their vital signs returned to baseline more quickly than those preterm infants receiving sucrose.[352] Another study evaluated the use of breast milk versus swaddling versus oral sucrose to relieve the pain of ETT suctioning and found no difference between them in relieving pain.[118] Breastfeeding for immunizations lowers pain scores and heart rates, shortens the duration of crying, and prevents lower oxygen saturations.[130] When compared with skin-to-skin care and swaddling, breastfeeding was more effective than either in reducing pain of immunizations in healthy term neonates.[134]

Several studies have compared the use of glucose versus sucrose for pain relief, with conflicting results. A comparison of oral glucose versus sucrose showed that glucose solution (33% to 50%) was more effective in reducing pain response in term newborns having heel sticks.[181] Another study found that 30% sucrose solution was more effective in reducing crying time than 10% to 30% glucose solutions.[211] When (30%) oral glucose solution was given to full-term newborns undergoing venipuncture compared with (1) EMLA cream[165] and (2) subcutaneous injections,[72] the infants treated with glucose had significantly lower pain scores. **Oral glucose and facilitated tucking by parents was found to be more effective and preferred over the use of opioids in preterm infants receiving heel sticks and pharyngeal suction.**[43]

A meta-analysis of 38 RCTs found that use of 20% to 30% oral glucose solutions reduced preterm infants' pain scores and crying with both heel lance and venipuncture,[63] but was ineffective for longer procedures such as eye examnations.[103] Another more recent study of the efficacy of oral glucose (25%) versus oral sucrose (24%) use for pain relief during heel lance in 94 preterm neonates in the first 48 hours of life found comparable pain relief.[238] **Various strengths of oral glucose solutions are effective in relieving neonatal pain**: (1) a 25% solution is more effective

at relieving pain from an IM injection than NNS alone[256]; (2) 2 mL of a 10% solution relieves the pain of venipuncture and nasopharyngeal suctioning[270]; and (3) a 5% solution relieves pain, decreases crying time and heart rate, and increases oxygen saturation in preterm infants receiving IM injections.[399] Efficacy of sweet solutions to relieve neonatal pain has existed since the first trials and reviewers of a recent meta-analysis recommend that placebo/no-treatment trials be abandoned for more ethical control groups.[191]

TACTILE INTERVENTIONS

A reassuring human presence (of parents or caregivers) during painful procedures for all neonates in the NICU is *mandatory*.[47] Body containment of extremities in a flexed position (e.g., holding, swaddling, nesting; providing an opportunity to grasp a finger or pacifier) decreases gross motor movements that contribute to the infant's increased level of arousal, reduces physiologic and behavioral stress, facilitates energy conservation in the preterm infant, and lowers pain scores.[69,84,395] **When swaddling and skin-to-skin care were compared for the relief of pain during venipuncture in premature infants, pain was relieved equally between the groups when compared with the control group.**[122] **Premature infants nested in the prone position experienced lower pain scores and salivary cortisol levels after a heel lance procedure compared with nesting in the supine position.**[225] Improper body positioning contributes to discomfort and pain. An RCT combining five tactile interventions (i.e., swaddling, side/stomach lying, shushing, swinging, and sucking) for infant immunizations resulted in less crying time and lower pain scores; these outcomes were greater than those obtained with sucrose alone.[190]

Facilitated tucking—gentle containment of flexed extremities in the midline on the trunk while side-lying or supine—during a painful procedure (e.g., heel stick) results in lower heart rate, shorter crying time, less sleep disruption, and fewer sleep-state changes.[102,193,321] One study of facilitated tucking and usual positioning for heel stick found a "surprising" result: no difference between the two positions in pain intensity for the premature infants.[112] **Pairing facilitated tucking with breast milk and NNS effectively reduces pain in premature infants during heel lance.**[316] **Several studies of facilitated tucking during endotracheal tube suctioning have been conducted with the results of lower pain scores in the preterm infants receiving facilitated tucking,** when compared with no intervention.[7,261] Facilitated tucking (provided by parents for endotracheal tube suctioning) showed that participation by parents was a safe, effective pain management strategy that provided parents with an active role in their infant's pain care and was also preferred by parents.[42] A more recent study by the same researchers found **lower pain scores with oral glucose and facilitated tucking by parents during heel stick and pharyngeal suction in very preterm infants.**[43] Facilitated tucking was perceived positively by mothers who were either internally motivated to provide it or were externally motivated by nurses who suggested their involvement.[41] However, two other studies of facilitated tucking[157] and facilitated tucking and oral sucrose[89] found that using facilitated tucking alone was less effective in pain management.

Use of a 2-minute massage of the ipsilateral leg before heel stick in preterm infants was safe and resulted in a decreased pain response (decreased pain score and heart rate) compared with nonmassaged preterm infants.[214] Massage of the arms and hands of infants for 2 minutes before an invasive procedure such as heel stick or other needle stick, including venipuncture, has been shown to reduce pain scores.[84,85] A more recent pilot study of the use of vibration on the lateral aspect of the leg during heel lance resulted in lower N-PASS scores and more stable heart rate during and 2 minutes after the procedure when compared with the control group, without any physiologic or behavioral adverse effects.[274]

Motoric boundaries (e.g., containment of extremities) assist a preterm infant to maintain a more secure, controlled response and facilitate self-regulation. **Therapeutic interventions include the use of positions that support flexion and restraint in physiologic position, periodic release of restraint and exercise of extremities, gentle change in body position, and positioning to guard operative sites.** Along with comfort measures, minimizing stimulation in the NICU environment enables a neonate who is agitated or in pain to use internal and external resources in organizing his or her behavior and develop self-soothing strategies (see Chapter 13). Individualizing care and handling to the infant's likes and dislikes and listing

these at the bedside help maintain consistency of care and build trust in these developing neonates.

Picking up, holding, and rocking provide tactile soothing, vestibular stimulation, and the calming effect of rhythmic, repetitive movement. Use of massage, rocking, and water mattresses provides tactile, vestibular, and kinesthetic stimuli that modify and accelerate behavioral state control and decrease stress behaviors (see Chapter 13).

AUDITORY INTERVENTIONS

Four small studies of the use of music therapy to relieve the stress and pain of procedures evaluated physiologic and behavioral responses in a total of 75 infants.[9] In two studies, intubated preterm infants were exposed to music/no music during routine suctioning. **Positive results in the music-exposed preterm infants included (1) improved oxygen saturation, (2) heart rates between 120 and 160 beats/min for a longer period, (3) more time in sleep state, and (4) quicker recovery time after suctioning.**[64,87] Two other studies exposed irritable, agitated, infants in a naturally occurring inconsolable crying episode to music and measured their responses. Again positive results of music therapy included (1) improved oxygen saturation, (2) better respiratory and heart rates, (3) state change to drowsy or quiet alert, and (4) fewer crying episodes.[93,229] A more recent study of **recorded maternal voice played during heel lance resulted in significantly lower PIPP scores and less oxygen desaturations with no side effects in the group of preterm infants hearing their mothers' voice,** when compared with the control group.[86] **Playing the same music that mothers listened to while pregnant resulted in less pain response to heel lance in preterm infants.**[239] Breastfeeding full-term healthy neonates during a heel lance procedure effectively reduced their pain response, but the addition of music therapy did not enhance pain relief.[423] Additional data from well-designed studies are required before use of music therapy for preterm infants during painful, stressful conditions can be recommended.[9]

Combination of auditory therapies and other nonpharmacologic interventions is more effective than use of single therapies to relieve pain. A randomized study of 62 preterm infants using a combination of music and touch during painful procedures found similar cortisol concentrations at birth and at 2 weeks of life between the experimental and control groups. However, at the beginning of hospitalization and after 2 weeks, **beta-endorphin levels were higher and the PIPP scores lower in the group exposed to the combination of music and touch.**[330] **Stable neonates with a PMA of 35 weeks who were exposed to recorded music and sucrose for heel stick procedure were in less pain than when the interventions were administered separately.**[354] Preterm infant pain was relieved during venipuncture with the use of eye covering and playing intrauterine ambient sounds.[6]

COMPLEMENTARY HEALING MODALITIES

Complementary healing (e.g., therapeutic touch [TT], acupressure, acupuncture, Reiki) is gaining increasing interest among neonatal health care providers. Little research exists, but clinical reports have depicted the benefits of pain relief with integration of these modalities. A study conducted with registered nurses (RNs) who provided TT to preterm infants (25 to 37 weeks of gestation) revealed that the infants' responses to TT included (1) decreased heart and respiratory rates; (2) enhanced restful periods; (3) improved sucking, swallowing, and breathing; and (4) a greater ability to interact with the environment.[187] Two more recent studies of the use of TT with a painful procedure have been conducted. In the first study, 10 preterm infants (34 to 40 weeks' conceptual age) received TT during a low-intensity sensory punctuate stimuli and responded with an increase in cerebral oxygenation.[202] The researchers concluded that **TT may have a protective effect on the autoregulation of cerebral blood flow in the preterm infant during painful stimuli.**[202] Another randomized study of the effects of TT before and after procedural pain (heel lance) found no comforting effect for 27 preterm infants less than 30 weeks' GA.[217] These researchers recommended use of other tactile interventions for pain relief. Reiki uses healing energy to restore balance within the body. Reiki has been used for neonates experiencing neonatal abstinence syndrome without adverse effects and resulted in a slight decrease in heart rate, which may signify relaxation.[331]

Acupuncture and acupressure may be safely used to treat pain, agitation, and drug withdrawal in the neonate.[160] A retrospective review

of 10 hospitalized infants exposed to acupuncture found a decrease in the use of sedatives and analgesics for agitation, successful weaning from ventilators, and transitioning to oral intake after oral aversion without adverse effects.[153] Use of acupuncture in neonates in one NICU decreased the amount of medication needed for agitation and withdrawal, was well tolerated, and was without complications.[161] In a small RCT, acupressure before heel lance was shown to shorten the procedure and the duration of crying in preterm infants.[1] However, in another study, use of noninvasive electrical stimulation of acupuncture needles in term infants receiving heel sticks was not shown to be effective in procedural pain relief.[284] Use of noninvasive magnetic acupuncture on the outer ears of newborns (mean gestational age 34 weeks) receiving heel stick procedures resulted in lower pain scores.[82] Acupuncture used for 2-week-old to 8-week-old infants with colic resulted in less crying and less colicky crying than standard care by the second week of treatment.[247] More research is needed to validate the use of these modalities for pain management.[153]

Activation of cutaneous sensory nerves with a transcutaneous electrical nerve stimulation (TENS) unit and application of thermal topical skin refrigerant blocks transmission of peripheral pain impulses from procedural pain. Low-frequency, monotonous sounds (e.g., heartbeat, vacuums) quiet the infant and increase behavioral organization. Use of music (see Chapter 13) and recordings of family voices soothe term and preterm infants, resulting in fewer state changes, less time in the arousal state, and increased behavioral organization. However, during circumcision, music (with or without a pacifier) is not an effective distraction or soothing strategy for relief of the pain of the procedure. Another recent study showed that **preterm infants presented with a familiar odor during venipuncture exhibited significantly less crying and grimacing,** compared with the preterm infants presented with an unfamiliar odor or no odor.[164] However, scents (such as amniotic fluid, breast milk, or maternal odors) presented to premature infants during a heel stick procedure did not reduce neonatal pain scores,[233] yet **the odor of mother's own milk did decrease pain scores during venipuncture and crying after the procedure.**[46] Another RCT of preterm infants exposed to breast milk odor, or recorded maternal voice or incubator cover during peripheral intravenous cannulation found that these interventions were simple, safe, and supportive during painful procedures.[5]

END-OF-LIFE CARE

When the decision is made to terminate or not begin aggressive medical intervention, the neonate receives end-of-life care, also known as *comfort care* or *palliative care* (see Chapter 32). Neonates who receive end-of-life care are at the threshold of viability, have multiple congenital anomalies that are incompatible with life, or are not responding to NICU interventions (e.g., deterioration in condition despite medical efforts).[320,336]

End-of-life care should combine comfort measures, pharmacologic management, developmental care (see Chapter 13),[383] and spiritual and psychosocial support for the neonate and family (see Chapters 29 and 30).[77,80,320,382,383] Parents are acutely aware of (and able to recall) their infant's suffering, including perceiving the infant's pain at the end of life.[360] The family is provided a quiet, private, homelike area in which to touch, hold, and interact with their terminally ill neonate. Use of skin-to-skin care; soft, soothing music; dimmed lighting; infant massage; holding; and rocking provide both a comforting environment for the infant and family, as well as parenting and comforting opportunities.[83,383] Parents, siblings, and extended family members remain with their infant during and after death. Clergy may be present for family support and may perform a religious service, such as a baptism or blessing.

For comfort care, all invasive procedures, including measurement of vital signs, monitors, machines, and artificial feeding, are discontinued. The infant, cleaned and wrapped in a warm blanket, is held by his or her family. Intravenous access may remain in place for administration of pain medications or sedatives. **Medication is administered in sufficient doses to provide comfort, relieve pain, and ensure that the infant does not suffer at the end of his or her life.**

In the earliest study documenting the use of analgesia for dying infants whose life support was withdrawn or withheld, 165 deaths in a university-based NICU were reviewed.[313] Opioid analgesia

was administered to 84% of infants when life support was withdrawn or withheld. Infants with major congenital anomalies (93%) and necrotizing enterocolitis (100%) were more likely to receive opioids than were ELBW infants (66% to 83%). Overall, opioid analgesia was administered to at least 65% of infants. Reasons for life support discontinuation also influenced administration of opioids: (1) futility of treatment (84% medicated), (2) severe lifelong impairment (85% medicated), and (3) suffering caused by treatment (100% medicated). The median dose of opioids was within the usual pharmacologic range in 64% of infants and greater in 36%. Of the infants receiving a higher dose, 94% had previously been receiving an analgesic and may have needed a higher dose as a result of tolerance. The median time until death from the discontinuation of life support was 18 minutes for those who received the standard dose and 20 minutes for those who received the higher dose.

A recent study of end-of-life care found that 85% of infants received analgesic and/or sedative medications before the withdrawal of treatment, 55% at withdrawal and 60% after treatment was terminated.[139] The majority of medication was given by continuous intravenous medications for sedation and pain related to diagnosis. Use of nonpharmacologic interventions for end-of-life care/pain was minimally documented in this exploratory, descriptive study. If there is no intravenous access, intranasal fentanyl has also been used in palliative care with dying newborns with no complications such as chest rigidity and drug-related apnea. Neonatal restlessness and labored respiratory efforts were calmed after the intranasal fentanyl, with the average time from last dose to death of 61 minutes.[188]

A survey of hospital staff providing pediatric palliative care found that 50% of physicians and 30% of nurses reported feeling inexperienced in pain management.[99] Providers also shared how personally distressing it is to witness a child's suffering, especially when pain relief was possible but not available or delivered. In the same study, families also described their anguish in watching their child experience and suffer any amount of pain and discomfort. **Unlike the health care providers, families thought that everything had been done to alleviate their child's pain.** Another recent study found that insufficient education in pain and palliative care of pediatric care providers was a barrier to use of palliative care in children.[113]

COMPLICATIONS

A neonate's complex behavioral response to pain has both short-term and long-term ramifications (Box 12.7).

These behavioral changes may disrupt parent-infant interaction and attachment, adaptation to the postnatal environment, feeding behaviors, and growth.[29,408] **An alteration in brain development and maldevelopment of sensory systems can occur when distorted or inappropriate sensory input occurs during a critical period in development.** Because of a **neonate's memory, painful experiences increase the infant's sensitivity to subsequent medical encounters.** These initial experiences may affect the development of attitudes, fears, anxiety, conflicts, wishes, expectations, and patterns of interactions with others.*

Younger infants are more susceptible to long-term consequences (see Box 12.7) because there is heightened sensitivity at earlier developmental stages. In the most immature preterm infants, lower pain thresholds and the lack of inhibitory controls influence hypersensitivity.[171] **When tissue injury occurs early in development, increased pain sensitivity develops both at the site of the damage (primary hyperalgesia) and in the surrounding skin (secondary hyperalgesia) because of hyperinnervation at the site.**[171,319] The lower pain threshold of the more preterm infant is also influenced by repeated exposures.[171] The consequences of this altered excitability include (1) perceiving nonnoxious tactile stimuli as noxious,[9] depending on the number of invasive procedures in the previous 24 hours[175]; (2) systemic responses of chronic pain and discomfort; (3) associating earlier pain with decreased behavioral responses to pain; (4) variable physiologic responses[171]; and (5) lower pain thresholds, pain tolerance, and higher pain intensity in adolescence.[65,404] **Ongoing studies demonstrate the importance of infant and family factors (Fig. 12.8) in ameliorating developmental alterations initiated by early and repeated pain exposures.**[171]

*References 19, 21, 33, 61, 62, 139, 179, 183, 184, 271, 303, 321, 327, 337, 346, 373, 391, 394, 397, 406, 419.

BOX 12.7 LONG-TERM CONSEQUENCES OF REPETITIVE PAIN*

- Less physiologic stability (e.g., alterations in heart and/or respiratory rates and blood pressure)
- Less postnatal growth (less weight gain and lower head circumference) in very preterm infants[401,408]
- Alterations in basal cortisol levels in extremely low gestational age preterm infants at 8 and 18 months that suggests a "resetting" of the endocrine stress systems with potential for negative implications for neurodevelopment and later health
- Cortisol dysregulation associated with lower IQ in 7-year-old boys born very preterm (but not girls) who have the brain-derived neurotropic factor gene variant[81]
- Alterations in cerebral blood flow,[266] increasing the risk for intraventricular hemorrhage and periventricular leukomalacia; altered white matter microstructure[370]
- Significantly thinner cerebral cortex, predominately in the frontal and parietal lobes[333,370]
- Inappropriate sensory input (pain) disrupts neural activity, and chronic activation of neuroendocrine system results in abnormal brain development.
- In extremely preterm neonates, disrupts the development of brain regions involved in somatosensory processing (i.e., thalamic volume loss; reduces thalamocortical maturation), which results in poor cognitive and motor function at 3 years corrected age.[126]
- Hyperinnervation (e.g., neural reorganization in the periphery and the spinal cord) associated with increased pain behaviors such as allodynia and hypersensitivity
- Altered pain responsiveness:
  - Heightened responsiveness to pain (hyperalgesia)/lower pain threshold
  - Decreased responsiveness to pain (associated with more exposure to painful experiences) in the NICU and later in infancy and childhood
- Reduced tolerance, and lower pain thresholds and higher pain intensity in adolescence (after being born preterm)[404]
- Altered behavioral and neurodevelopment[94,163]
- Temperamental difficulties at 3 months of age[287]
- Altered hypothalamic-pituitary-adrenal (HPA) axis function up to school age in children born very preterm, especially in males.[60]
- Shortening of telomere (region of repetitive nucleotide structure at each end of a chromosome) length in very preterm infants that is associated with repeated NICU pain and stress[327]

* References 19–28,33,62,95,138,139,172–174,179,183,184,271,303,320,327,345,353,372,389–393,396,405,417,418

Alteration of parent-infant interactions and relationships; temperament and pain expression

NICUs with a higher level of infant pain management are associated with better neurobehavioral performance (i.e., better attention and arousal, less lethargy, and better reflexes as measured by the NICU Network Neurobehavioral Scale [NNNS]) in very preterm infants.[286] Studies to evaluate the long-term effects of pharmacologic and comfort interventions are also needed.[61,171,182,183,278,334,408]

As mentioned, unanesthetized surgery and/or unrelieved pain causes suffering that might itself be a risk to life.[29] Maintaining metabolic homeostasis by the appropriate use of anesthetics and analgesics improves postoperative outcome by preventing (1) protein wasting, (2) electrolyte imbalance, (3) impaired immune function, (4) sepsis, (5) metabolic acidosis, (6) pulmonary and cardiac insufficiency, (7) hypermetabolic state, and (8) death.[17,30,120,158] **Increasing evidence confirms that exposure to prolonged, severe, or untreated pain increases morbidity and alters brain development and subsequent behavioral and physiologic responses to pain.**[13,16,19,20,22,29,66,138,172,268,408]

Opioid analgesics may produce respiratory depression severe enough to require mechanical ventilation. Naloxone (0.1 mg/kg IV or IM) is the specific antidote for opioid overdose (see Table 12.13). Lower doses of naloxone (0.001 to 0.01 mg/kg IV or IM) can be used for moderate respiratory depression. Complete opioid reversal with 0.1 mg/kg naloxone increases agitation and stress response in neonates with ongoing pain. Subsequently, it is more difficult to manage the neonate's pain until the effects of the naloxone wear off. **Lower doses of naloxone should be used and the dose titrated to prevent this outcome. An ampule of neonatal naloxone should always be immediately available with the appropriate dose precalculated on the infant's emergency card. Flumazenil is a specific antagonist for the benzodiazepines and should be used to treat respiratory depression (see Table 12.13). Respiratory depression may produce hypoxemia, so a pulse oximeter should be standard equipment along with cardiorespiratory monitoring.**[13,384] **All equipment for assisted ventilation should be at the bedside.**[13]

An overdose of local anesthetics can cause seizures, ventricular tachycardia, bradycardia, and cardiovascular collapse. Toxic doses for

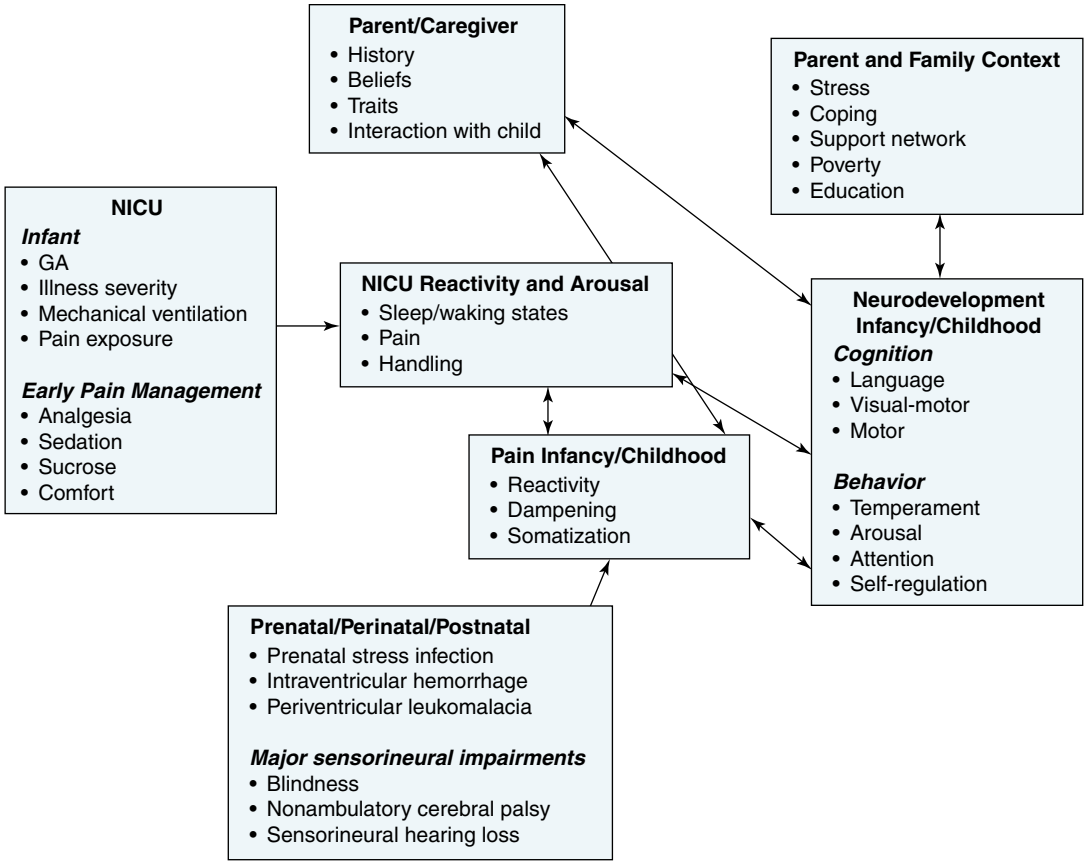


FIGURE 12.8 Model of long-term effects of pain showing complex, interactive, bidirectional relationships among multiple biologic and environmental factors. *GA,* Gestational age; *NICU,* neonatal intensive care unit. (From Grunau R. Early pain in preterm infants: a model of long-term effects. *Clin Perinatol.* 2002;29:376.)

neonates should be carefully calculated, and lower doses should be administered. Benzodiazepines or phenobarbital can be used to treat refractive seizures; cardiopulmonary resuscitation (CPR) and defibrillation may be necessary to treat cardiovascular complications. **Administration of intralipids 20% in a dose of 1 to 2 mg/kg/day is a specific antidote for cardiac toxicity from local anesthetics. Patients who are receiving epidural analgesia for postoperative pain control should be monitored for signs of potential CNS toxicity** (e.g., irritability, jitteriness, twitching, myoclonic jerking). If an opioid is being administered with the local anesthetic infusion, then respiratory depression is also a possibility, and patients should be monitored as described. Clonidine in the epidural infusion can lead to hypotension and decreased heart rate. Other extremely rare complications of epidurals are nerve injury and/or paralysis.

Hematoma formation can occur (1.2%) with the placement of a dorsal penile nerve block. Using a ring block usually avoids this problem. **Epinephrine-containing solutions must *never* be used, because this can lead to compromise of the blood supply to the penis and severe tissue damage.**

Tolerance and Withdrawal

***Tolerance* is the need for escalating doses of drug to achieve the same effect.** Tolerance (1) occurs sooner with the use of synthetic opioids (e.g., fentanyl) than with naturally occurring opioids (e.g., morphine); (2) is related to the duration

of use—the longer the use (>5 days),[25] the more likely tolerance is to develop (use for less than 72 hours usually is not associated with tolerance); (3) develops more rapidly with continuous infusions versus intermittent therapy; (4) may develop more rapidly in preterm neonates than in term neonates; and (5) occurs more often in males than in females.[24,383,384,405]

Physical dependence **is the state in which continued drug is needed to prevent the signs of withdrawal.**[405] Withdrawal arises when discontinuing the drug causes symptoms such as irritability, diarrhea, tachycardia, hypertension, insomnia, restlessness, diaphoresis, or palmar sweating and muscle twitches. **Addiction occurs when there is psychological and physical dependence** and is associated with active drug-seeking behavior and use (abuse) of the drugs for nonmedical conditions. **Infants are incapable of this level of cognition and therefore cannot become addicted to analgesics and sedatives.**[160,373] Tolerance, dependence, and withdrawal can occur with opioids and benzodiazepines. **Medications should not be restricted because of fear of addiction. Family members should be made aware of this.**

Critically ill infants sometimes need long-term infusions of opioids or benzodiazepines to provide analgesia and sedation. ECMO and prolonged mechanical ventilation are two examples of this situation. Use of fentanyl for more than 5 to 7 days can lead to tolerance and withdrawal (also known as *opioid abstinence syndrome;* see Chapter 11). **Tapering doses to wean neonates from opioids will depend on the duration of the medication's use and the infant's response to the changes.** For short-term use, decrease opioid dose by 25% to 50% of the drug dose per day, so that the drug is discontinued within 2 to 3 days. For longer opioid use, decrease doses by no more than 10% to 20% every 1 to 3 days. Infusion regimens can be changed to intermittent administration before the drug is discontinued.[384] **Oral forms of opioids should be used whenever possible.** Shorter-acting medications such as fentanyl and midazolam can be switched to methadone and lorazepam, which have the advantage of being longer acting and being available in an oral form. **Addition of oral clonidine 1.5 to 3 mcg/kg twice daily can help alleviate withdrawal symptoms. The dose of clonidine can be titrated up to 5 to 10 mcg/kg twice daily as tolerated.** The side effects of clonidine include bradycardia, hypotension, and sedation. In addition, minimal handling and a quiet, darkened environment help decrease external stimuli. A pacifier, swaddling, and holding are effective comfort measures.

PARENT TEACHING

Mothers of neonates in the NICU report dissatisfaction with pain management, worry about their infant's pain and pain management, and a desire to participate in comforting their distressed infants.[141,145,392] A multicenter international study is the first to provide a comprehensive description of parental concerns, distress, information needs, and involvement in care of their infant in pain.[141] Both mothers and fathers from 11 NICUs participated in completing questionnaires: (1) both parents reported a moderate degree of stress; (2) stress responses were slightly higher for mothers; (3) mothers' stress was related to the sights and sounds of the NICU and their inability to perform their maternal role; and (4) mothers reported higher anxiety levels. Specific parental concerns about pain included (1) effects of pain on the infant, (2) immediate medical problems caused by pain, and (3) long-term effects of pain. Parents reported few worries about the effects of pain medications. Parents rated their infant's worst pain as moderate to severe and had expected there to be less pain and that their infant would receive a high degree of pain relief.

Pain management is a priority concern for parents. Seeing their babies in pain and being unable to protect them from pain is very stressful.[223] A recent study found that when preterm infants are exposed to a greater number of invasive procedures, their mothers' memories of their infant's pain during these procedures is associated with increased PTSD symptomatology.[409] Comparing maternal and paternal responses of their knowledge, self-efficacy, and satisfaction with their infant's pain management in a single NICU resulted in findings of adequate knowledge by parents, moderate to high self-efficacy, and satisfaction with their infant's pain management.[406] **The majority of parents in this study preferred to receive written information about pain and wanted the opportunity to be present and comfort their infant during and after painful**

procedures.[406] Another study found that 97% of surveyed parents accessed the Internet daily, preferred the Internet for information rather than books or brochures, and wanted more information on how they could comfort their infant and more participation in comforting their infant during painful procedures.[308]

An RCT to increase parental involvement in pain management for their NICU infants was conducted to evaluate reduction in parental stress and postdischarge parenting ability.[144] Although NICU-related stress was not reduced, parents who received information about pain and comforting techniques were better prepared to be active participants in their infant's pain care and have more positive views about their parenting role after discharge.[144]

Parents in two studies received primarily verbal information (i.e., 81%[145] and 58%[142]) rather than any written (4%)[142] information about pain and pain relief. Nurses (41%), more commonly than physicians (28%), provided information about pain to parents.[142] Although parents were usually satisfied with the pain information they received, 30% indicated that they wished they had received more information about infant pain.[142] Fifty percent of parents reported that they were shown how to recognize if their infant was in pain and how to provide comfort.[145] In the more recent study, 18% of parents were shown how to assess pain in their infant, and 55% were shown how to comfort the infant.[142]

In the multicenter study, 57% of parents reported that they would prefer to be with their infant during procedures.[145] Yet most parents had never (52%) or not often (24%) been asked about their preference. Parents who would have preferred to be absent during procedures reported higher stress levels, anxiety, and current worry about pain for their infant than did parents who preferred to be present. **Eighty-seven percent of parents stated that they wanted greater involvement in their infant's pain care.** Generally, the parents in this survey reported a high level of satisfaction with their infant's pain care.[142]

Parental stress was related to (1) their estimation of infant pain, (2) their worries about infant pain, and (3) their degree of satisfaction about information about infant pain care.[142] The influence of these factors on the degree of parental stress were "strikingly consistent" among the diverse NICUs in the study. More research is needed to determine whether (1) more parental information, involvement, and satisfaction with pain care reduces parental stress; (2) greater parental involvement in pain care improves parent-infant attachment, interaction, competence, and confidence after discharge; (3) culturally and socially diverse families respond similarly; and (4) barriers exist to providing more parental information and facilitating more involvement.[142]

The lack of information (Box 12.8) and passive involvement of parents in pain care for their infant[12,142,323,362] should be addressed in the NICU. Parents are excellent observers of their infant and often recognize when the infant is experiencing pain, even before the care provider does.[276] The health care provider loses credibility and parental trust when he or she does not acknowledge and effectively treat the infant's pain.[276] Listening to parents' concerns about their

BOX 12.8 PARENT/CAREGIVER TEACHING
PAIN IN NEWBORNS

- The body that is in pain is "stressful" to the infant.
- The body that is in pain cannot grow, cannot heal, and may not survive.
- Newborn infants, both full-term and preterm, feel pain in the NICU. Remember that pain (and repeated pain) may have long-term consequences.
- Newborns in the NICU deserve to have their pain assessed, adequately treated with medications and comfort measures, and re-evaluated to determine whether the therapies have relieved their pain.
- Newborn infants, both full-term and preterm, ***do not*** become "addicted" to medications that are used for pain relief, although they may develop tolerance and withdrawal, which can be managed by the health care provider.
- Comforting distressed infants and children is basic to the maternal/paternal role.
- No research or reports have documented a newborn forming a negative association with the mother/parent while she or he was providing comfort during a painful event.
- Research shows that skin-to-skin contact with the mother before, during, and after a painful procedure decreases the pain response in preterm and full-term infants.[168,355]
- Breastfeeding full-term and preterm newborns before, during, and after a painful procedure markedly decreases their pain response (e.g., crying, grimacing, less tachycardia).[167,355] Other nonpharmacologic interventions that can be used by parents include NNS, oral sucrose, facilitated tucking, swaddling, and recorded music.[122,323]

infant's pain, including the parents' report of their assessment, communicating the plan of care about analgesia or sedation, and offering the rationale behind the medication decision-making help the parents become active participants in the management of their infant's pain.

Parents of medically fragile infants have identified specific sources of stress in the NICU: (1) parental role alterations, especially inability to comfort the infant, and (2) infant appearance and behavior, especially pain and difficulty breathing. **The most common fear expressed by parents is that their infant will experience undue pain while being cared for in the NICU.** Three years after their infant's NICU experience, mothers can still recall the pain and procedures that their infants endured.[417] The care provider's sensitivity to the neonate's pain and advocating for pain relief are comforting for parents.[141,276,415] Teaching parents to report their assessments and encouraging parents to comfort their infants will help them in the attachment process and foster a trusting relationship with the health care team. **Comfort measures are ideally provided by parents, who may then actively participate in their infant's pain relief.**[12,40,47,105,144,323]

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RESOURCE MATERIALS AND WEBSITES

American Chronic Pain Association at www.theacpa.org or 1-916-632-0922.

American Nurses Association. *Pain Management Nursing Scope and Standards of Practice*. 2nd ed. Washington, D.C: ANA; 2017.

American Pain Foundation at www.painfoundation.org or 1-888-615-PAIN.

American Pain Society at www.ampainsoc.org or 1-847-375-4715.

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City of Hope. City of Hope/Palliative Care Resource Center at. www.cityofhope.org/prc.

Continuing education for professionals at www.painedu.org.

Dannemiller Memorial Education Foundation at www.pain.com.

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End-of-Life Nursing Education Consortium (ELNEC): *ELNEC Pediatric Palliative Care Training Program—a comprehensive national program to improve end-of-life care for neonatal and pediatric patients* at www.aacn.nche.edu/ELNEC.

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Meldrum M, ed. *Opioids and Pain Relief: A Historical Perspective*. Seattle, WA: International Association for the Study of Pain Press; 2003.

Mogil J, ed. *The Genetics of Pain*. Seattle, WA: International Association for the Study of Pain Press; 2004.

Partners for Understanding Pain at www.theacpa.org or 1-800-533-3231.

Pediatric Pain Sourcebook at http://painsourcebook.ca/index.html.

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13 THE NEONATE AND THE ENVIRONMENT IMPACT ON DEVELOPMENT

SANDRA L. GARDNER AND EDWARD GOLDSON

For centuries, the newborn baby has been considered a tabula rasa—a blank slate on which parents and the world "write" to create the individual. In the first half of the 20th century, research emphasized the contributions of the environment in shaping the infant and child. Only recently has the individuality of the infant been recognized as a powerful shaper of the caregiver, the care given, and thus the environment.

This chapter explores the psychosocioemotional development of term and preterm neonates. **Infant development is a reflection of the dynamic relationship between endowment and environment.** Understanding of the dynamic relationship between endowment and environment is enhanced by a review of the principles of development in Box 13.1. First, the developmental tasks of infancy are presented, along with the influences of endowment and environment on mastery. Home and family life, in which most infants are raised, is then contrasted with the experiences of babies in the neonatal intensive care unit (NICU). Intervention strategies to normalize the NICU environment also are presented, along with strategies for parent teaching. The developmental and social outcomes of infants exposed to the NICU are then presented.

DEVELOPMENTAL TASKS OF THE NEONATE AND INFANT

Neonates begin extrauterine life able to attend with their sensory capabilities, communicate with their environment through a complex repertoire of behaviors, and store remembrances. Infancy (birth to 12 months) is the time of further development and maturation of these capabilities through self-mastery and adaptation to the extrauterine environment.

Biorhythmic Balance: The Primary Developmental Task of Newborns

In utero, the fetus depends on the mother's physiologic systems to regulate its own systems. At birth, the neonate's basic physiologic needs (i.e., feeding, elimination, cleaning, heat balance, stroking, communicating) are met in new and different ways. The process of emerging from a physiologically dependent state as a fetus into a physiologically independent neonate introduces new variables for both mother and infant in the development of their extrauterine relationship.

The primary task of newborns is to establish independent biorhythmic balance by stabilizing the function of sleep-wake cycles, respiratory and heart rates, blood chemistry levels, metabolic processes, and eating patterns. Biorhythmic balance is the establishment of innate, cyclic recurrence of biologic functions. **Although biorhythmic balance is internally determined, caregiving interaction between newborn and parent or caregiver either facilitates or disturbs this transition.**[334] After birth, this balance is facilitated by contact with familiar surroundings (the mother's body) (see Chapter 5).

When immediate recontact between the neonate and the mother is not possible (e.g., when the mother refuses or is ill) or when the neonate is

BLUE type highlights content that is particularly applicable to clinical settings.

BOX 13.1 PRINCIPLES OF DEVELOPMENT

- Development is a continuous process of increasing complexity from conception to maturation (i.e., development also occurs in utero).
- Growth (i.e., number and size of cells) and development are influenced by genetic traits and environmental experiences.
- Development occurs in an orderly sequence largely determined by readiness or maturation.
- The sequence of development is the same in all children; the rate of development is individual.
- Development is cephalocaudad (head→foot), centripetal (from the outside toward the center), and from gross to specific (e.g., peripheral→central→lateralization).
- The first 5 years are marked by a rapid period of growth of all body systems. During this time, behavior patterns are developed and are greatly influenced by the environment.
- Environmental stimulation influences conceptual development and has an effect on cognitive function.
- Learning occurs when behavioral change does not result solely from maturation; learning is facilitated by reinforcement of the behavior through experience.
- Development of the infant occurs within the framework of interaction with a caregiver and the family.
- Equifinality postulates multiple paths to the same developmental outcome: complex developmental patterns rather than simple development milestones.

Modified from Barnard K, Erikson M. *Teaching Children With Developmental Problems.* 2nd ed. St Louis, MO: Mosby; 1976; Illingworth RS. *The Development of the Infant and the Young Child.* 5th ed. Edinburgh, UK: Churchill-Livingstone; 1972.

preterm or sick and requires immediate emergency medical intervention or transport, the primary "mothering" role is temporarily transferred to professional (medical and nursing) care providers. Interactional dynamics necessary for reestablishing biorhythmic balance and fostering the psychosocioemotional development of the newborn also are transferred into the NICU.

Just as in a home or family setting, the infant's personality and behavioral development are affected by the nature and dynamics of the stimuli and relationships encountered with the staff in a nursery or NICU setting. The level of function or dysfunction in the biorhythmic balance affects the neonate's long-range outcomes and is interwoven with the development of a sense of self and a basic trust.

Sense of Self

In utero, the fetus has continuous tactile-kinesthetic stimulation that contributes to the development and maturation of the central nervous system (CNS) and establishes kinesthesis as the most natural pathway for growth and development. The interaction between infants and the extrauterine environment also is kinesthetic. However, tactile contact and vestibular stimulation are also essential for (1) the development of a physical identity (body image), (2) organization and sorting of stimuli, (3) coordination of sensorimotor skills, (4) a psychological and social sense of self, (5) normal neurophysiologic development (physical and cognitive abilities), and (6) emotional stability and temperament.[52]

Daily caregiving and interactions such as feeding, diapering, holding, and playing with the parent or caregiver provide infants with reciprocal stimuli for further developing their identity. Through the manner in which the infant is handled, he or she receives messages about how the caregiver feels about him or her.

Response cues given by an infant affect the caregiver's response to and interaction with the infant.[52] As the infant quiets in response to caregiving, the parent is positively reinforced to continue nurturing and soothing behavior. Withdrawal, irritability, or continuous crying is perceived by the caregiver as rejection or inadequacy and may result in parental frustration, depression, withdrawal, and decreased interaction. Repeated exposure to the caregiver's style and nonverbal messages thus enables the infant to adapt to these patterns of caregiving. **The self of the infant is formed through interaction with people and objects within the environment.**

Because the nature (amount and type) of the kinesthetic interaction between infants and caregivers influences how infants develop and mature, a lack of appropriate stimulation can have long-term negative consequences. **Stimulus deprivation results in impairment or retardation of, or deviancy in, skill development for productive living.** The degree or extent of impairment depends on the severity of the restrictions and limitations encountered.[52,392] Institutionally reared infants who had minimal contact and no social interaction with their caregivers displayed significant developmental delays.[344] The effect of kinesthetic deprivation was seen in the minimal expression of social skills

(e.g., cooing, babbling, crying), minimal interest in objects in the environment, increased self-stimulation (rocking), touch aversion, flat or withdrawn affect, and retarded mental and motor development. **Environmental deprivation may also affect the physical growth of the infant.** Montagu[287] stated that infants can overcome mental and nutritional deprivation as long as they are not deprived of tactile stimulation.

The Psychosocial Task: Trust Versus Mistrust[122]

Trust versus mistrust in self and the environment is solidified during infancy.[52,122] The response of the environment from the moment of birth is the means through which neonates continue to develop trust in themselves and decide on the reliability of their new environment. **Two major factors influence the development of trust versus mistrust: (1) the infant's ability to communicate needs to the environment and (2) the reliability and contingency of the responding environment.**

In the course of routine caregiving, an infant associates the caregiver with either comfort and trust or lack of need satisfaction and mistrust. The infant cries to communicate a need (e.g., "I'm hungry"; "I'm wet"). The caregiver responds to the infant and meets the need—the infant is fed; the diaper is changed. Thus, the newborn learns to communicate when the need arises again, because the environment or caregiver has responded and will respond. **This *contingent response* of the caregiver to the infant's need is the necessary reinforcement for the development of trust in self, others, and ultimately humankind.** As a result, the infant develops a sense of mastery over his or her world and a sense that it is okay to experience needs and that they will be met.

Caregiving that ignores or delays needs gratification is noncontingent on the infant's cues for care. Need meeting that is externally defined by the caregiver's agenda (e.g., feeding schedule, rigid or inflexible routines, medical or nursing procedures in the NICU) discourages the infant from being aware of and experiencing needs and communicating them. Such infants eventually detach themselves (emotionally and kinesthetically) from the sensation of their needs, thus no longer experiencing or communicating them.[53]

As a result, these infants conclude that they and their needs (which they perceive as one and the same) are not important and that they have no effect on their environment. They do not cultivate their sense of self or their own existence, physically (where their boundaries end and another's begin) or psychologically (their identity, which exists independent of another).

Survival depends on the caregiver's meeting the newborn's needs. Need meeting is either contingent on the infant's cues or noncontingent on an external agenda. **The degree of the mother's emotional investment and connectedness with the newborn will determine the nature and quality of the caregiving.** Likewise, the temperament and responsiveness of the infant will affect the mother's feelings of competence, success, and emotional connectedness to her infant.[53] This relationship facilitates the ongoing development of a good sense of self (e.g., esteem, confidence, emotional security) and mastery of the world. **Caregivers who do not perceive infants as individuals do not respond to their "need cry" or interact with them during caregiving.** This style fosters the development of mistrusting, suspicious, helpless, emotionally insecure, and isolated children and adults.

ENDOWMENT

Infants possess innateness and individuality. **Primitive reflex behaviors, higher cognitive abilities, temperament, and sensorimotor competencies are the endowment of the individual infant.** Individual variation and use of these endowments are influenced by the environment of the newborn.

Even before conception, the genetic endowment of the parents and preceding generations affects the fetus or newborn. Everything that the individual will inherit from his or her parents is determined at the moment of conception. Of the vast number of possible combinations of chromosomes, chance determines which characteristics the individual receives. Thus each individual, except monozygotic twins, is genetically and biologically different from every other person. Either a faulty gene (e.g., sickle cell anemia) or an altered number of chromosomes (e.g., Down syndrome) is responsible for inherited defects (see Chapter 27).

Although after the moment of conception, hereditary endowment can never be changed, it is influenced by the intrauterine environment. Some birth defects are caused by teratogens or poisons—any environmental agent (e.g., drugs, virus, chemical, pollutant) that interferes with normal fetal development. An individual's potential for growth and development is strongly influenced by his or her genetic endowment. As Montagu[287] stated, "Genetic endowment determines what we can do—environment what we do do."

The exact influence of genetics for most psychological traits is unknown. Introverted (timid, shy, withdrawn) and extroverted (active, friendly, outgoing) personality types may be partially genetically controlled. The degree to which intelligence is inherited is currently unknown, although the intelligence of children is most often similar to parental intelligence (i.e., intelligence is more similar between child and biologic mother than between child and adoptive mother).

Freedman[145] studied newborns of many ethnic groups to determine whether there were any similarities in disposition within the group or differences from other ethnic groups. He found that Chinese American newborns were more adaptable, less irritable, and easier to console than white American newborns. Maneuvers such as the Moro and covering the face with a cloth elicited different responses, depending on the newborn's ethnic origin.

The same environmental stimuli elicit different behavioral responses, which are individual and genetically influenced. These genetically influenced behaviors are also influenced by environment—both internal and external. Thus, an individual may be more vulnerable to or more resilient in a specific environment. Therefore, we are totally endowment and totally environment (100% endowment + 100% environment = an individual).[145]

Temperament

Parents often notice behavioral differences in their children from the first day. These differences are obvious in motor activity, irritability, and passivity. Some infants are quiet and placid, others are irritable and easily upset, and others are somewhere in between (Table 13.1). These temperamental qualities enable the following three basic types of infants to be identified:

- The "easy" child, who is seen as regular, pleasant, and easy to care for and love
- The "difficult" child, who is difficult to rear and reacts with protest and withdrawal to strange events or people
- The "slow to warm" child, who reacts with withdrawal or passivity to new events

Neurologic Development

Brain growth of the fetus and newborn occurs in two stages.[109]

STAGE I

Stage I is from 10 to 18 weeks of pregnancy. **The number of nerve cells that the individual has develops during this period.** Any environmental perturbation (e.g., maternal malnutrition, medications, infections) that affects brain growth during this stage also may affect neonatal behavioral responses.

STAGE II

Stage II is from 20 weeks' gestation to 2 years of age. This period marks a brain growth spurt and is the most vulnerable period of growth of the dendrites of the human cortex.

The maturity of an infant is reflected in his or her behavior. Infants of a younger gestational age have less mature responses than infants of an older gestational age. A neurologic assessment of the newborn includes evaluation of (1) newborn reflexes, (2) neonatal states, (3) psychosocial interaction, and (4) sensory capabilities. The neonate is born with behaviors that are unlearned, instinctual, and of an adaptive and survival nature. They reflect the state of the nervous system and the level of neonatal maturation (Table 13.2). Serial testing of reflex behavior gives more reliable data than one observation. Observations indicative of major deviations include asymmetry—total absence or no response on one side or in upper versus lower extremities.

Psychological Interaction and Neonatal States

For years, newborn behavior was thought to occur only on a reflexive, instinctual level. Through the work of Brazelton[57] and

TABLE 13.1 CRITICAL FINDINGS
Behavioral Categories Descriptive of Individual Temperament

TEMPERAMENTAL QUALITY	RATING
Activity level	*Low*—Decreased movement when dressed or during sleep *High*—Increased movement when asleep; increased wiggling and activity when diaper changed
Rhythmicity	*Regular*—Establishes own feeding; sleep and bowel movement patterns are fairly predictable *Irregular*—Amounts of sleep, feeding variable; "no 2 days are alike"; no pattern established
Approach and withdrawal	*Positive*—Eagerly tries new foods, interested in new surroundings and people *Negative*—Rejects new foods, new toys, and new environments; apprehensive, cries with new people
Adaptability	*Adaptive*—Little resistance to first bath; may enjoy bath *Nonadaptive*—Startles easily; resists diapering, bathing, and other manipulating
Quality of mood	*Positive*—Pleasant, easygoing disposition; easy to comfort; smiles *Negative*—Fussy; cries easily and is not easily comforted by external stimuli; unable to comfort self easily
Intensity of mood	*Mild*—No crying when wet; frets instead of crying when hungry *Intense*—Vigorously cries; rejects food
Sensory threshold (intensity of stimulus necessary to elicit a response)	*High*—Not startled or interested by noise or other stimuli *Low*—Noise, activity, or other stimuli enough to interrupt infant's behavior
Distractibility	*Distractible*—Rocking, pacifier, toy, voice, music decrease fussing *Nondistractible*—No stimuli decrease distress until need is met—food; stop changing diaper; bath over
Attention span and persistence	*Short*—Cries when awakened but stops immediately, mild objection if needs are not immediately met *Long*—Repeatedly rejects substitutions for perceived needs (no pacifier until diaper is changed; no water if milk is wanted)

Data from Thomas A, Chess S. *Temperament and Development.* New York: Brunner-Mazel; 1977.

TABLE 13.2 CRITICAL FINDINGS
Neonatal Reflex Behaviors

BEHAVIOR	BEGINS (IN UTERO) (WK)	INTEGRATES
Protection		
Moro reflex	28	At 6–8 mo to allow sitting and protective extension of the hands
Palmar grasp	28	At 5–6 mo to allow voluntary grasping of objects
Plantar grasp	28	At 7–8 mo with foot rubbing on objects; complete at 8–9 mo for standing and walking
Babinski reflex	28	Same as for plantar grasp
Tonic neck reflex	35	At 4 mo, so rolling over and reaching or grasping may occur
Gag[a] reflex	36	Protects against aspiration—does not disappear
Blink reflex	25	Does not disappear
Crossed extension	28	Disappears around 2 mo of age
Survival		
Rooting[a]	28	At 3 mo; decreased response if baby is sleepy or satiated
Sucking[a]	26–28	Not yet synchronized with swallowing
Swallowing[a]	12	32–34 wk, stronger synchronization with sucking; perfect by 34–37 wk

[a]Although isolated components of feeding behaviors are all present before 28 weeks' gestational age, they are not effectively coordinated for oral feedings before 32–34 weeks' gestational age.[154,278,378] Coordination of respiration with sucking and swallowing during bottle feeding is consistently achieved by infants more than 37 weeks' postconceptual age.[63]

others, newborns have been shown to have the ability to interact with and shape their environment. With the Neonatal Behavioral Assessment Scale (NBAS),[57] care providers can observe and score the interactive behavior of newborns. The NBAS enables **assessment of the infant's individual capabilities for social relationships rated on the infant's best performance.** Six categories of abilities are considered in evaluating an infant's performance: habituation, orientation to auditory and visual stimuli, motor maturity, state changes, self-quieting ability, and social behaviors.

Response decrement (i.e., *habituation*) is the protective mechanism through which a fetus or infant decreases responsivity to external stimuli. Habituation represents the cerebral behavior of memory—the fetus or infant stores the memory of the stimulus and, with repeated presentation, learns not to respond.[387] Infants who are able to habituate are not interested in nonnovel repetition in the environment and protect themselves from overstimulation.

Infants who become "bored" with their toys have habituated to them—infants like variety. *Dishabituation* **represents increasing attention to a new stimulus (e.g., new mobile, toy, face) after habituation to an old stimulus.** The fetus or infant thus "recognizes" the novelty of the new stimulus and chooses to respond.

An infant who is unable to habituate will continue to react vigorously to the same stimuli. Compared with term infants, preterm infants are more reactive (e.g., less able to control their level of excitation) and less able to self-regulate (e.g., modulate reactivity, reflected in habituation rate and self-soothing abilities).[115] **Very-low-birth-weight (VLBW) infants are less able to (1) modulate attention, (2) take brief breaks from processing information, and (3) habituate to stimuli.[115] Thus the preterm is less able to deal with multiple sources of stimuli and is easily overstimulated.[6]**

Neonates are able to imitate the facial and manual gestures of adults.[280] Infants as young as 12 days imitate gestures such as mouth opening and tongue protrusion. Because a neonate has never seen his or her own face, this innate ability to match behaviors to those of another is a remarkable use of the cerebral cortex. Imitation may operate as a positive feedback mechanism to caregivers; thus it is significant in parent-infant reciprocity and represents early learning behaviors.

Learning, a function of the cerebral cortex, occurs with habituation and imitation. Early cognitive development is important to later learning and future cognitive function. Learning occurs in the context of experience and influences structural maturation; there is marked CNS development during the first 2 years of life.[57,109]

State of consciousness influences the reactions of a newborn to internal and external stimuli. The infant's state at the time of observation must be considered in interpretation of the findings (Table 13.3).

Clinical application of the NBAS includes evaluation of infant capabilities after illness, prematurity, or maternal medications. **The most important application of the NBAS is in anticipatory guidance for parents.** Demonstration of parts of the examination for parents enables them to become familiar with their infant's individual patterns of behavior, temperament, and states.

Circadian Rhythm

Circadian rhythms are cyclic variations in function that occur daily at about the same time. **Humans cycle their bodily functions (e.g., temperature, hormonal changes, blood pressure, urine volume, salivary cortisol secretion, sleep-wake cycles) in a 24-hour period.[190,358,359]** These daily fluctuations are innately controlled by the individual's "biologic clock" in the suprachiasmatic nuclei (SCN) in the anterior hypothalamus. The SCN are located at the base of the third ventricle, above the optic chiasm. The circadian pacemaker must be reset daily by the relay of photic (light) information from the retina to the SCN, along the direct pathway from the retinohypothalamic tract (RHT) to the SCN.[358] During the 18th week of prenatal life, the SCN form and continue maturation after birth. In utero, the fetus expresses endogenous circadian rhythms (in heart/respiratory rates and steroid secretion) that are influenced by the mother.[358] The RHT has been identified in human newborns of 36 weeks' gestation; SCN are functionally innervated by the retina at stages equivalent to 25 weeks after conception in human infants.[358]

In infants, the development of circadian rhythm is influenced by genetic factors, gender, brain maturation, and the environment.[358-360,416]

TABLE 13.3 **CRITICAL FINDINGS**
Newborn States and Considerations for Caregiving

NEWBORN STATE	COMMENTS
	SLEEP STATES
Deep sleep (non–rapid-eye-movement [REM] or quiet sleep): Slow state changes Regular breathing Eyes closed; no eye movements No spontaneous activity except startles and jerky movements Startles with some delay and suppresses rapidly Lowest oxygen consumption	Infant is difficult if not impossible to arouse. Infant will not breastfeed or bottle feed in this state, even after vigorous stimulation. Infant is unable to respond to environment, which is frustrating for caregivers. Term infants may exhibit a "slow" heart rate (80–90 beats/min), which may trigger heart rate alarms and result in unnecessary stimulation by NICU staff. At birth, preterm infants have altered states of consciousness. Early dominant states are light sleep, quiet, and active alert. "Protective apathy" enables the preterm to remain inactive, unresponsive, and in a sleep state to conserve energy, grow, and maintain physiologic homeostasis.[358] As maturation occurs, there is an increase in quiet alert.
Light sleep (REM or active sleep): Low activity level Random movements and startles Respirations irregular and abdominal Intermittent sucking movements Eyes closed, REM Higher oxygen consumption	Full-term infants begin and end sleep in active sleep; preterm infants are more responsive (than term infants) to stimuli in active sleep. Infant may cry or fuss briefly in this state and be awakened to feed before truly awake and ready to eat. Lower and more variable oxygenation states
	AWAKE STATES
Drowsy or semidozing: Eyelids fluttering Eyes open or closed (dazed) Mild startles (intermittent) Delayed response to sensory stimuli Smooth state change after stimulation Fussing may or may not be present Respirations are more rapid and shallow	Infants may awaken further or return to sleep (if left alone). Quietly talking and looking at the infant or offering a pacifier or an inanimate object to see and listen to may arouse the infant to the quiet, alert state. Less mature infants (30 weeks) demonstrate a more drowsy than quiet alert state than more mature infants (36 weeks).
Quiet alert, with bright look: Focuses attention on source of stimulation Impinging stimuli may break through; may have some delay in response Minimal motor activity	Immediately after birth, term newborns exhibit a period of quiet alert, which is their first opportunity to "take in" their parents and the extrauterine environment. Dimmed lights, quiet talking, and stroking optimize this time for parents. Best state for learning to occur, because infant focuses all of attention on visual, auditory, tactile, and sucking stimuli; best state for interaction with parents—infant is maximally able to attend and reciprocally respond to parents. Best state for oral feeding efficiency in term and preterm infants.[165]
Active alert—eyes open: Considerable motor activity—thrusting movements of extremities; spontaneous startles Reacts to external stimuli with increase in movements and startles (discrete reactions difficult to differentiate because of general higher activity level) Respirations irregular May or may not be fussy	Infant has decreased threshold (increased sensitivity) to internal (hunger, fatigue) and external (wet, noise, handling) stimuli. Infant may quiet self, may escalate to crying, or with consolation by caregiver, may become quiet alert or go to sleep. Infant is unable to maximally attend to caregiver or environment because of increased motor activity and increased sensitivity to stimuli.
Crying—intense and difficult to disrupt with external stimuli Respirations rapid, shallow, and irregular	Crying is the infant's response to unpleasant internal or external stimulation—infant's tolerance limits have been reached (and exceeded). Infant may be able to quiet self with hand-to-mouth behaviors; talking may quiet a crying infant; holding, rocking, or putting infant upright on caregiver's shoulder may quiet infant.

Data from Blackburn S. Fostering behavioral development of high-risk infants. *JOGN Nurse* 1983;12(suppl 3):76S-86S; and Brazelton TB. *Neonatal Behavioral Assessment Scale*. 2nd ed. Philadelphia, PA: International Medical Publishers/Lippincott; 1984.

There are individual differences in the development of circadian rhythms, in both preterm and full-term infants.[358-360,416] These circadian rhythms in the neonate are influenced by feeding, environmental lighting, interactions with mother, and chronologic/postconceptual age.[358-360,415,416] Infant biorhythms have been studied in the areas of temperature, heart and respiratory rates, blood pressure, sleep-wake cycles, rest-activity patterns, endocrine secretion, and feeding frequency.[358-360,415]

SLEEP CYCLES AND PATTERNS

Active (or light) sleep is characterized by rapid eye movements (REM), whereas quiet (or deep) sleep has no rapid eye movements (i.e., non-REM sleep; see Table 13.3). At 29 to 30 weeks' gestation, sleep differentiates into REM and non-REM sleep.[160] At birth and for the first few weeks of life, term newborns generally distribute sleep over a 24-hour period and sleep from 16 to 19 hours a day. As sleep begins, a term infant enters active, rather than quiet, sleep and spends more time in active sleep than does an adult.[111]

Active sleep durations vary from 10 to 45 minutes, whereas quiet sleep lasts about 20 minutes.[111] An infant's sleep cycle is 50 to 60 minutes, compared with an adult's 90- to 100-minute cycle. Although day-night rhythms are difficult to detect in the neonatal period, some infants exhibit such rhythms as early as 1 week of age.[358,359] **The first study of the sleep-wake cycles of healthy term newborns in the immediate postnatal period found sleep-wake cycles as early as 6 hours of life, with a preponderance (52.1%) of active sleep for longer periods than quiet sleep.[212] Mode of delivery also influenced sleep, with a longer active sleep and shorter period of quiet sleep in infants delivered by elective C-section than for those delivered by vaginal birth or emergency C-section.** Sleep-wake cycles are altered when term infants have hyperbilirubinemia.[463]

Maturation of infant sleep is characterized by (1) increased organization of sleep states, (2) decrease in total sleep time, (3) increase in quiet sleep, (4) decrease in active sleep, and (5) increase in active and quiet waking.[111] Arousability from sleep is altered by gestational and postnatal age. In term infants, arousal thresholds are significantly elevated in quiet sleep compared with active sleep (at 2–3 weeks and at 2–3 months of age), so that spontaneous arousal is greater in active (REM) than in quiet (non-REM) sleep.

Infants have their own "clock" for sleep-wake, hunger, and feeding or fussy times. This clock often does not coincide with the family's rhythms and may cause disruption and conflict. Sleep-wake states reflect the underlying status of the neurologic system. **The infant's maturity at birth greatly affects his or her rhythms and development of normal circadian rhythm.** Early relationships with caregivers provide the organization and stabilization necessary for sleep regulation and other biologic functions.[415]

In preterm infants, active and quiet sleep cycles are less organized and of shorter duration (a sleep cycle is about 30–40 minutes) than in term infants.[110] Active sleep is "lighter" than quiet sleep—there is more response to stimuli in active sleep.[110] Quiet sleep is a more controlled state and occurs more frequently in term infants than in premature infants. Quiet sleep does not become significant in the preterm until approximately 36 weeks' gestation. Hence, a third sleep state, *transitional sleep,* has been identified for premature infants.[326] This state is characterized by quiet sleep with periods of closed eyes, regular or periodic respirations, no body movements, and no REM. **Before 36 weeks' gestation, a preterm infant's predominant sleep state is transitional sleep.** As the preterm infant matures, he or she spends progressively less time in transitional sleep, has more quiet than active sleep, and has more awake, alert time. However, a preterm of 40 weeks' postconceptual age does not have sleep patterns that are as organized as those of a term newborn.[326] **Spontaneous arousal from sleep is greater in active sleep compared with quiet sleep.** Long-term follow-up studies fail to show a difference in sleep distribution between preterm and term infants when corrected for age.[383] Both preterm and full-term infants who are exposed to an appropriate light intensity at home develop day-night rhythmicity by 44 and 48 weeks' postconceptual age, respectively.[359,360,383]

As day and night rhythms in sleep-wake cycles develop, diurnal rhythm in hormone production also develops: (1) melatonin production is detectable at 12 weeks of age; and (2) variations in cortisol levels appear between 3 and 6 months of age.[358] **Sleep disruption may interfere with growth and development by altering neuronal maturation, cortex development, and growth hormone**

secretion.[5,66] Human growth hormone has a rhythmic pattern associated with sleep-wake cycles. The highest peaks of growth hormone in infants occur during REM (active) sleep. A fetus (29–32 weeks' gestation) spends 80% of the time in utero in REM sleep; a term newborn's sleep is 50% REM sleep.[110,111] **Because growth hormone secretion depends on the regular recurrence of sleep, any disturbance of the sleep-wake cycle results in irregular spikes of growth hormone during a 24-hour period. Sleep disruption, especially of REM sleep, also interferes with healthy visual development, increases behavioral problems and sleep disturbances, and reduces the size of the cerebral cortex.**[160,283]

Although infant circadian rhythms are synchronous with those of the mother, desynchronous rhythms at birth may occur.[326,358] An infant whose cycles are discrepant from his or her family's may be perceived as "difficult." Gradually, through caregiving, parents teach the infant synchronization with family rhythms.[415] By 9 months of age, most term infants develop day-night fluctuations that are similar to adult patterns.

Sensory Capabilities

At birth, a neonate's senses are developed and functioning. Sensory development proceeds in a specific order: tactile/vestibular, olfactory/gustatory, and auditory/visual. Stimuli (e.g., type, timing) to one sense affect the development of other senses. Sensory enhancement or deprivation of a later-developing sensory system (e.g., vision) could either accelerate or decelerate the development of behavior mediated by earlier-developing sensory systems (e.g., tactile and olfactory).[397] Through the neonate's sensory perception, learning occurs by (1) habituating to some stimuli while attending to other stimuli, (2) discriminating between related and unrelated sensory events, and (3) integrating multisensory stimuli. As the neonate takes in the sensory information, he or she associates features of the environment that occur together (e.g., sound, smell, sight, touch of "mother" or "father"), demonstrating complex and intermodal abilities for handling the sensory input from the environment.

TACTILE/KINESTHETIC

Touch is the major method of communication for neonates and infants. Touch is the first sense to develop (at about 7.5 weeks' gestational age) and the last sense to fade. In utero, a fetus's existence has been primarily one of movement—floating within the amniotic fluid and experiencing rhythmic maternal movements. In response to maternal touch of her pregnant abdomen, the fetus displays an increase in arm, head, and mouth movements.[264] The senses of touch, temperature, and pressure are all well developed, and receptors lie in the newborn's skin. Pleasant touch is associated with a slowing of the heart rate, a decrease in physiologic arousal, and increased engagement.[128] Even preterms as young as 28 weeks' gestation tactilely memorize the shape of an object by manipulating it in their hands and discriminate between objects.[262] **The sensitivity to touch is especially well developed in the face, around the lips (root reflex), and in the hands (grasp reflex).** Because newborns are nonverbal, they pick up messages through the manner in which they are held and handled—by the adult's "body language." Infants are often barometers for adult feelings; if the adult is tired and irritable, the infant knows and may respond with irritability and crying.

Infants love to be held, rocked, and carried; note the soothing effects on a crying infant. Adults do not spoil infants by providing these important stimuli. Increased carrying of infants contributes to less crying at 6 weeks of age.[36] In response to being held, infants adjust their body posture to the body of the caregiver. Adults describe an infant as "cuddly" (assumes a comfortable, relaxed curl; snuggles to adult body; and attempts to root or suck) or "noncuddly" (sprawls; tenses or stiffens; and pushes away). **The most comforting position for a crying infant is upright on an adult's shoulder.**[210] Responsiveness to tactile stimulation has been found to be greater in female than in male neonates.[210]

HEARING

The fetus in utero has heard the voices of mother, father, and siblings beginning in the second trimester of pregnancy, at about 27 weeks of pregnancy.[293,397] These voices are "familiar" to newborns, so they "know" and have learned their family and are able to differentiate them from the voices of strangers.[100,101,293,298] Neonates prefer their mother's voice and the maternal language that they heard in utero.[293] Studies have suggested that fetuses and neonates

exhibit memory.[100,101,293,298] Newborns who had been read a particular story while in utero responded to the story reread to them after birth with a recognition and attentiveness that was not exhibited in response to unfamiliar stories.[100,101] A more recent study presented fetuses with music five times per week and measured their brain activity at birth and at 4 months of age. Brain activity at birth and at 4 months of age was much stronger when the neonates and infants heard the "familiar" music they had listened to in utero.[327] Antenatal and postnatal maternal singing of lullabies to the fetus resulted in improved maternal-infant bonding after birth and less maternal stress.[331] Neonatal outcomes in this study included (1) significantly less crying in the first month of life, (2) less colic in the first and second months of life, and (3) less wakening during the night. Another study shows that **preterm infants have lower pain scores and better behavioral states during heelstick when they listen to the same music that their mothers listened to during pregnancy.**[214] The ability to hear the outside world, particularly the spoken word, is a prerequisite to further verbal language development.[293]

Recent research has documented a delay in the development of the fetal primary and nonprimary auditory cortex in the brain.[286] By 26 weeks' gestation, the primary auditory complex (which receives auditory signals from the ears) is more developmentally advanced than the nonprimary auditory cortex that processes and understands auditory signals. From 26 weeks to term, the nonprimary auditory cortex in preterm infants matures quickly and partially "catches up" with the maturation that would have occurred in utero. However, by 40 weeks' corrected age (CA) both auditory regions in preterm infants were less developed than in neonates born at term gestation. This **disturbance in the maturation of the nonprimary auditory complex in premature infants was associated with poorer language performance at 2 years of age.**[286]

Fetal responses to sound include increases in breathing, body movements, fetal heart rate, cerebral blood flow, and glucose use and changes in behavior states, as well as recognizing and habituating to familiar sounds.[298] In response to hearing a maternal voice the fetus decreases arm and head movements.[264] Neonates with an intact CNS are able to orient and respond to the auditory environment. In response to a sound, the neonate will demonstrate the following:

- Change in motor activity (eye blink, decrease in activity, limb movements, head turn)
- Change in heart rate (if the infant is quiet, the heart rate increases with stimuli; if the infant is crying, the heart rate decreases with stimuli) and/or change in respiration (increase in rate, decrease in amplitude, or decrease in respiratory cycle rate)
- Smile
- Startle or grimace
- Alert or arouse
- Cry or cease to cry
- Stop sucking

The response to sound depends on the sound's quality. The intensity of intrauterine noise is approximately 85 dB. When frequency and pitch are low, the infant is soothed and distress is decreased; high frequency and pitch alert and distress the infant and disturb sleep.

Frequencies less than 4000 Hz (the range of human speech is 500–3000 Hz) produce the most response in newborns. **Infants are maximally reactive to the human voice in typical speech patterns (rather than disconnected syllables). Infants prefer the high-pitched (e.g., female) voice over the low-pitched (e.g., male) voice.**

Experience with sound improves an infant's behavioral responses to sound. Stimuli presented for 5 to 15 seconds elicit the best reaction. Stimuli lasting longer than several minutes are less effective because the term infant habituates to the sound and ceases responding. **The ability to habituate to sound is indicative of an intact CNS.**[298] **Full-term newborns habituate to sound better and faster than do preterm infants.** Infants exhibit startle behavior if the stimulus rapidly reaches maximal loudness. Infant state is important in evaluation of response to auditory stimuli; light sleep is the optimal state. Infants quiet and soothe in response to rhythmic sounds (rather than dysrhythmic ones). Neonates move their bodies in rhythmic synchrony *(entrainment)* with the spoken word.

VISION

Eye development begins 22 days after conception. **The eyelids fuse at about 10 weeks' gestation and remain fused until about 26 weeks' gestation.** Eyelid opening is a function of maturity—more mature neonates open their eyes more than younger gestation neonates. At birth, photoreceptors

are already developed, but maturation is not complete for several months. The fetus can distinguish light from dark and recoils from a bright light shone at the mother's abdomen. A recent study showed that more fetuses at 34 weeks' gestation turned toward a face-shaped light shown through their mother's abdomen than toward the inverted light shape. Researchers concluded that the **preference for the human face exhibited by newborns is developed before birth.**[352] Even at term birth, the visual system is immature; significant development occurs over the next 6 months to a year. **The ability to fix, follow, and alert is indicative of an intact CNS.**[282]

At birth, infants can see an object within 8 to 10 inches of the face (visual acuity of 20/140).[130] Within seconds after birth, the neonate can recognize his or her mother's face—the voice that they have heard for the last trimester of pregnancy comes from the face they now see! The cradled-in-the-arms position of feeding is the exact distance from the adult's face that the newborn can see. In response to an interesting visual stimulus, neonates stop sucking to look, alert, and attend to the object; horizontally scan the object; and fix and follow a moving object in a 90-degree arc.

Infants prefer the human face as a visual stimulus, prefer a patterned over a nonpatterned stimulus, and attend longer to larger patterns with more complex patterns and angles.[130] Infants prefer black and white because of the greater contrast and will focus on the outside of a figure where the contrast is the greatest[282]; color discrimination occurs around 2 to 3 months.[160] Newborns are sensitive to bright light and will tightly close their eyes in its presence. They prefer moderate, diffuse lighting. **Newborns exposed to cycled light (e.g., day-night changes) open their eyes more than those exposed to continuous bright light.** Presentation of visual stimuli enables development of the neural pattern for vision. During the infant's first year of life, visual investigation of the environment is a primary mode of learning.

SMELL AND TASTE

In utero, the fetus learns his mother's scent by exposure to amniotic fluid.[45,397] The fetus increases its amniotic fluid consumption when saccharin is added to the fluid and decreases consumption with the injection of distasteful substances. Taste may be a way the fetus monitors the intrauterine environment. **Olfaction is well developed at full term and preterm birth.**[262] **Olfactory cues guide the full-term newborn to the maternal nipple.** Flavors and smells in the mother's diet are present in amniotic fluid and in mother's breast milk so that infants show a preference for these familiar flavors and smells at birth and later in infancy.[45,397,414,427]

At 5 days of age, a neonate can differentiate his or her mother's breast pad and demonstrates a preference for the smell over that of a "stranger"; full-term newborns stop crying and increase their mouthing behaviors when exposed to their mother's odor.[398] Premature infants exposed to the odor of their own mother's milk have a persistent decrease in salivary cortisol levels that continue after the stimulus is removed.[254] The infant's response to pleasant odors is to arouse and suck. After several presentations of the stimulus, the infant will habituate to the odor. Infants withdraw from unpleasant odors such as vinegar and ammonia. They are also able to differentiate tastes, preferring sweet solutions[414,427] and refusing, by turning the head away, bitter, acid, and sour substances. Intrauterine growth restricted (IUGR) 1-day-old newborns have been shown to strongly prefer a sweet solution (24% sucrose) that is inversely related to their degree of IUGR.[22] Asphyxiated infants demonstrate a loss of olfaction that parallels the suppression of brainstem reflexes and activities.

COMMUNICATION SKILLS

A neonate's ability to communicate is a naturally endowed survival skill. **Crying is an infant's language to communicate needs.**[249] Crying also may be a response to the environment: noisy, cold, overstimulating, multiple caregiving, or lack of synchrony. Because the cry brings someone to meet the need, the infant soon learns that the caregiver gives attention and the world is a trustworthy place. **The more responsive the caregiver is to the infant's crying, and thus the infant's needs, the less crying behavior is necessary.**[36,249] **Learning occurs as the infant associates comfort with the caregiver.** The temperament of the individual infant and his or her ability to habituate to disturbing stimuli influence the amount of crying behavior. Tension in the caregiver or the environment is communicated nonverbally to the infant and may potentiate or contribute to the infant's crying.

The amount and tone of the newborn's cry are influenced by birth weight, gestational age, and the events of birth. **Types of cries include birth cry, hunger cry, pain cry, and pleasure cry.**[85,86] **Infants separated from their mothers in the first 90 minutes after birth exhibit a "separation distress call" (also seen in other mammal species) that ceases at reunion.**[85,86] The newborn's cry physiologically affects the mother: her breasts change and prepare to nurse. Neonates possess a repertoire of self-quieting behaviors when in a fussy state: (1) hand-to-mouth efforts, (2) sucking on fist or tongue, and (3) use of visual or auditory stimuli from the environment.[57]

After birth, crying develops a diurnal pattern: term infants cry more during the day than at night. Persistent crying (>3 hours a day) is more likely in breastfed babies, whereas early-evening crying is more likely by formula-fed infants. Postnatal age is a significant predictor of crying. Crying decreases with increasing chronologic age.[404] The neonatal cry may be a signal of robustness or wellness, a signal of pain, or diagnostic of existing conditions or trauma. CNS insult often results in a high-pitched, shrill cry.

A smiling infant is a joy to the caregiver. Smiling may be either spontaneous (from birth) or a response to the social human face (at 4–12 weeks of life). A smile is most easily elicited by the stimulus of a moving, smiling human face. The ability to smile begins before 40 weeks in a preterm infant, as observed during REM sleep. The social implications of the smile include positive feedback to the caregiver that the infant is happy and contented, which results in parental feelings of adequacy and competence.

ENVIRONMENT

Prenatal Environment

In utero, the fetus depends totally on the mother's emotional and physical health and well-being for his or her own. Through the mother the fetus receives nurturance, housing, and stimulation to develop the body, the sensory organs, and the rudiments of personality and temperament.

Conditions present at birth may not be congenital but, rather, the result of the effect of uterine environmental conditions on development. Maternal-fetal programming, known as the *Barker hypothesis,*[29] postulates that the maternal prenatal environment influences the developing fetal brain and also the long-term permanent effects on health and susceptibility to disease.[58]

Intrapartal Environment

Birth is a major transition from physiologic dependence to physiologic independence. At term, a neonate's physiologic systems are developed, sensory organs function, and the foundation of personality and temperament is established. Birth is disorienting and disruptive. The amount of disruption depends on the degree of trauma incurred during the labor and birth processes. Not having a social support system compounds the stress, often escalating it beyond the mother's tolerance and coping skills. Anxious and fearful women have longer labors and more delivery complications than women who are confident about themselves and their infants.[372] **The shift toward family-centered birth enables mothers to receive support from their families, be active participants in the birth process, and have immediate contact with their newborns** (see Chapter 29).

A neonate also is influenced by medications and the events of labor and birth (see Chapter 2). Maternal medications for analgesia and anesthesia affect neonatal behaviors, resulting in decreased sucking ability, lethargy, and decreased habituation. They also give less feedback to their parents than unmedicated infants do. The parents may feel rejected, tend to stimulate the infant less, and thus begin a pattern of suboptimal interaction.

Postnatal Environment

Home and family are the primary media through which newborns (1) reestablish their biorhythmic balance, (2) stabilize themselves in the extrauterine world, (3) develop a sense of self and mastery in the world, and (4) become socialized as human beings. Socialization teaches the adaptive psychosocial skills necessary for survival and functioning in society. Cultural and family values, behavioral expression, and ways of meeting social and emotional needs are learned within the family. **Thus, the home and family environment is considered to be a "socializing" environment for human development.**

CAREGIVER FACTORS

The dyadic relationship continues postpartum between the caregiver and the infant—the behavior of one reinforces the behavior of the other. The infant's physical and emotional needs are satisfied by caregivers. The infant's response to the caregiver depends on how the infant perceives and receives ministrations; this response affects the level of emotional satisfaction the caregiver receives from the interaction. Parental expectations have a major effect on their perceptions and their behavior and ultimately affect the child's development. **Parents must work out the discrepancy between the wished-for and the actual child, especially if the infant is preterm or ill or has an anomaly. How attached the parents are to the infant influences their relationship with and ability to care for their infant** (see Chapter 29). If the pregnancy has failed to produce a normal, healthy infant, the parents must grieve the loss of their expectations. Parents have problems attaching to and caring for the infant until they have completed their grief work (see Chapter 30).

A caregiver and an infant have a reciprocal interaction when their cycles and signals are synchronized with each other. The biorhythmic cycle of the newborn has been in synchrony with one person (mother) in utero, and the infant is accustomed to her cycles and rhythms for developing adaptive behavior. **Consistent, sensitive maternal caregiving enables a newborn to regulate his or her rhythms to those of the mother and begin adapting to the postnatal environment.**[380,391] Mother and fathers "filter" the environment for their baby while still enabling variability and unpredictability. From the relationship with their parents, the infant expands their adaptation to the family and the larger world of society.

Experience in relating to infants influences the caregiver's efficiency in interpretation of and sensitivity to infant cues. Multiparous women have more sensitivity to infant cues than do primiparous mothers. Mothers with little or no experience exhibit more difficulty in quieting a crying infant. **The competence of parents may be improved through acquisition of knowledge about infants so that the quality of interaction between parent and infant is enhanced.** Better informed first-time mothers may result in significant differences in sensitivity to infant cues and social and emotional growth fostering behaviors in early (first 24 hours) mother-infant interaction.[450] In addition to experience, maternal hormones, oxytocin and estrogen, enable mothers to retain and respond to their infant's vocal cues.[394]

Consistency and sensitivity in maternal responses[391] is especially important as the infant continues to learn the accepted patterns of cues from the caregiver. Cared for by one or two people, an infant is able to develop synchrony with and expectations of the parents. Single caregiving improves establishment of biorhythms for sleep-wake cycles, feeding, and visual attentiveness. Consistent cues soon elicit a consistency of response from the infant. Consistency and promptness of maternal (and other caregivers) response results in less infant crying during the first year of life. A predictable and responsive environment enables the infant to progress to varied types of communication (not just crying). Care by parents provides for mutual cueing and mastery of the environment through interaction. Inconsistent cues distress and confuse the infant. **Multiple caregivers, who may not be knowledgeable about a particular infant, may confuse the infant, increase distress with feeding, cause irritability, and upset visual attention.**

Regardless of how stable or unstable, consistent or inconsistent it is, family life has a rhythm, synchronicity, and predictability of its own. Through interaction with parents and siblings, infants further develop their ability to form relationships. From these primary relationships, the foundation and format for other relationships are established. The quality of subsequent relationships depends on the quality of the relationship experienced within the primary family from birth throughout infancy.[156]

NEONATAL FACTORS

The neonate is not a passive recipient of the environment of the family but, rather, is an active participant in shaping that environment. Infants send cues about their ability and readiness for interpersonal interactions. In their first 4 months of life, infants' interactions with persons differ from their interactions with inanimate objects. The excitement generated by interpersonal interaction is seen in an infant's arm and leg movements, bodily movement toward the other person, smiling, vocalizing, and increased visual attention. Because of the infant's immaturity, he or she is unable to maintain a continuous interaction. **Maternal or care provider sensitivity**[391] **to the attention-withdrawal cycle**

of interaction enables the adult to modulate his or her behavior in synchrony with the infant's cues. Successful interaction with an infant includes reading the infant's cues, responding appropriately, and not overwhelming the infant with too much stimulation (thus overstepping the infant's tolerance for interaction). Overwhelming the infant results in withdrawal for progressively longer periods to protect himself or herself from overstimulating and insensitive others.

Attachment of the newborn to the mother/parent functions to keep the infant in proximity for caregiving and promotes brain and emotional development.[397] Just as the parent has expectations, the infant also has physiologic and emotional needs that require care. Relief from the discomforts of hunger, cold, sleeplessness, and boredom enables the infant to respond positively to the care provider.

Care-eliciting behaviors are those neonatal cues used to signal the caregiver that attention is needed. Crying, visual following, and smiling are care-eliciting behaviors. Newborn responses to care include quieting, suckling, clinging and cuddling, looking, smiling, and vocalizing. These social interactions positively reward the care provider and encourage and promote continued care. Infant characteristics that modify maternal attitudes include (1) a healthy or sickly infant; (2) an attractive, pretty infant or an infant with obvious congenital anomaly; (3) a premature infant; (4) a calm and contented or a fussy and irritable infant; and (5) an infant responsive to or rejecting of maternal care. A mother's or care provider's ability to soothe the infant reinforces a feeling of success (or failure) in his or her feelings of competence.

The infant's gender also affects the cues and the caregiver's response. Male infants exhibit more startles, more muscle activity, and more physical strength. In response, caregivers hold them more as a means of soothing.[210] Females exhibit more tactile and oral sensitivity, more smiling, and more responsivity to sweet taste. As a result, girls are more often soothed by talking, eye-to-eye contact, and a pacifier.[210]

The infant's level of neurophysiologic development influences the appropriateness of maternal and caregiving behaviors. The neurologically mature term infant who has already mastered autonomic, motoric, and state regulation is able to actively elicit and respond to caregiving behaviors.[57]

BOX 13.2 CRITICAL FINDINGS

STAGES AND CHARACTERISTICS OF BEHAVIORAL ORGANIZATION IN PRETERM INFANTS

Als & Brazelton[a]	Gorski[b]
Physiologic homeostasis—stabilizing and integrating temperature control, cardiorespiratory function, digestion, and elimination. Characteristics: become pale, dusky, cyanotic; heart and respiratory rates change—all symptoms of disorganization of autonomic nervous system.	"In-turning"—physiologic stage of mere survival characterized by autonomic nervous system responses to stimuli (rapid color changes caused by swings in heart and respiratory rates); no or limited direct response; inability to arouse self spontaneously; jerky movements; asleep (and protecting the central nervous system from sensory overload) 97% of the time. Preterms (<32 weeks) are easily physiologically overwhelmed by stimuli.
Motor development may infringe on physiologic homeostasis resulting in defensive strategies (e.g., vomiting, color change, apnea, bradycardia). State development becomes less diffuse and encompasses full range: sleep, awake, crying. States and state changes may affect physiologic or motor stability. Alert state is well differentiated from other states; may interfere with physiologic or motor stability.	"Coming out"—first active response to environment may be seen as early as 34 to 35 weeks (provided some physiologic stability has been achieved). Characteristics: remains pink with stimuli, has directed response for short periods, arouses spontaneously and maintains arousal after stimulus ceases; if interaction begins in alert state: maintains quiet alert for 5 to 10 min, tracks animate or inanimate stimuli, spends 10% to 15% of time in alert state with predictable interaction patterns. "Reciprocity"—active interaction and reciprocity with environment at 36 to 40 weeks. Characteristics: directs response, arouses and consoles self, maintains alertness, interacts with animate/inanimate objects, copes with external stress.

[a]Data from Als H, Brazelton TB. A new model of assessing the behavioral organization in preterm and full-term infants: two case studies. *J Am Acad Child Psychiatry.* 1981;20:239.

[b]Modified from Gorski PA. Stages of behavioral organization in the high-risk neonate: theoretical and clinical considerations. *Semin Perinatol.* 1979;3:61.

Because of the immaturity of the CNS, a preterm infant lags behind a term infant in care eliciting and responsivity to the care provide[275,444] (Box 13.2). Because a young preterm infant's priority is mere survival, interaction with

the environment and care providers will occur at the expense of physiologic stability.[413] Although overwhelming the term infant results in withdrawal from interaction, overwhelming the preterm infant results first in a real threat to physiologic survival and then to withdrawal from interaction.

The ability of an infant to be a social partner and to respond in a social interaction is developmentally determined and influenced by the infant's physical condition. The response of preterm infants (weight <1500 g) to social stimulation (e.g., talking and talking combined with touching) develops over time: (1) at 29 to 32 weeks' gestation, respond with distress (e.g., eye closing) to all forms of social stimuli; (2) at approximately 33 weeks' gestation, begin to respond with increased attention to talking; they remain distressed with combined stimuli; and (3) at approximately 35 to 36 weeks' gestation, pay more attention to talking; more distress at combined stimuli is seen in high-risk infants (e.g., preterms <1500 g) and better habituation seen in healthier infants.[114] **Sicker preterm infants have a more difficult time attending to and modulating their response to social interactions than do healthier preterm infants.**[114,115,444] Although VLBW preterm infants respond to talking with increased attention and eye opening, the addition of touch results in increased eye closing and facial grimacing.[107] Sicker infants demonstrate the same pattern of response but in a more exaggerated way that reflects their increased reactivity and decreased ability for self-regulation.[115,413]

Because preterm infants are not as neurologically mature as term infants, the NBAS has little value with this population. **A behavioral assessment scale for preterm infants, the Assessment of Preterm Infant's Behavior (APIB), has been developed that evaluates the preterm infant's behavioral organization along five subsystems of functioning: autonomic, motor, state, attentional-interactive, and self-regulatory.**[12] This examination delineates the quality and duration of the preterm infant's response, the difficulty in eliciting the response, and the effort and cost to the preterm infant of achieving and maintaining a response. Because it, too, is an interactive test, the nature and amount of organization provided by the care provider is an indication of the preterm infant's lack of integrative skill. As the preterm infant matures and advances in development of organization, he or she is more able to interact with the environment (animate and inanimate). However, it must be remembered that this maturation process is "uneven"; as the preterm infant advances in one area of development, he or she may become, at least temporarily, more vulnerable in other areas.[156]

Another examination, the Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS), assesses neurologic integrity and behavioral factors of high-risk infants (e.g., preterms, drug-exposed infants) by evaluating neurobehavioral organization, neurologic reflexes, motor development, muscle tone (active/passive), and signs of (drug) withdrawal and stress.[412] The NNNS differs from the NBAS in that the NNNS (1) was developed for at-risk populations, not for the normal newborn; (2) is more structured and standardized than the NBAS; and (3) gives results more reflective of infant capabilities rather than infant-examiner interaction.[412] The NNNS is performed on medically stable infants, between more than 30 weeks' gestation and 46 to 48 weeks' postconceptual age, for research purposes and for clinical practice.[412] Clinical applications include the following[412]:

- Evaluates the infant's personality and temperament as capacities for state regulation of arousal, response to stimuli, self-soothing, and tolerance of handling
- Documents the physiologic and behavioral manifestations of drug withdrawal or stressors in the environment
- Documents the capacity to habituate, orient to stimuli, and respond to handling, as well as muscle tone and quality of movement
- Evaluates infants withdrawing from in utero drug exposure and those being weaned from analgesia in the NICU
- Determines when the infant is ready for discharge
- Is used as a teaching and care-planning tool when the examination includes parents and other care providers
- Is a tool that bridges the assessment from early gestation/neonatal period to 2 months corrected age when other tools are unreliable

INTERVENTIONS

Life in a special care nursery is characterized by sensory deprivation of normal stimuli that the preterm infant would have experienced in the womb and that term infants would experience at

home with their families. However, **the NICU is also an environment of sensory bombardment**—constant noise, light, and tactile stimulation; intrusive, invasive procedures; upset of sleep-wake cycles; and multiple caregivers. **Rather than too much or too little stimulation, infants in the NICU receive an inappropriate pattern of stimulation (e.g., noncontingent, nonreciprocal, painful [rather than pleasant], and multiple stimuli).**[7,156,158] Because the immature CNS of the premature infant cannot tolerate these stimuli, the easily overstimulated preterm infant protects himself or herself by physiologic and interactional defensive maneuvers that are maladaptive.

Inappropriate patterns of stimuli that stress the preterm infant in the NICU environment influence brain structure and function during a critical period of brain development.[96,260,397] The first study to examine a relationship between stressors in the NICU and alterations in brain development was published in 2011. This prospective cohort study used the Neonatal Infant Stressor Scale (NISS)[304] to measure daily exposure to stressors of preterms (<30 weeks' gestation) for the first 14 and 28 days of life and from admission to the NICU until term equivalent postmenstrual age (PMA) or discharge.[386] Magnetic resonance imaging (MRI) examinations were performed at term equivalent age (about 36–44 weeks' PMA) and the association between exposure to stressors and abnormal brain development was then calculated. **The most immature, sickest preterms were exposed to the highest number of stressors and procedures, particularly in the first 14 days of life. Higher exposure to stressors was associated with decreased brain size in the frontal and parietal sections.[386] Increased stress was also associated with altered microstructure in the temporal lobes,** especially the right lobe, that resulted in less mature, poorly developed connections between the temporal lobes.[386] **A combination of destructive and developmental mechanisms contribute to the encephalopathy of prematurity.**[433] White matter injury to the developing brain is recognized as the cause of common motor, behavioral, and cognitive problems in surviving premature infants[117] (see Chapter 31).

A study by the same investigators found **altered neurobehaviors at term equivalent in a prospective study of preterm infants (<30 weeks' estimated gestational age).**[338] Using the NNNS, differences in neurobehavior were examined between preterm infants at term and full-term controls, between 34 weeks' PMA and full-term equivalent, and relationship of neurobehavior to perinatal exposures (such as days of intubation, postnatal steroids, oxygen use after 36 weeks' corrected age).[338] **At term equivalent, preterm infants exhibited a broad range of altered behaviors** (Box 13.3). Studied preterms between 34 weeks' PMA and term equivalent also exhibited behavioral and motor changes that were not influenced by any of the measured perinatal exposures. At 34 weeks' PMA, preterms with significant cerebral injury had increased excitability compared with non–brain-injured preterms.[338] The researchers concluded that the **neurobehavioral changes occurring before term may present a rich opportunity in the NICU for interventions to ameliorate developmental disadvantages evident in the studied preterms by term equivalent age.**

Altered neurodevelopmental outcomes and resulting altered neurobehavior may also affect the infant's ability to attach to parents. A study

BOX 13.3 ALTERED NEUROBEHAVIOR IN PRETERM INFANTS IN NICU

Preterms (at Term Equivalent) Compared with Full-Term Infants

- Poorer orientation
- Lower ability to tolerate handling
- Lower ability to self-regulate
- Poorer reflexes
- Increased stress
- More excitability
- Altered muscle tone—hypotonic or hypertonic

Preterm Infants From 34 Weeks' Premenstrual Age Compared to Term Equivalent

- Changes in motor function:
  - Declining quality of movement
  - Increasing hypertonia
  - Decreasing hypotonia
- Changes in behavior:
  - Increasing arousal
  - Increasing excitability
  - Decreasing lethargy

Adapted from Pineda RG, Tjoung TH, Vavasseur C, et al. Patterns of altered neurobehavior in preterm infants within the neonatal intensive care unit. *J Pediatr.* 2013;162:470.

BOX 13.4 OUTCOMES OF INDIVIDUALIZED DEVELOPMENTAL INTERVENTION IN THE NICU*

Physiologic Benefits	Developmental Benefits	Cost Savings
Decrease in:	Improvement in:	Shorter length of stay
Incidence of IVH or pneumothorax and severity of BPD, ROP, NEC	Behavioral organization of autonomic, motor, attention modulation, and self-regulatory abilities	Earlier discharge at younger age
Ventilator/CPAP use	Interactive capability of infant with staff and parents	Decrease in hospital charges
Need for supplemental oxygen	Quality of parent-infant interaction (perception of preterm as better regulated, more autonomous, and more gratifying; enhanced competence in parental role)	
Need for gavage feedings/IV nutrition	Less parental personal stress	
Number of apneic episodes	Feelings of closeness with preterm	
Need for sedation/analgesia	Cognitive function/IQ	
Increase in:	Development of feeding skills (earlier full oral feedings)	
Daily weight gain; head growth/length	Fewer behavioral problems and attentional difficulties	
Stability of cardiorespiratory function	Continuation of maternal ability to read and respond to infant behavioral cues/appreciation of the infant	
Sleep states/sleep duration	Better psychomotor outcome at 2 years of age	
Significant electrophysiologic differences in frontal, temporal, central, occipital, and parietal lobes of the brain	Increase in maternal conflict and anxiety when care is not consistent	
	Better sentence comprehension at 36 months	

* References 7–9, 11, 205, 208, 226, 256, 270, 271, 289–292, 301, 311, 335, 371.

BPD, Bronchopulmonary dysplasia; *CPAP,* continuous positive airway pressure; *IQ,* intelligence quotient; *IV,* intravenous; *IVH,* intraventricular hemorrhage; *NEC,* necrotizing enterocolitis; *NICU,* neonatal intensive care unit; *ROP,* retinopathy of prematurity.

involving very preterm/VLBW infants, full-term infants, and their mothers examined the security of the infant's attachment to the mother at 18 months of age.[455] A majority of the full-term (72%) and the very preterm infants (61%) were securely attached. However, more very preterm infants (32%) had disorganized attachment than the full-term infants (17%). **Researchers concluded that neurodevelopmental problems in the very preterm infants altered their ability in social relationship with their mothers.**

Research has shown medical, developmental, and cost benefits to low-birth-weight (LBW) infants from individualized behavioral and environmental care in the NICU (Box 13.4). **The most effective interventions (1) follow the Newborn Individualized Developmental Care and Assessment Program (NIDCAP),*; (2) are contingent on the infant's responses, thus are interactive and individualized; (3) create an environment that balances protection from sensory overload with provision of enough stimulation to promote emerging capabilities; and (4) collaborates with the parents in planning, providing, and evaluating developmental care.[7,11,255]**

The first randomized controlled trial (RCT) of individualized developmental care (NIDCAP)[11] for VLBW (inborn and transported) infants conducted in three diverse NICUs showed improvement in medical well-being and neurobehavioral and family function.[11] Neurobehavioral benefits included better autonomic or motor system regulation and self-regulation and reduced need for facilitation.[11] Given the diversity of the NICU settings and populations, the biggest differences in beneficial outcomes were appreciated in the most challenged settings (e.g., NICUs initially using the least developmental care, families with multiple social and cultural vulnerabilities, the sickest infants).[11]

Another RCT studied the effectiveness of NIDCAP initiated within 72 hours of NICU

* References 8, 9, 11, 270, 271, 335.

admission in 30 preterms (28–33 weeks' gestational age [GA]) on brain structure and function.[7] **The group of preterms receiving NIDCAP showed significantly better neurobehavioral functioning at 2 weeks' and 9 months' corrected age on mental and psychomotor development than that of the control group.** Changes in the brain on MRI included a more mature brain fiber structure between brain regions (e.g., frontal to occipital; frontal to parietal) than is consistent with enhanced neurobehavioral functioning. **The study's conclusion is that the quality of early experiences (e.g., before term) significantly alters brain structure and function.[7] Several more recent RCTs of NIDCAP show improved health and neurodevelopmental outcomes, shorter length of stay, and less chronic lung disease (CLD) for VLBW preterms and severe intrauterine growth restricted (IUGR) preterm infants at 2 weeks' corrected age, 9 months corrected age, and at 8 years. Higher quality of developmental care in the NICU is associated with better neurobehavioral performance (i.e., better attention and self-regulation, less excitability and hypotonicity, lower stress scores, and better language skills at 36 months).**[289-291]

Preterm infants are not the only infants at risk from the stress of overstimulation in the NICU. **Acutely ill infants and chronically ill infants with prolonged hospitalization also experience stress.** A term infant with persistent pulmonary hypertension (see Chapter 23) is particularly vulnerable to repeated handling, procedures, and interventions that decrease Pao_2. Thus, these infants are managed on a minimal intervention regimen: Care is organized, coordinated, and individualized to decrease noxious stimuli and physical manipulations. The chronically ill infant with bronchopulmonary dysplasia (BPD) has been shown to improve when behavioral or environmental changes were initiated.

The ultimate goal of intervention strategies in the NICU is to facilitate and promote infant growth and development and thus task mastery.[334] During rapid stages of brain development, neuroprotection of the preterm and sick term infant's brain in the NICU by providing an environment that nurtures brain growth and minimizes brain injury is essential.[50,247] **In the NICU, these goals are achieved by the following:**

- Altering the environmental and caregiving stressors that interfere with physiologic stability
- Promoting individual neurobehavioral organization and maturation by identifying and facilitating stable behaviors and reducing stressful behaviors
- Conserving energy
- Teaching parents to interpret infant behavior
- Promoting infant-parent interaction and caregiving

Core measures for evidence-based developmental care have been identified: (1) protected sleep; (2) pain and stress assessment and management; (3) developmental activities of daily living, such as positioning, feeding, and nonnutritive sucking (NNS); (4) family-centered care; and (5) a healing environment.[93]

Establishing biorhythmic balance and physiologic homeostasis is necessary for survival and is enhanced by a sensitive, responsive NICU environment. **An unresponsive environment may so stress the preterm infant that apnea, bradycardia, and other physiologic instabilities severely compromise and prolong recovery.**[156,227,334,413] For the hospitalized infant, development of the sense of self and trust is undermined by noncontingent stimulation that prevents establishing a sense of competence and control of the environment.[158] When the ventilated infant experiences hunger or is wet, he or she cannot signal the care provider with a cry because of the tube. Thus, the infant experiences a need but cannot signal and bring care and relief. The infant soon learns that he or she is not in control of the situation. Similarly, another intubated infant may be quietly asleep and not experiencing a need, but it is "care time," so the nurse moves, wakes, changes, and generally disturbs the infant. This infant also soon learns about not being in control of the situation.

Hospitalized infants, especially those with prolonged stays, may exhibit the classic signs of institutionalized infants or infants suffering from maternal deprivation (Box 13.5).[392] It is the goal of "environmental neonatology"[158] to prevent this maladaptive behavior by altering the NICU to be more developmentally appropriate and responsive to infants. **Normalizing the environment begins with an assessment of the stimulation to which the individual infant is exposed.** The type (i.e., noxious versus pleasant;

BOX 13.5 CRITICAL FINDINGS

CLASSIC SIGNS OF "HOSPITALITIS"

Asocial Behavior

- Gaze aversion—fleeting glances at caregiver with inability to maintain eye contact
- Flat affect—social unresponsiveness (little fixing and following; little smiling) to caregiver
- Little or no quiet alert state—infant abruptly changes state and often is described as "either asleep or awake and crying" (crying is only "awake" state); out-of-control crying

*Touch Aversion**

- Becomes hypotonic or hypertonic with caregiving or attempts at socialization
- Fights, flails, and resists being cared for or held
- Aversive responses (see Table 13.4) to caregiving or holding

Feeding Difficulties

- Have multiple origins, including delayed onset of oral feedings, touch aversion around mouth secondary to invasive procedures, multiple caregivers, feeding on schedule rather than demand
- Rumination syndrome—voluntary regurgitation, a form of self-comfort and gratification when environment is not nurturing or gratifying

Failure to Thrive

- Poor or no weight gain despite adequate caloric intake
- Develops mental delays (language, motor, social, emotional)

* Infant associates human touch with pain.

contingent versus noncontingent), amount, and timing of stimulation should be noted. To decrease noxious stimuli, no infant should have "routine" care (e.g., all infants are suctioned every 2 hours; all infants have a glucose test every 4 hours).[156] **Care should be individualized by asking these questions: "Why are we doing this procedure?" and "Is this procedure necessary for this infant's care?"** Overstimulation in the NICU occurs when 81% to 94% of all contacts are medical or nursing procedures, an average of 40 to 132 of which are performed per day.[124] The frequency, pattern, and trends of caregiver encounters and disturbance have not changed over the past 20 years,[19,68,334] although caregivers grossly underestimate the amount of handling to which NICU infants are exposed. Nurses, who are best able to control overstimulation, provide the majority of handling, sleep disruption, excessive disturbance, and noncontingent interaction to these fragile infants (number of contacts ranging from 79 to 164 times, evenly distributed over a 24-hour period).[19] Painful, invasive procedures that are not vital to the individual infant are stress-producing events that should be eliminated (see Chapter 12).

Rest may be the most important environmental change.[181,334] Sleep disruption is stressful to preterm and sick term neonates in the NICU and alters weight gain, visual development, state regulation, cortical growth, and physiologic stability.[66,160] **Disturbing preterm infants for care every 3 to 4 hours during the night and exposure to light for less than 15 minutes does not prevent preterm infants from developing circadian rest-awake/active patterns or appropriate weight gain as long as they are exposed to regular light-dark cycles.**[199] In a study of ventilated extremely LBW (ELBW) infants, the relationship between hypoxemia and state revealed that sleep disruption with its accompanying motor activity was associated with hypoxemia more often than when these infants were in active/quiet sleep.[227] Recommendations of this study include (1) using strategies (e.g., clustering care, kangaroo care [KC]) to promote sleep in ventilated infants and (2) sleep cycling analogous to in utero patterns (e.g., more quiet sleep) to improve ventilatory stability, decrease hypoxemia, and improve oxygenation.[227] **Quiet sleep for preterm infants is enhanced by (1) no caregiving; (2) social interaction, especially with the parents in skin-to-skin care; (3) NNS; and (4) lateral positioning.**[236] A recent study showed that rapid sleep onset in premature infants in the NICU is facilitated by distal skin vasodilation.[28] Quiet sleep is disrupted with routine and intrusive care.[184] Individualized developmental care promotes sleep.[5]

Although rest periods are necessary for normal growth and development and optimal immune function,[361] **care continues to be evenly distributed over 24 hours without adequate periods of undisturbed rest.**[5,334] **Rest periods of less than 60 minutes are ineffective and insufficient for the preterm to complete a normal sleep cycle.**[334] The length of rest periods in most NICUs has not changed (Table 13.5), and institution of a rest period (even only 1 hour in length) does not necessarily decrease the amount of disturbance.[185] A recent study of "hands

TABLE 13.4 CRITICAL FINDINGS
Self-Regulatory Versus Stress Behaviors

ORGANIZATION	DISORGANIZATION
Physiologic	
Cardiorespiratory: stable heart and/or respiratory rate; regular, slow respirations	Cardiorespiratory: increase or decrease in respiratory rate; irregular respirations; apnea; gasping; bradycardia; blood pressure instability; sneezing, hiccoughs, coughing, sighing
Color: pink, stable	Color: mottling, duskiness; cyanosis—central or generalized; pallor or plethora
Gastrointestinal: tolerates feedings	Gastrointestinal: abdominal distention; spitting up; vomiting; gagging; stooling
Behavioral	
Body movements smooth and synchronous: consistent tone of all body parts; arms and legs flexed with smooth movements	Tremors, jittery and jerking movements; hypotonia or hypertonia (flaccid trunk, extremities; movements arching, flailing, extended extremities; finger splays, fisting)
States: well-defined sleep-wake	Unable to modulate states: sudden state changes; more active than quiet sleep; awake states with gaze aversion, frowning, grimacing, staring, irritability, wide-eyed "help me" look
Self-quieting behaviors: hand-to-mouth, hand or foot clasping, finger folding or grasping, sucking, foot or leg bracing	Limited use of self-quieting behaviors (may need assistance from caregiver)
Attentive behaviors: alert gaze; fixes and follows visual stimuli; ceases to suck or slows suck rate, turns toward auditory stimuli, smiles; imitates; opens mouth, extends tongue; vocalizes: coos, babbles, habituates to stimuli	May demonstrate any of the foregoing stress signals when attempting to interact with one or more modes of stimuli (e.g., rocking, talking) simultaneously in environment (either animate or inanimate)

Data from Als H, Brazelton TB. A new model of assessing the behavioral organization in preterm and full-term infants: two case studies. *J Am Acad Child Psychiatry* 1981;20:239; and Gorski PA. Stages of behavioral organization in the high-risk neonate: theoretical and clinical considerations. *Semin Perinatol* 1979;3:61.

TABLE 13.5 REST PERIODS FOR NICU INFANTS: RESEARCH BASIS

AUTHOR, YEAR	LENGTH OF REST PERIOD
Korones, 1976[211]	Range of mean rest periods 5.6–19.2 min
Duxbury, 1984[113]	Average time of 30.2 min
Evans, 1994[124]	Time between handling: 1–38.45 min in first nursery 1–60 min in second nursery
Appleton, 1997[19]	2–59 min
Levy, 2017[233]	50.9 min (+26.2 min); median 2.3 min

NICU, Neonatal intensive care unit.

on" care evaluated 25 term and near-term infants in the NICU and found **that the maximum duration for rest between handling sessions was 50.9 minutes (+26.2 minutes) with a median of 2.3 minutes between handling contacts.**[233] Regardless of behavioral state, the infant was disturbed: (1) 29.5% in active sleep, (2) 23.1% in quiet sleep, (3) 29.9% when awake, and (4) 17.4% in an indeterminate state. With sleeping neonates, awakenings and arousals occurred 57% of the time. With "hands on" care, shallow

breathing—primarily when the infants were in active sleep—occurred between 16% and 28% of the time, apnea occurred 8% of the time, and oxygen desaturations occurred 19.5% of the time.[233] **Nurses have a low level of knowledge about neonatal sleep and should be prime advocates for guarding sleep and knowing that adequate sleep is necessary to protect the development of the neonate's brain while in the NICU.**[257]

A fetus in utero and a term infant at home relate to a minimum of caregivers and thus need to learn one or only a few sets of cues. **Consistency of caregivers is essential for an infant's developmental agenda. Multiple caregivers in the NICU confuse the infant by providing many care-related cues for the infant to learn—many techniques of handling and many emotional, nonverbal messages to decode. *Primary nursing* minimizes the number of care providers, because the primary nurse and one or two associates always (or as much as possible) care for the infant; assess, revise, and write the care plan; and coordinate care.**[247] ***Primary nursing*** **also adds consistency and continuity for parents and satisfaction for nurses.**[247]

The infant's state or level of arousal provides an appropriate context for caregiving. Some infants exhibit a low threshold for stimuli; they are easily overwhelmed and fatigued. Others with a higher threshold are quieter, more difficult to arouse, initiate less, and thus receive less interaction.[12] **Organizing care to be reciprocal to the infant's state reinforces the infant's competence in signaling a need (sense of self) and having it met (sense of trust and mastery).** As the infant matures, feeding on demand rather than on a schedule not only teaches this valuable lesson but also increases absorption and use of caloric intake.[156,384] If the infant is asleep, ask: "Should we do this now? Would another time be better?" In some centers, physicians make an appointment with the nurse to examine the infant at a time that is optimal for the infant.

Because preterm infants exhibit short duration of state cycles until around 38 weeks, they have decreased tolerance for stimuli. **The smaller, sicker, and less mature the infant, the less he or she is able to handle stimuli.** Some preterm infants tolerate all care done at once and long periods of rest; others do not and need care spread out to decrease overstimulation and decompensation. ***Clustering of care*—performance of several procedures together in a short period—**may result in more physiologic alterations (changes in cardiorespiratory stability, changes in blood pressure, increased cortisol levels, and heightened pain responses) than a single care-taking event or the actual length of the handling episode.[183] **Studies show increased and prolonged behavioral motor responses and increased cortisol levels indicative of stress during clustered care; clustered care is especially stressful for preterms less than 28 weeks' gestational age.**[182] Clustering care may not ensure long rest periods, because 50% of all rest periods in several NICUs were shorter than 10 minutes (see Table 13.5).[124] **If the practice of clustering care—with its prolonged disturbance of the preterm infant—results in alterations of vital signs, oxygen saturation, and infant stress and fatigue, then care should be individualized and provided to minimize physiologic and behavioral disturbances.**[171,183,227,334] A study of medically stable preterms found that after nursing interventions, these infants generally sleep, either from satiety or from the significant energy expenditure associated with caregiving.[399]

Even "preterm growers" may be unable to tolerate more than one stimulus at a time. They feed best if visual, auditory, and social stimuli are not provided until after the feeding. As the infant matures and is able to tolerate integrated experience, multimodal stimuli are provided.[449] Studies of multimodal stimuli (e.g., auditory, tactile, vestibular, visual) provided to preterms demonstrate (1) increased alertness, (2) earlier discharge, (3) faster progression to full oral feedings, (4) improved organization of behavioral states, (5) stable respiratory rate and oxygen saturation, and (6) a significant decrease in resting heart rate.[449,450]

Alterations in the individual infant's daily schedule are made to accommodate a more flexible or structured schedule—whichever is better for the infant.[158] **Assessing the infant before, during, and after an interaction or intervention guides the care provider in adapting care and the environment to the individual infant** (Table 13.6).

An organized infant is able to interact with the environment without disrupting his or her physiologic and behavioral functioning.[12] **When a disorganized preterm interacts with the environment, signs of physiologic and behavioral stress may occur (see Table 13.4), in which case the interaction should cease.**[171,210] The potential effects of stress and trauma to fragile preterm infants have not only short-term but also long-term impacts on their

TABLE 13.6 PARAMETERS FOR ASSESSING INTERACTION AND INTERVENTION WITH NEONATES

TIME FRAME	ASSESSMENT
Before	
Gather baseline data **before** touching the infant	Gestational age and postconceptual age Diagnosis Level of physiologic homeostasis: Previous vital signs Oxygenation state—continuous pulse oximetry or transcutaneous monitor Neonatal state: Sleep—deep, light, drowsy Awake—quiet, active alert, crying Self-regulatory versus stress behaviors (see the Critical Findings in Table 13.4)
During	
Gently and as unobtrusively as possible assess physiologic and behavioral signs during intervention	Level of (current) physiologic homeostasis—vital signs and changes: Observation (without touching infant)—color, posture, general appearance, respiratory rate, temperature (skin, incubator), blood pressure (transducer), oxygenation (from continuous monitor) Quiet (with minimal disturbance)—auscultate heart, lungs, and abdomen; axillary temperature, blood pressure (cuff); head-to-toe assessment; oxygenation (saturation decreases with distressful, disturbing stimuli) Neonatal state change: Sleep—deep, light, drowsy Awake—quiet alert, active alert, crying Self-regulatory versus stress behaviors (see Table 13.4)
After	
Assess physiologic and behavioral signs after intervention (delayed reactions may occur minutes after care)	Level of physiologic homeostasis Vital signs—Returned to baseline values? More stable or less stable than baseline values? Neonatal state change—Return to baseline state? To a higher state? Unable to be consoled? More consolable left alone?

outcomes.[337,386] An intubated preterm infant cared for in a NICU with a strict suction "routine" every 2 hours responds with profound cyanosis, lowered $TcPo_2$ and pulse oxygenation, and bradycardia and requires bagging after every suction (with no secretions obtained), an obviously unnecessary and stressful intervention. In a less rigid, more individualized care setting, that same infant may signal the need for suction by becoming restless, by a decrease in oxygenation, or by heart rate changes (tachycardia or bradycardia). Suctioning improves the infant's condition—the infant lies quietly and has improved oxygenation, and the heart pattern stabilizes. This infant has signaled his or her need, and the care providers have read the cues and responded with a stabilizing intervention—the infant has not been stressed by an unnecessary procedure.

Knowledgeable professionals are able to role model for and teach parents how to relate to their premature infant.[208] Parents are taught to recognize and use infant states to maximize appropriate interaction.[208] The drowsy premature infant may be unable to engage in eye-to-eye contact with their parents or be able to sustain it for too short (for the parents) a period. Waiting until the infant is more awake to initiate eye contact is more rewarding for the parent and less stressful for the infant. **Role model for parents that their infant is an individual and, although premature, can signal for more or less stimulation** (see Table 13.4).

A preterm infant who is lightly touched may startle, jerk, or withdraw from parental touch. In response, the parent suddenly and sadly pulls his or her hand away and is reticent to touch the infant again. Intervention includes helping parents read cues and learn appropriate responses to their infant. Teach parents how to recognize a stressed infant and how to intervene. **At the same time, be sure to acknowledge the parents' knowledge of the infant and support them. Above all, do not patronize. Professionals have much to learn from parents, who are "professionals" in their own right. The prime rule of relating to infants is this: The infant leads; the adult follows.**

Feeding a premature infant may be difficult because the infant "goes to sleep" during feedings. The usual parental ministrations of talking to the infant, soothing with touch, or holding upright on the shoulder may not work with a fussy, irritable preterm infant.

The preterm infant's behavior may be so disorganized, unpredictable, or misunderstood by the parents that an appropriate response is not possible.[6,156] Thus, parents often become exhausted, bewildered, and frustrated in their encounters with their preterm infant's behavioral response to their care as rejecting and unloving: "My baby doesn't like me." **Teach parents that their infant's disorganization with stimuli is related to prematurity (i.e., an immature CNS) and not to parent ministrations. Reassure them that as the premature infant grows and displays maturational changes, he or she will be able to tolerate more stimulation** and will be more responsive to their care.

Just as parent-infant interaction is responsible for normal development of the term infant, parent-infant interaction is crucial in the development of at-risk infants. Many parents of premature infants have been observed making heroic efforts over long periods to interact with their less alert, active, and responsive infants.[156,275] Parenting the preterm has been described as "more work and less fun." **Setting parents up to succeed involves placing parents in situations in which they will experience positive feedback from their infants.** Suggesting and role-modeling intervention strategies show parents what and how to play and interact with their infants. Parent participation in intervention strategies is ensured by stressing how important it is to infant development, that professionals are too busy to provide all the necessary interventions, and that parents are in a unique position to provide developmental care in the hospital and at home after discharge. **Parents, with help from professionals, are the ideal planners and providers of developmentally appropriate intervention strategies[380]** (see Table 13.1).

A rooming-in setting for parents and their at-risk newborns is the best environment for cues to be learned and care given according to these cues. **Unlimited and unrestricted contact of parents and newborns should be the policy in every normal, medium-risk, and high-risk nursery** (see Box 29.2). Providing a single-room NICU, a family room, bonding room, or apartment in which parents and their soon-to-be-discharged newborn can room-in helps the transition from hospital to home care. Rooming-in before discharge gives mothers and fathers an opportunity to assume full responsibility for their infant's care, tests the reality of caregiving, helps them learn caregiving activities and their infant's behavior patterns, and confirms their readiness for independent parenting and the infant's readiness for discharge.

Intervention Strategies

Because infants experience their environment through sensory processes, intervention strategies are based on tactile/kinesthetic, auditory, visual, olfactory/gustatory, and communication skills. **Interventions must be individualized according to the infant's state, sensory threshold, physiologic homeostasis, and stability or stress cues.**[124,183,227]

CIRCADIAN RHYTHMS

In utero, the states of the fetus are regulated by the sleep-wake cycles of the mother. In the NICU, multiple intrusions disrupt regulation.[358-360] How this affects an infant is not fully known, although limited energy may be drained, the infant may be subjected to further stress,[6,158] neurodevelopment altered, and outcomes of therapeutic interventions may not be optimized. To minimize interruptions and excessive handling, infants should not be awakened when asleep; if they must be awakened for care, it should be during active sleep by talking softly and stroking gently.[5,110] Appointments for examinations should be made before feeding to decrease unnecessary disturbance of sleep but with enough rest time (if needed) before actual feeding.

Adequate numbers of caregiving encounters—physical assessment, vital signs, diaper or linen change, and procedures—must be balanced against constant manipulations.[123,156] **Because essentially all NICU (levels II and III) infants are continuously monitored, "laying on of hands" every 1 to 2 hours is often unnecessary. Thorough physical assessment and vital sign recording every 4 hours is easily alternated with recordings from the monitors every 4 hours. Thus, the infant is evaluated every 2 hours but not disturbed that often.** An acutely ill infant may need closer observation, but alternating "hands-on" with monitor readings accomplishes the goal without overwhelming an infant with few reserves. **One systematic review recommends regulating elective care (i.e., routine laboratory draws, x-rays, and cardiac assessments) so that it is not being done during sleep.**[422]

Sleep-wake patterns are influenced by feeding method[404] and schedule,[60,61] temperature, position, CNS maturation, birth weight, caregiving practices, and environmental effects (e.g., ambient light, noise, day/night).[221,358-360,415] **In the NICU, activity/rest patterns are evident as early as 35 weeks' post-conceptual age and cycle at 3-hour intervals, related to feeding schedules.**[60] During the first week at home, the 3-hour sleep-wake cycle established in the NICU is replaced by a circadian rhythmicity.[61] Sleep-wake patterns in breastfed and bottle-fed infants differ. During the first month of life, full-term breastfed infants awaken more and sleep less during the night.[149]

Day-night cycles are facilitated by afternoon naptime and nighttime in which the dimming of lights or covering of incubators and cribs with blankets and quieting of NICU noise enable infants to sleep. Deep, quiet sleep is facilitated by quiet and dark, soft music or nature sounds, gentle stroking of the head, and self-regulated tasks (self-sought proximity of infant to "breathing bear").[403] Maintaining daily naptime and nighttime hours helps infants reset their diurnal rhythms and become accustomed to sleeping in dim light and a quiet environment. **Percentage of sleep time and duration of sleep for preterm infants in the NICU is longer at night than during the day,** and better sleep patterns were associated with being male, younger PMA and chronological age, smaller in body weight, and less illness severity.[221] Among convalescing preterm infants (<34 weeks' gestational age), four standard rest periods per day resulted in (1) increased daily weight gain, (2) increased sleep, (3) less-active states during nap time, (4) decreased occurrences of apnea, and (5) by 3 weeks, less quiet waking time and longer uninterrupted sleep episodes.[181,411] **Uninterrupted sleep and diurnal rhythmicity also are associated with improved state organization in VLBW infants and with less fussing and crying.**[359,360]

TACTILE AND KINESTHETIC INTERVENTION

Because the sense of touch is highly developed in utero, even a very immature preterm has acute tactile sensitivity. **For newborns, human touch is the most important tactile stimulation.** Not all touch is equal, however, nor is it responded to equally by term or preterm infants who are well, critically ill, or recovering from illness. One study has shown the effect of the vulnerability of LBW infants in their response to the nurturing touch of their mothers. Nurturing maternal touch was associated with a secure attachment in robust infants; in highly vulnerable, sick LBW infants, this same nurturing touch was associated with a less secure attachment.[444] Any type of tactile stimulation is composed of six factors: duration, location, action, intensity, frequency, and sensation. **Tactile sensation both arouses and quiets. Gentle but firm handling quiets infants because they feel more secure; light, uncertain touch often results in agitation and withdrawal. Handling for routine care (e.g., vital signs, changing the diaper or position, venipuncture for blood draws or placement of IV lines, feeding, heelsticks, suction, and physical or neurologic examinations) can result in hypoxia, increased intracranial pressure, episodes of apnea/bradycardia, agitation, elevated pain and stress scores for VLBW preterms, and increased or decreased heart rate and blood pressure.**★ Applying developmentally supportive care to "routine" procedures such as diapering decreases the physiologic stress response in fragile preterm infants and offers them repeated opportunities to enhance their neurodevelopment.[123]

Handling. How a neonate is handled during care affects his or her physiologic and behavioral response. Use of body containment during

★References 68, 98, 99, 123, 125, 241, 332, 399, 462.

suction decreases the physiologic and behavioral responses to this stressful procedure.[402] Comparing preterm responses to swaddled and unswaddled weighing, unswaddled infants exhibit more physiologic distress, more motor disorganization, poorer self-regulation, and more need for caregiver facilitation than when they were swaddled for weighing.[302] **Transferring preterm infants from the incubator to the parent for holding or KC is stressful.** One study evaluated physiologic disorganization in preterms according to the method of transfer from the incubator for KC (nurse picking up the baby and transferring to the parent versus the parent picking the baby up directly from the incubator).[307] Both transfer methods resulted in increased physiologic and motor disorganization (i.e., oxygen desaturation, tachycardia, cyanosis/pallor, hypotonia, decreased self-regulation, and increased need for caregiver facilitation to maintain physiologic stability during transfer). In both methods of transfer (which lasted 6–9 minutes), the ventilator was disconnected (for 5 seconds). **Both the infant's desaturation readings and tachycardia recovered to baseline levels faster with the parent transfer.**[307]

Excessive handling of preterm, VLBW, or sick neonates results in significant physiologic consequences, such as blood pressure changes, alterations in cerebral blood flow, hypoxia, and other stress behaviors.[241] One study of ventilated VLBW infants found an average of 53 handling episodes, for an average length of 3 minutes over a 24-hour period.[68] These infants had pain scores significantly higher after than before handling regardless of the reason for the handling (i.e., invasive/noninvasive or social/nonsocial).[68] A recent study compared the frequency and severity of hypoxemia episodes (SpO_2 <75%; SpO_2 <85%) in 24 mechanically ventilated premature infants during daytime (0900-1700) and nighttime (2100-0500) hours.[193] **Nighttime hours had fewer and less severe hypoxemia episodes when compared to daytime hours. The researchers concluded that the babies were handled less frequently and had less sensory stimulation during the nighttime hours.** A particularly vulnerable group of preterm infants, those with periventricular leukomalacia (PVL), react to handling and multisensory stimulation (e.g., auditory, tactile, visual, vestibular) with an increase in heart rate above their already higher resting heart rate.[377] These CNS-injured preterms require close observation and monitoring during handling, stressful procedures, and interventions.[450]

A total body position change is not considered a painful procedure, but in LBW preterm infants with endotracheal tubes and umbilical artery catheters, the handling necessary to change the infant's position elicits pain behaviors.[126] **Nonpainful tactile stimulation (e.g., routine nursery handling) of preterm infants has been shown to produce equal or higher levels of physiologic stress activation than does a painful stimulus (e.g., heelstick).**[68] In the same study, the relatively low behavioral activation during "routine handling" led the researchers to conclude that this tactile stimulus was not unpleasant to the infants, even though it produced a high level of physiologic stress response.

In the NICU, infants who are repeatedly subjected to painful, intrusive procedures develop touch aversion—the association of human touch with pain. Tactile vulnerability has also been found in infants who require multiple postnatal medical interventions, who are exposed to illicit drugs in utero, and whose mothers had their own predisposition regarding being touched (a genetic component?).[443] These infants cry uncontrollably, squirm away, flail arms and legs, and recoil when touched, knowing that pain will soon follow. An infant who has received ventilatory therapy may have touch aversion around the mouth: The infant is averse to facial stroking and rooting, has a hypersensitive gag reflex, and refuses to nipple feed. Painful procedures should be minimized to those absolutely (medically) indicated—no infant should be subjected to "routine" painful procedures. During those necessary procedures, it is essential to provide body containment, comfort measures (e.g., a pacifier), and adequate pain relief (see Chapter 12).

Touch. Touch that is not related to caregiving (i.e., social contact) should be provided by parents and professionals when the preterm infant is aware, alert, and receptive. When parents touch their babies, the amount and types of touch vary widely—most frequently, holding, stroking, rubbing, or placing a finger in the infant's hand. Preterm infants respond individually and physiologically to their parents' touch; there is more variation in heart rate and oxygen saturation levels compared with baseline values. These variations depend on gestational age, infant state, and the amount of handling before parent

handling.[170] **Less touching by the nurse within the 2 hours before parental holding results in less mean decrease in heart rate during parental holding.[170] Parents provide more positive touch (kissing and stroking); preterm infants are more likely to smile and sleep for their parents** compared with responses after a nurse's touch. In animal studies, increased parental touching in infancy results in changes in brain structure, decreased levels of stress hormones, and better ability to survive a stressful environment.[437] **Parental touch of preterm humans enables them to withstand the stress of illness and the NICU environment.** Recent research on somatosensory processing found that the degree of prematurity at birth determines the extent to which the immature brain responds to light touch, so that **supportive experiences (such as breastfeeding and skin-to-skin contact) are associated with stronger brain responses,** and **painful stimuli are associated with a reduced brain response to the same touch stimuli.**[259]

Nonpainful touch such as stroking (of the head, trunk, or hands) during care may calm, soothe, and prevent touch aversion. **Stroking of physiologically stable preterm infants has been associated with increased activity and alertness, a faster regaining of birth weight, more rapid weight gain, less crying and apnea, enhanced developmental status, and better social scores.[169,171] In another study, systematic stroking of ventilated preterms resulted in no adverse effects on oxygenation and respiratory or heart rates.[104] However, in preterm infants (26–30 weeks' gestation) who are not physiologically stable, stroking results in decreased oxygen saturation, signs of behavioral stress (e.g., grasping, grunting, gaze aversion), and more avoidance cues (e.g., grimacing, yawning, fussing or crying, tongue protrusion).** Other behavioral and physiologic effects include heart rate and blood pressure changes, changes in respiratory rate and rhythm, increase in avoidance signals (e.g., increased startle reflex, agitation, crying), increase in activity and movement, and decreased visual responsivity.[99,170,241,307]

If the preterm infant becomes agitated with stroking, a hand firmly placed on the head and lower back, buttocks, or abdomen often quiets.[91,169] **Hand placement without stroking does not decrease oxygen saturation or alter heart rate and has a soothing effect (i.e., decreases active sleep, increases quiet sleep, decreases respiratory and heart rates, decreases motor activity and behavioral distress) on small preterm infants.[171,172,188,285] Handle gently to avoid stressful reactions (e.g., flailing, arching, oxygen desaturation) and enable the infant to become calm and rest between caregiving.** Parents should be taught and encouraged to provide their preterm with "gentle human touch"[169,285] in the form of supportive containment with their hands, use of gradual and rhythmic action, observation of infant responses (see Table 13.4), and modification, alteration, or cessation of touch when necessary.[169,171]

Therapeutic touch (TT), a complementary therapy of balancing and increasing energy to promote healing, does not require physical contact, as hands are suspended over the body. A randomized double blind study of the use of TT on 10 physiologically fragile, very preterm infants showed no adverse effects (i.e., oxygen desaturations or apnea).[451] Clearly more research is indicated.[388]

Massage. The touching and stroking of massage stimulate nerve pathways and aid myelinization by increasing hypothalamic activity and production of the growth hormone *somatotropin*. In animal studies, touch deprivation decreases growth hormone secretion, which results in undergrowth of all organ systems; a return to normal secretion occurs with tactile stimulation.[374] Massage affects the maturation of the brain's electrical activity and simulates intrauterine development as observed in term infants.[166] A growth gene that responds to tactile stimulation has been discovered; this suggests a genetic origin for the touch-growth relationship.[134] Because touch stimulation of the inside of a neonate's mouth increases the release of gastrointestinal food absorption hormones (i.e., gastrin, insulin), it is postulated that the tactile stimulation of massage leads to a similar hormone release. Assays of glucose and insulin levels in heelstick samples of preterm infants suggest that massaged infants show increased levels of insulin.[134]

Research on massage therapy with preterm infants has been conducted on medically stable, growing infants (i.e., preterm growers). A recent systematic review found clear benefits of massage in hospitalized preterm infants.[14] Despite positive outcomes of massage research in Table 13.7 and its cost effectiveness in decreasing length of stay, only

TABLE 13.7 BENEFITS OF MASSAGE WITH PRETERM INFANTS: RESEARCH BASIS

STUDY	RESULTS
Three times/day massage of preterms with physiologic and biochemical measurements[373]	21% increase in daily weight gain Discharged 5 days earlier Superior performance on habituation Fewer stress behaviors (mouthing, grimacing, clenched fists) Increase in catecholamine secretion in neonatal period (analogous to the normal developmental increase after birth) Increase in vagal activity
10 healthy preterm "growers": three times/day massage for 15 min in a randomized sequence of 5 days of massage and 5 days without massage[217]	Energy expenditure significantly lower after 5 days of massage than after 5 days without massage in metabolically and thermally stable preterms Decreased energy expenditure may contribute to enhanced growth caused by massage
Massaged for 15 min three times/day for 5 days: 68 preterms (mean GA = 30 wk) with either light- or moderate-pressure massage[135]	Fewer stress behaviors and less activity from first to last day of the study Moderate-pressure group: significantly more daily weight gain; more relaxed, less aroused than light-pressure group
80 preterms randomized to moderate-pressure massage or standard care[106]	Increase in vagal activity and gastric motility, which may contribute to greater weight gain in massaged preterms
72 preterms randomized to massage or control therapy[107]	Greater increase in body temperature in massage versus control preterms (even though incubator portholes were open for the massage but not for the control group)
Massaged or exercise for 10 min three times/day for 5 days[108]: 30 preterms randomized to moderate-pressure massage *or* passive flexion and extension of limbs 21 preterm infants (8 males and 13 females)[389]	Greater weight gain in both massage and exercise groups due to different mechanisms: • Massage increased vagal tone • Exercise increased calorie consumption Massaged male infants had improved autonomic nervous system function during caregiving and sleep compared with nonmassaged male preterms. There was no difference in heart rate variability between massaged and nonmassaged female preterm infants.[389]
40 stable preterm infants randomized to 20 minutes of massage twice daily for 4 days or no massage [33]	Lower level of transcutaneous bilirubin and more defecation in massaged versus non-massage group.[33]
Mother Massage	
104 VLBW infants (≥750 to ≤1500 g; ≤32 wk GA) randomized to control or standard care with maternal massage four times/day of face and limbs with passive limb exercises[281]	Significantly lower incidence of late-onset sepsis Discharged from the hospital 7 days earlier Improved neurodevelopmental outcomes at 2 years CA with massage[343]
66 stable preterm infants (32 massaged by their mother; 34 control group)[1]	Lower pain scores after massage with heelstick and at discharge; higher cognitive scores at 12 months' CA compared with control group. No difference in weight gain, LOS, breastfeeding duration, and motor skills between two groups.
Medically stable preterms (33–37 wk GA; BW 1500–1999g) randomly assigned to massage group or massage with sunflower oil by their mothers three times/day for 14 consecutive days[129]	Oil massage group: mean weight at 1 month and 2 months of age significantly greater than body massage alone group
Eight minutes of mother massage of preterms within 24 hours of discharge and repeated on day of discharge[3]	Less maternal anxiety on the day of discharge when mothers massaged their preterm infants[3]
Olive oil massage for 10 days, three times/day for 15 minutes versus massage without olive oil[191]	Daily average weight gain with olive oil massage (21 g) compared to weight gain of 7 g without olive oil[191]

BW, Birth weight; *CA,* corrected age; *GA,* gestational age; *LOS,* length of stay; *NICU,* neonatal intensive care unit; *VLBW,* very low birth weight.

38% of NICUs practice massage on their stable preterm infants.[136,439] Massage therapy provides social touch rather than painful touch, prevents or treats touch aversion, and should be taught to and provided by parents in the hospital and at home.[276] Confidence in parenting skills and tactile communication between parents and infant is encouraged when parents massage their infant. **Because massage has not been studied in acutely ill preterm infants, its use should be confined to preterm growers.**[134,429] Chronically ill infants (e.g., babies with BPD or congenital heart disease) may exhibit physiologic and behavioral disorganization with massage, so the risk-benefit ratio must be assessed carefully. The M technique, used for fragile infants who do not tolerate conventional massage, is a gentle, structured stroking technique that reduces stress and anxiety. Outcomes of those exposed to the M technique included (1) lower heart rate, (2) increased oxygen saturations, (3) increase in quiet sleep, and (4) fewer behavioral distress cues.[388]

Varying sensations and touch patterns keep infants interested in stroking and massaging. As a preterm infant matures and is able to tolerate variety, he or she should be introduced to different textures (e.g., lambskins, stuffed toys, cotton, satin). Baby clothes provide various textures, decrease heat loss (especially hats), and make the infant more attractive. ("He looks like a real baby!"; "She looks like a girl because her shaved head is covered!")

Holding. When the infant is preterm or a sick term baby, holding him or her—an essential step of parent attachment—is disrupted. Some NICUs promote parental holding as soon as possible, whereas others have specific protocols about weight criteria and extubation before parents are able to hold their infant.[143] A national survey on holding policies found (1) written protocols for conventional holding (26%) and for KC (40%), (2) for extubated infants: 73% offered KC, 99% conventional holding, and (3) for holders of extubated babies: mothers 73% KC, fathers 68% KC, and 99% conventional holding for both parents.[143] Potential benefits of enhanced parent-infant interaction and attachment, closeness of parents to their infant, increased lactation, and improved parental self-esteem are factors that influence staff to facilitate holding.[143]

A prospective cohort study of parental presence and holding in the NICU found significant neurobehavioral benefits for preterm infants less than or equal to 30 weeks' gestation.[354] **Early parenting (i.e., holding) in the NICU resulted in lower arousal and excitability, better quality of movement, less stress, and less hypertonic muscle tone, thus a developmental advantage.**[354] Another study conducted in an urban NICU with low levels of parental presence and holding compared the neurodevelopmental outcomes of preterm infants (<30 weeks' gestation) cared for in single-family rooms versus open ward NICU rooms.[337] The study outcome showed that at age 2 years, children cared for in the private rooms had lower language acquisition, more externalizing behaviors, and a trend toward lower motor scores than those in open wards. The researchers were surprised by their findings and remarked on the relative **sensory deprivation of the preterms in private rooms whose parents were not often present and handling their infants. Long periods of sensory deprivation—lack of parental presence, holding, and auditory stimuli—may be as detrimental as the sensory overload of a noisy, open NICU.**[337] A qualitative study of factors affecting parental presence found that active involvement in the care of their extremely preterm infants, including skin-to-skin holding, increased their motivation to be present and their feelings of control.[176] Factors discouraging parental presence included excessive noise[38] and light levels in the NICU and dismissive staff attitudes.[176] A more recent study of predictors of parental involvement in the care of their premature infants (n=81; <32 weeks' gestational age) found that being Caucasian, older, married, employed, having fewer children, having familial support, and providing breastmilk were all associated with more parental presence.[339] More holding of the infant was associated with fewer medical interventions, an employed father, being Caucasian, fewer children, and having family support. **Outcomes of parental holding resulted in better reflex development at term age, and skin-to-skin holding resulted in better reflexes and less asymmetry at term and better gross motor development at 4 to 5 years of age.** [339] **Communicating to parents the importance of their presence and their care for their baby, as well as providing a welcoming, nurturing, and comfortable place for parents is the responsibility of all the NICU staff, especially nurses.**

KC (Fig. 13.1), skin-to-skin contact between parents and infant by placing the infant in a

vertical position between the maternal or paternal breasts, benefits both parents and neonates (Box 13.6). Another position, "supported diagonal flexion," for skin-to-skin care has been studied to facilitate more face-to-face exchanges between mother and infant in the NICU.[62] **Supported diagonal flexion resulted in more eye contact between mothers and their infants, more maternal vocalizations, caressing, and decreased postpartum depression scores without altering physiologic stability in the premature infants.** KC for the healthy preterm has been used in the delivery room, in the transitional period (see Chapter 5), for adoptive parents, and for transport. National surveys of holding/KC have been conducted and have found that KC is practiced more commonly in subspecialty (level III) than in specialty (level II) care NICUs.[120,143]

KC is well tolerated in the first week of life by preterm infants with current or resolving neonatal illness. KC of preterm infants for even 1 hour has been shown to provide benefits: significant decrease in heart and respiratory rates and increased temperature and oxygen saturations, especially in SGA and female preterms.[47] An RCT of healthy preterms (33–35 weeks' GA) found that KC for 3 hours improved breathing patterns and resulted in no apnea or bradycardia or periodic breathing or temperature instability.[248] KC improves gas exchange in preterm infants of less than 1800 g. The smallest infants (<1000 g) remained more clinically stable (i.e., smallest increase in heart rate, highest decrease in respiratory rate and increase in oxygen saturation, no hypothermia) compared with infants larger than 1000 g.[141]

A randomized study of three holding methods (i.e., KC, cuddled, and a no restrictions method) in preterms between 32 to 35 weeks' gestation **concluded that both KC and cuddled holding by parents may provide equal developmental**

FIGURE 13.1 Kangaroo care.

BOX 13.6 BENEFITS OF SKIN-TO-SKIN CONTACT/KANGAROO CARE

Parental

- Activates maternal/paternal processes of search for meaning and mastery of the experience of premature birth
- Increases maternal/paternal self-confidence, competence, and self-esteem; lower levels of stress related to "incompetence"[139]
- Enhances parent-infant attachment[83]
- Increases parental oxytocin levels[432] and decreased cortisol levels resulting in decreased anxiety levels[83,90]
- More stress in mothers of late-preterm infants related to more facilitated progression of the mother-infant relationship[369]
- Initiates and maintains maternal/paternal behavior
- Positively affects mother's mood/behavior; less maternal depression; calming (decrease in salivary cortisol levels)[41,83,303]
- Favorable impact on maternal parasympathetic nervous system as measured by heart rate variability[64]
- Lowers parental heart rate and blood pressure[197]
- Positive and personally beneficial experience
- Positively affects parental identity and knowledge of infant[363]; positively affects the process of becoming a parent[18]
- Increases confidence in meeting infant's needs
- More frequent visiting
- Parental eagerness for infant's discharge
- A restoring experience and an energy-draining experience[18]
- Long term:
  - More consistent/contingent maternal/paternal responses at 15 months of age
  - More sensitive, less intrusive, more reciprocal interactions from 6 months to 2 years from both mothers and fathers
  - More affectionate touch, more adaptive to infant signals, and infants more alert during interactions at 3 to 6 months
  - Less maternal/paternal separation anxiety at 6 months
  - Improved family cohesiveness
  - Fewer reports of difficulties with breastfeeding
  - 20-year follow-up of original cohort: parents more protective and nurturing[79]

Continued

BOX 13.6 BENEFITS OF SKIN-TO-SKIN CONTACT/KANGAROO CARE—CONT'D

Neonatal

- Thermal synchrony: mother's body temperature rises and falls to maintain infant in neutral state (see Chapter 6)
  - Higher body temperature resulting from advanced maturation of thermoregulation
  - Distal skin vasodilation promoting rapid sleep onset[28]
- Cardiopulmonary:
  - Adequate or improved oxygenation; reduction in oxygen requirement[197]; minimal decrease in cerebral oxygenation while gavage feeding[263]
  - Fewer/no episodes of periodic breathing, apnea, and bradycardia
  - Lower diaphragm electrical activity while being ventilated by NARS[390]
  - Lower heart rate/stable respiratory rate[83]
  - Higher vagal tone: indicative of quicker maturation of the autonomic nervous system (even in infants with complex congenital heart disease)[173]; favorable impact on premature infant parasympathetic nervous system as measured by heart rate variability[64]
  - Stable vital signs, oxygen saturation, and temperature before, during, and after cardiac surgery[174]
- Breastfeeding:
  - Increased milk supply
  - Increased incidence and length (even in very-low-birth-weight preterms)[138,381]
  - Increased exclusive breastfeeding[51]
  - Positive effect on growth in VLBW infants[381]
  - Distinct oral microbiologic pattern and an accelerated pace of microbial repertoire maturity[178]
  - Attainment of full breastfeeding in the NICU at a median age of 35 weeks' PMA[313]
- Behavioral:
  - Increased alert activity
  - The longer the period of KC the more the preterm neonate made physical contact attempts with mother during breastfeeding[308]
  - Increased deep, quiet sleep[34]
  - Improved self-regulation: sleep-wake cycles, arousal, sustained exploration
  - Better emotional regulation and arousal modulation for interaction and rest
  - Decreased stress response: decrease in beta-endorphin and cortisol levels[432]; less stress response to diaper change[253]
  - Decreased or no crying[125,126]
  - Increased en face positioning
  - Better orientation and habituation
  - Less pain response to painful procedure in both preterm and term infants (see Chapter 12)
  - Accelerated brain maturation
- Earlier discharge/ lower cost:
  - Increased weight gain[127,381]
  - No increased infection/fewer infections[51]; decreased severity of infection and mortality; decolonization from resistant bacteria on the infant's skin[220]
  - Out of incubator earlier
- Decrease in mortality of infants with birth weight <2000 g[51]
- Regulatory interaction:
  - Behavioral
  - Sucking
  - Neurochemical (decline in plasma oxytocin levels)[209,442]
  - Metabolic
  - Sleep-wake cycles/improved sleep organization
  - Cardiovascular
  - Endocrine
  - Immune
  - Circadian
- Long-term:
  - Increased length and head circumference at 9 months and 1 year of age
  - Less crying at 6 months of age
  - Higher psychomotor scales at 6 months and higher mental scales at 6 months to 2 years
  - Enhanced mental and psychomotor development at 1 year
  - Better self-regulation, less frustration, and better able to calm themselves at 1 year of age
  - Improved cerebral motor pathways and synaptic efficacy at adolescence
  - Enhanced cognitive development and executive functioning from 6 months to 10 years; by 10 years of age: attenuated stress response, improved autonomic functioning, organized sleep, and better cognitive and behavioral control
  - 20-year follow-up of original cohort: fewer school absences, less hyperactivity, aggressiveness, externalization, and socio-deviant behavior in young adults. Larger volume of left caudate nucleus on brain MRI[79]

MRI, Magnetic resonance imaging; *NARS,* noninvasive neutrally adjusted respiratory system; *NICU,* neonatal intensive care unit; *PMA,* post menstrual age.
Data compiled from references 51, 65, 89, 131, 141, 155, 242, 243, 245, 248, 250, 306, 309, 310, 362, 363, 376, 377.

benefits in the form of early behavioral organization to preterm infants.[303] All infants being held either conventionally or by KC should be monitored continuously for vital signs and oxygen saturation.[248]

Parental holding is often (17%–33%) limited or not supported by nurses and physicians.[43,143] Parents identify both the hospital staff and the environment of the NICU as barriers and supportive of KC.[43,228] A recent phenomenologic study found that NICU nurses attempt to balance the developmental needs of infants with parental readiness to participate in skin-to-skin care.[215] A second phenomenologic study found that information, communication, consistency, and support from staff to parents along with knowledgeable staff assisted in parents performing and having positive experiences with KC.[228] Barriers to holding infants include (1) infant safety concerns (e.g., accidental extubation, loss of arterial/venous lines, vital sign or oxygenation instability) and (2) reluctance of professionals and families to initiate or participate in KC (e.g., adding to RN workload and belief of losing control because of limited access to the infant, difficulty providing care, lack of experience, used for babies who are not developmentally ready, belief that technology is better than KC, belief by professionals that mother would feel trapped and stressed).[120,143,296] From the caregiver's perspective there are four themes in the process of facilitating skin-to-skin care: (1) varying thresholds of getting started, (2) defining adequate resources, (3) dealing with the demands and complexities of the neonate, and (4) balancing parental readiness for skin-to-skin care with the neonate's needs.[431] More than 60% of NICUs responding to one survey stated that low birth weight and gestational age were not contraindications for KC; many NICUs did not permit KC for babies on high-frequency oscillator ventilation (HFOV) or vasopressors.[120]

"Risky populations" for KC include infants who are intubated (Fig. 13.2), have arterial/venous lines and chest tubes, are on pressors to maintain blood pressure, and are on HFOV. A prospective, nonrandomized study in a level III NICU found **a low risk of mechanical complications and no increased risk of infectious complications with skin-to-skin contact in neonates with an indwelling umbilical venous catheter.[75]** One of the national surveys found that 64% of NICUs offered conventional holding to parents of intubated infants and 45% offered KC of intubated infants. The second survey found that 60% of NICU nurse managers thought that intubated infants should not receive KC.[120,143] In one study, 43 intubated, hemodynamically stable preterms less than 1500 g were assessed for 90 minutes (15 minutes of transfer; 60 minutes of KC; 15 minutes of transfer) and found to have stable heart rates, oxygen saturations, axillary temperatures, and mean arterial blood pressures.[23] The researchers concluded that KC was safe for these ventilated preterms under their study conditions. A more recent study of 40 preterm infants (27.6 to 28.9 weeks' gestation) receiving invasive (endotracheal tube ventilation) and noninvasive (continuous positive airway pressure [CPAP] and high-flow nasal cannulae) respiratory support found no difference in physiologic parameters (i.e., regional cerebral oxygenation, heart rate, pulse oximetry values, temperature, or FiO_2) while being held skin to skin for 90 minutes when compared to incubator care.[242]

FIGURE 13.2 Kangaroo care of awake, alert, intubated, and ventilated premature infant.

On the basis of a 3-year study in five NICUs of mechanically ventilated infants receiving KC, selection criteria (Box 13.7) and a safe protocol (Box 13.8) for KC in this population have been developed.[250,251] During this study, no adverse physiologic or behavioral events or accidental extubations occurred. None of these babies was agitated, and all slept and tolerated KC well. Previously

BOX 13.7 SELECTION CRITERIA FOR KANGAROO CARE WITH VENTILATED INFANTS

- Birth weight >600 g; ≥30 weeks' GA
- Ventilator for at least 24 hr before first kangaroo care
- SIMV: <35 breaths/min; F_{IO_2} <0.50 (50%)
- Stable vital signs (TPR, B/P) and oxygen saturation
- Stable blood gases, bilirubin level
- No signs/symptoms of sepsis
- Not receiving vasopressors; no chest tube
- Lines (Broviac, umbilical, arterial, IVs) well secured

B/P, Blood pressure; F_{IO_2}, fraction of inspired oxygen; *GA,* gestational age; *IV,* intravenous; *SIMV,* synchronous intermittent mandatory ventilation; *TPR,* temperature, pulse, respiration.

Modified from Ludington-Hoe S, Morgan K, Abouelfrettoh A. A clinical guideline for implementation of kangaroo care with premature infants of 30 or more weeks' postmenstrual age. *Adv Neonatal Care.* 2008;8:S3.

reported parental perceptions of KC with ventilated babies include the following:

- Ambivalence toward KC: yearning to hold the infant yet being apprehensive about it
- The necessity of a supportive environment
- The special quality of parent-infant interaction: intense connectedness and active parenting

Perhaps these parental and staff concerns may be overcome with careful selection of infants, education about KC, a consistent procedure for transfer, increase in confidence of the staff assisting parents in KC, and a clinical guideline for implementing KC.[177,250,251,309,310] Parents and staff need education about KC, and staff can offer KC to parents instead of waiting for parents to request this intervention.* Recommendations about KC include the following:

*References 120,177,228,248

BOX 13.8 PROTOCOL FOR KANGAROO CARE WITH VENTILATED INFANTS

In Preparation for Transfer

1. Record baseline vital signs, oxygen saturation, and ventilator settings. Secure and maintain continuous monitoring of these parameters during kangaroo care (KC) to determine infant's tolerance of KC.
2. Place infant supine on a clean blanket (folded in fourths) with assistance of second person, and note changes in vital signs, saturations, or ventilator settings.
3. Auscultate chest and evaluate breath sounds, suction endotracheal tube, and change diaper.
4. Drain water from ventilator tubings to decrease resistance, maintain airflow, and prevent retrograde water flow toward infant when moved or positioned lower than or at the level of the ventilator.
5. Assess infant's responses: Wait 15 minutes to enable physiologic adaptation (e.g., return of baseline vital signs/oxygenation for 3 minutes). If still unstable at 15 minutes, the infant is probably not stable enough for KC at this time.
6. Position the reclining chair near the ventilator, making sure there is ample tubing length.
7. Two or three staff members will assist the parent in transfer of the infant:
   - One person gathers lines to one side of the infant.
   - One person transfers and secures the ventilator tubing.
   - One person assists the parent.

Transfer Procedure

1. After a staff member disconnects the endotracheal tube (ETT) from the ventilator, the parent slides his or her hands under the blanket and infant, lifts both, and places the infant prone against his or her chest in one movement. Reconnect the ventilator tubing and let the infant stabilize. (If the infant was not placed on a clean blanket or it was soiled before transfer, the parent can lift the baby and a clean blanket is placed over the infant when he or she is prone on the parent's chest.)
2. Disconnect ventilator tubing from ETT and move parent backward toward recliner, having him or her sit down when he or she feels the edge of the chair against the calves of the legs. Reconnect the ETT to the ventilator tubing.
3. Assist the parent in being comfortable by raising the footrest, position the infant in a flexed position with head and neck in a neutral position to avoid ETT movement (e.g., downward into the bronchi with head flexion or possible extubation with head extension) and/or obstructive apnea with head flexion or extension if the infant is on nasal continuous positive airway pressure.
4. Secure the ventilator tubing by draping it over the parent's shoulder. *Do not tape the tubing to the blanket, parent clothing, etc.*
5. If using ISC temperature control (on the radiant warmer/incubator), turn to air control, set temperature at 33°C while the baby is receiving KC, and monitor the infant's skin temperature from the temperature gauge on the radiant warmer/incubator. (There is then no need to uncover or cold stress the infant to take a temperature.)
6. Maintain continuous electronic monitoring throughout KC; check both the infant's and/or parent's condition every 10 minutes during KC.
7. If the infant's condition remains stable, facilitate KC for a minimum of 1 hour.

BOX 13.8 PROTOCOL FOR KANGAROO CARE WITH VENTILATED INFANTS—CONT'D

Transfer after Kangaroo Care

1. Slowly place the recliner in an upright position and assist parent to move forward to the front edge of the chair.
2. One staff member handles the lines and another disconnects the ETT from the ventilator lines.
3. Assist the parent to stand, reconnect the ETT to the ventilator tubing, and let the infant stabilize.
4. In one movement, disconnect the ventilator tubing and place the infant in the radiant warmer/incubator.
5. Reconnect the ventilator tubing to the ETT, stabilize, and secure all lines inside the radiant warmer/incubator.
6. Document KC, length of session, and how the infant and parent tolerated KC.

ISC, Infant servocontrol.

Modified from Ludington-Hoe S, Ferreira C, Swinth J. Safe criteria and procedure for kangaroo care with intubated preterm infants. *J Obstet Gynecol Neonat Nurs.* 2003;32:586; and Ludington-Hoe S, Morgan K, Abouelfrettoh A. A clinical guideline for implementation of kangaroo care with premature infants of 30 or more weeks' postmenstrual age. *Adv Neonatal Care.* 2008;8:S3.

- It is an important therapeutic intervention for healthy preterms (gestational age ≥34 weeks) and their mothers in a modern, well-equipped NICU[248,447] as recommended by the World Health Organization.[457]
- It is a simple, safe, cost-effective intervention that reduces severe infant morbidity without serious side effects, and more well-designed randomized controlled trials are needed.[89]
- Parents need education, a trusting relationship, individualized support, and consistent information and communication from health care providers to be comfortable with KC.[228]
- Nursing staff members need education about the benefits of KC and confidence and competence in skills to transfer and evaluate families and infants during KC.[177]
- Well-written NICU protocols for KC should contain criteria for initiation, positioning, transfer to/from KC, care practices while in KC (including use of continuous cardiorespiratory monitoring, proper positioning of head, endotracheal tube, stability of arterial and venous devices, and all life support equipment), provision of privacy, parental role, and interventions for neonatal instability.[27,228,309,310]
- Written information for parents about the benefits of KC, expectations of parents during KC, and preparing for KC (e.g., eat, go to the bathroom, bring a drink) assist parents and provide consistent, complete information to all families.[228]

One should note that fathers can also participate in KC without endangering the infant. Aside from the positive effects on the baby, paternal KC enhances the engagement and attachment of the father, helps fathers attain their paternal role, adapt to the crisis of preterm birth, includes the father in the infant's care, and facilitates more equal parenthood.[43,228,312] A recent study of the effects of the first skin-to-skin contact of fathers in the NICU with their preterm infants found a decrease in paternal physiologic stress responses (i.e., lowered blood pressure and cortisol levels).[425] The HUG Your Baby program improves fathers' understanding of their preterm infant behaviors, lowers paternal stress, and improves paternal confidence.[198]

Bathing. **There is a lack of evidence of the safety and efficacy of sponge bathing preterm babies in the NICU on a daily or every-other-day schedule.[144] Sponge bathing critically ill infants (28–34 weeks' gestational age) results in significant increases in behavior state and activity levels (i.e., motor stress behavior, stability, reorganization), increase in stress cue frequency, increase or decrease in heart rate, decrease in oxygen saturation preterm, and need for enhanced temperature support.**[234,332,401] These detrimental effects caused by handling were exhibited most frequently by neonates of younger gestational ages. Because sponge bathing of critically ill preterm infants clearly increases physiologic risk and provides no clear benefits, the procedure of routine bathing of these infants is unnecessary and not recommended.[21,252,333] **Frequency of sponge bathing can be reduced to from every other day to 3 or 4 times weekly** without increasing skin flora colony counts or colonization with pathogens.[144,225,252,348] (See Chapter 19.)

Waiting to bathe these infants until they are physiologically stable with introduction of the bath as a "recovery milestone" for parents to complete is a more developmentally and physiologically appropriate practice.[333] In one study, late preterm infants (LPI) who were tub bathed experienced less hypothermia and were significantly warmer at 10 minutes and 30 minutes after bathing compared with LPIs who were sponge bathed.[244] Parents may tub bathe the premature grower, and this may provide a soothing, relaxing, tension-relieving experience of multiple textures (i.e., water, water temperature, soap, washcloth).

A study of the effects of tub bathing on preterm infants (done by nurses) found disruption of sleep and an increase in stress behaviors. The study recommended considering the effects of "routine" nursing procedures and modifying handling of the preterm to promote recovery, growth, and development and to decrease stress.[234] It is evident that **more supportive behaviors by the nurse (i.e., position support and containment) enhanced the preterm infant's self-regulation during bathing.[235]**

Swaddled bathing (i.e., swaddled in a flexed, midline position in a blanket while bathing) provides containment and helps the infant self-regulate. Benefits of swaddled bathing are listed in Box 13.9. A protocol for swaddled bathing is available with best results occurring with an initial water temperature of 100° to 101° F and a bath length of 8 minutes.[349]

Self-Consoling. Consoling hand-to-mouth behaviors are observed more frequently during caregiving (by nurses, rather than parents) and before and after feeding (especially in gavage-fed infants). **Hand-to-midline behaviors are encouraged by cradling the infant for feedings (for both bottle and gavage feedings if the infant tolerates it) with both arms in the midline.** If a premature infant needs an oxygen hood, using one large enough so that the infant's whole upper body will fit inside encourages hand-to-mouth quieting (Fig. 13.3). VLBW preterm infants whose whole body was not inside the oxygen hood have been videotaped expending energy in persistent attempts (30–40 minutes) to self-console and reduce stress by trying to get their hands to their mouths. In a recent study, **preterm infants who displayed more stress behaviors also displayed more self-consoling behaviors.[146]**

Use arm restraints only when necessary, and immobilize the extremity in a physiologic position. Release and exercise the restrained

BOX 13.9 BENEFITS OF SWADDLED BATHING[76,116,132,349]

- Decrease in physiologic and motor stress
- Better energy conservation
- Improvement in state control
- Less crying and agitation
- Fewer stress cues
- Less temperature instability

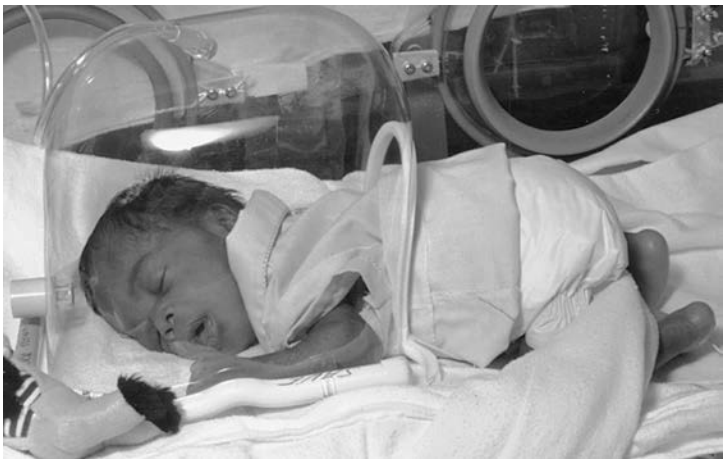

FIGURE 13.3 Preterm infant in oxygen hood that is large enough to accommodate upper body to facilitate hand-to-mouth behavior. Note sling that helps maintain flexion without frog-leg position.

extremity with each caregiving encounter. Avoid restraining both arms so that one is free for hand-to-mouth behaviors. If both must be restrained (e.g., the infant pulls out the orogastric tube), give the infant a pacifier.

Positioning. Preterm infants display motor development that is different from that of term infants.[288,370] A continuous assessment of muscle tone, response to positioning and handling, oral-motor function, and response to sensory stimuli provide data for individualizing intervention. The goal of intervention is to provide opportunities for normal development and organization of the sensory systems, detect early developmental problems, and educate parents about stimulation, handling, and positioning. Although some studies have shown that specific positioning for premature infants does not significantly affect development, others have shown that a developmental approach to care of VLBW infants greatly reduces the long-term negative effects of prematurity.[297]

Preterm infants usually have less developed physiologic flexion in the limbs, trunk, and pelvis compared with term newborns (Table 13.8). Even at 40 weeks' postconceptual age, preterm infants have less flexion than their full-term counterparts have. For preterm infants, long periods of immobilization without a positioning device on a firm mattress with the influences of gravity result in a number of abnormal characteristics: (1) increased neck extension with a right-sided head preference, (2) shoulder retraction and abduction (reduces forward rotation and ability to reach midline), (3) increased trunk extension with "arching" of the neck and back, (4) frog-leg position: hips abducted and externally rotated, and (5) ankle and feet eversion (Fig. 13.4).[288,413] These characteristics interfere with development of eye-hand coordination, head control in prone/sitting, crawling/walking, cognitive development, and equilibrium.[370] Box 13.10 **lists the reasons for proper positioning in the NICU.**

The infant should be provided with a variety of positions to avoid overstretching of the joints, facilitate development of flexor tone, and prevent deformities. Goals of proper positioning include (1) optimizing alignment (e.g., neutral neck/trunk and foot positions), semiflexed, midline extremity posture; (2) supporting posture and movement within containment boundaries (avoiding producing a barrier of immobilization), (3) modifying positioning and handling to support behavioral state regulation of sleep-wake states; and (4) providing positions that encourage controlled, individual exposure to stimuli while monitoring for signs of behavioral stress from overstimulation and adjust stimuli accordingly. A physical therapist can be helpful in facilitating these positions. Systematic, targeted education for nurses and residents as well as "position champions" significantly improved positioning of infants in the NICU after 18 months.[78,265]

A change in body position influences ventilation by alteration of lung function, but how often should repositioning occur? Sixty preterm infants receiving respiratory support (mechanical

TABLE 13.8 DEVELOPMENT OF TONE*

GESTATIONAL AGE (WK)	DEVELOPMENT
28	Completely hypotonic and lacks all physiologic flexion
32	Hips and knees begin to show some flexion while arms remain extended
34	Flexor tone apparent in legs
36	Loose flexion of arms and legs evident and grasp reflex present
40	Develops tone in utero and develops flexed position in intrauterine space; after birth, reflex activity and central nervous system maturity help term infant unfold and extend; term infant holds all four limbs in flexed position

*Muscle tone develops in caudocephalic and centripetal (distal to proximal) directions and interacts with simultaneous cephalocaudal development of movement to help affect posture. Although knowledge of normal development before term helps detect signs of abnormality, variability of ±2 weeks' gestational age must be considered.[112]

From Anderson J, Auster-Liebhaber J. *Phys Occup Ther Pediatr.* 1984;4(1):89; Dubowitz LM, Dubowitz V, Goldberg C. Clinical assessment of gestational age in the newborn infant. *J Pediatr.* 1970;77:1; Palisano R, Short M. *Phys Occup Ther Pediatr.* 1984;4(4):43.

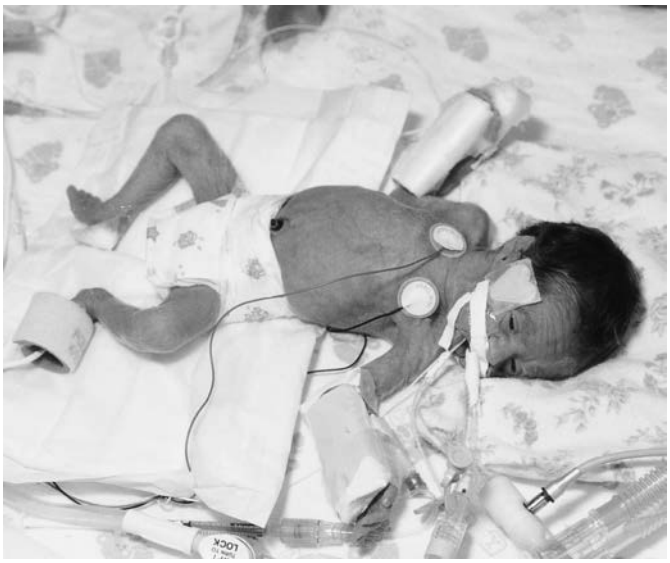

FIGURE 13.4 Premature infant hypotonic resting posture exhibiting the W configuration of arms, frog-leg position of the legs, abducted hips, externally rotated ankles, everted feet, and asymmetric head position. This position promotes positional deformities and developmental gaps and delays. (From Hunter J. The neonatal intensive care unit. In: Case-Smith J, ed. *Occupational Therapy for Children.* 4th ed. St Louis, MO: Mosby, 2001.)

BOX 13.10 REASONS FOR PROPER POSITIONING

1. Inhibits or shortens dystonic phase while infant remains in fetal position during postnatal period
2. Facilitates hand-to-midline and midline orientation[112]
3. Stimulates visual exploration of environment (through head to midline)
4. Facilitates development of head control (making feeding easier and helping respiratory problems)[112]
5. Helps balance flexors and extensors to facilitate symmetric posture[288,297,370]
6. Helps develop antigravity movement
7. Enhances comfort and decreases stress
8. Has an organizing effect that facilitates development of flexor tone[112]
9. Promotes normal and prevents abnormal development[112,370]
10. Helps enhance development of motor skills, reflexes, and postural tone[297,370]

From Pelletier-Sehnar JM, Palmeri A. High-risk infants. In: Pratt PN, Allen AS, eds. *Occupational Therapy for Children.* 2nd ed. St Louis, MO: Mosby; 1989.

ventilation or CPAP) had their end-expiratory levels and ventilation distribution measured at 30 minutes, 2 hours, and 4 hours after repositioning.[186] The three body positions used during the study were prone, quarter turn from prone, and supine. **Spontaneously breathing infants had better ventilation homogeneity 2 hours after repositioning and global end-expiratory levels at 4 hours. Infants receiving both CPAP and mechanical ventilation had improved ventilation homogeneity at 2 hours after repositioning that continued to be maintained at 4 hours. Those infants on CPAP had an improved global end-expiratory level at 2 hours after repositioning.**

Side-lying is used to improve visual awareness of hands, encourage hands-to-midline movement, and discourage the frog-leg position. In this position, the infant can bring the hands to the mouth for sucking and self-comforting. Side-lying is best maintained with swaddling or commercial positioning devices rather than single blanket rolls (Fig. 13.5). Position extremities so that the bottom arm is in a comfortable position and the upper shoulder and hip are slightly forward of the weight-bearing lower hip or shoulder, provide a small roll (e.g., folded cloth diaper or washcloth or small bean-stuffed toy), and bundle for security but not so that the upper extremity compromises chest expansion. Alternating sides reduces head molding and may prevent atelectasis of the dependent lung. The head and trunk should be maintained in neutral alignment (e.g., the head and trunk are in

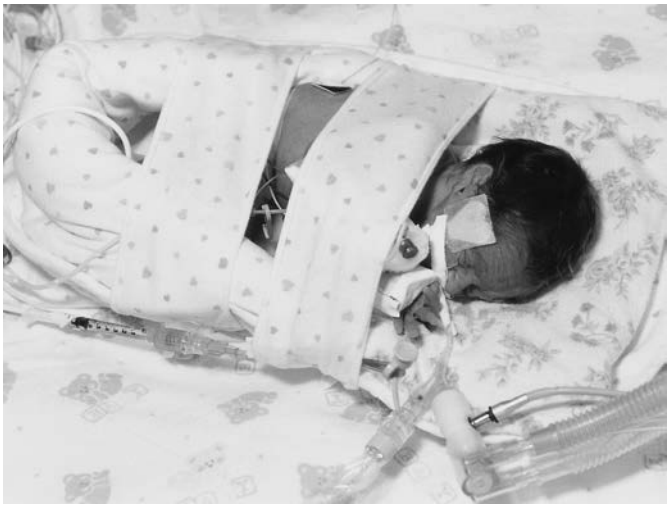

FIGURE 13.5 Small preterm infant in side-lying position supported in flexion and with a midline orientation of the extremities. (From Hunter J. The neonatal intensive care unit. In: Case-Smith J, ed. *Occupational Therapy for Children.* 4th ed. St Louis, MO: Mosby, 2001.)

the same vertical plane). **The left lateral position has been shown to improve oxygenation, lung mechanics, and breathing patterns in preterm infants, similar to the benefits of prone positioning.**[159] However a recent study showed that **lateral positioning of preterm infants** (median gestational age of 28.6 weeks) **receiving nasal CPAP resulted in increased respiratory rates.**[460] Left lateral position reduces gastroesophageal reflux, whereas right lateral position reduces gastric residuals.[118] **Longer sleep duration and less wakefulness in preterm infants occur when they are positioned flexed in the lateral position** compared to lateral positioning without flexion.[421]

To accommodate their ventilators, umbilical catheters, and other devices, acutely ill preterm infants may be positioned supine; the preterm neonate's head should be in the midline. Positioning VLBW infants supine with their heads turned to either side causes mechanical obstruction of cerebral venous return and alters cerebral blood flow, which may contribute to the development of intraventricular hemorrhage (IVH).[330] Cerebral (and mesenteric) tissue oxygenation was recently measured in clinically stable VLBW infants in two supine positions (i.e., with head tilted up 30 degrees and lying flat) and prone (lying flat).[103] Regardless of position these stable VLBW infants were able to maintain stable cerebral and mesenteric tissue oxygenation, both before and after feeding.[103]

Supine positioning does not promote flexion and may be stressful to acutely ill infants. Earlier studies found an increase in apnea, bradycardia, and periodic breathing in supine positioning, although a more recent study of 22 preterm infants with apnea and bradycardia found no significant difference in the incidence of clinically significant events between supine and prone positioning.[202] Placed supine, infants exhibit more startle behaviors, agitation, motor disorganization, calorie expenditure, and sleep disturbance (higher number of arousals/hour)[284] from environmental stimuli.

Prolonged supine positioning is associated with the hypertonic "arched" position (hyperextension of head, neck, and shoulder girdle) of many chronically ventilated infants (Fig. 13.6). Use of a gel or water pillow under the infant's head and neck (e.g., to the nipple level to prevent neck flexion or used as a mattress under the head or body of a VLBW infant) provides comfort and maintains neutral alignment.

Supine positioning should promote as much flexion as possible. Use of a positioning device of foam with the middle cut out and sloping under the scapulae is another method of obtaining supine flexion. Use of hip support results in less lower extremity abduction and external rotation than in infants without such hip support. Pillows filled with polystyrene beads (i.e., preterm beanbags) require skill for optimal positioning and

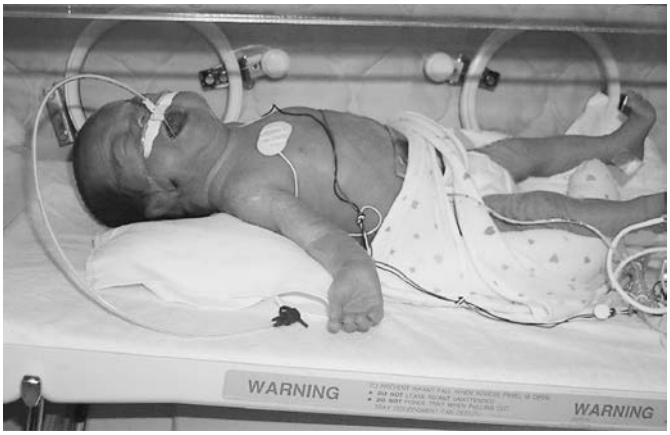

FIGURE 13.6 Supine positioning without positioning supports results in motor disorganization, agitation, arching posture, and burning of significant calories. (From Hunter J. The neonatal intensive care unit. In: Case-Smith J, ed. *Occupational Therapy for Children.* 4th ed. St Louis, MO: Mosby, 2001.)

close infant monitoring but are useful in providing positioning for very small premature infants (1000–1500 g).

Body containment increases the infant's feeling of security, promotes quieting and self-control, enhances physiologic stability, promotes energy conservation, reduces physiologic and behavioral stress, and enables stress to be better endured.[402] Without positional supports, many premature infants "travel" (no matter how many times they are returned) to the sides or bottom of their incubator. Parents and professionals are inclined to move the uncomfortable-looking infant back to the middle of a "boundary-less" world. Infants should be left where they feel safe and comfortable; if they become uncomfortable, they will let you know. **Providing boundaries (e.g., blanket rolls, positioning devices) stops this migration and the expenditure of precious calories that could go to growth.** Use of a **conformational positioning device that provides containment, boundaries, and security facilitates better sleep in preterm infants with less active awake time and crying** when compared to a standard mattress.[216]

Small, acutely ill premature infants who are positioned supine are often extremely agitated, thrashing arms and legs, tachycardic, and expending precious energy and calories. Instead of needing medications, these infants often are calmed by providing a nest of blankets or a commercial nesting device (which simulates the boundaries and security of the uterus). This artificial womb must be closely surrounding the infant to promote flexion, security, and quiet rest (Fig. 13.7). If agitation recurs, a limb (usually a leg) has extended outside the infant's secure boundary; flexing and returning it to the "womb" quiets the infant.[12] **Nesting and swaddling premature infants increases both total sleep and quiet sleep time.**[2]

Body containment maneuvers such as swaddling, holding on to a finger or hand, and crossing the infant's arms in the midline and holding them securely help with self-regulation during feeding, procedures, or other stressful manipulations.[91] A recent study of swaddling found wide variation in the positioning of the neonate's arms and legs.[140] **Safe swaddling includes positioning the baby's extremities in slight flexion and abduction.** Placing an infant's hips and knees in an extended position with swaddling increases the risk of hip dysplasia and dislocation.[189] Because being wrapped in a blanket with extremities flexed simulates in utero position, swaddling (1) improves flexed posture and flexor muscle tone, (2) facilitates behavioral responses, and (3) improves the development of primitive reflexes. **Swaddling is associated with a small but significant risk of sudden infant death syndrome (SIDS) when infants are placed on their backs for sleep, and swaddled infants placed prone have the highest risk of SIDS.** Swaddling is used most often in young infants to reduce crying and should not be initiated in infants older than 4 months of age; it should cease when an infant attempts to turn over and be completely stopped by 6 months of age.[329]

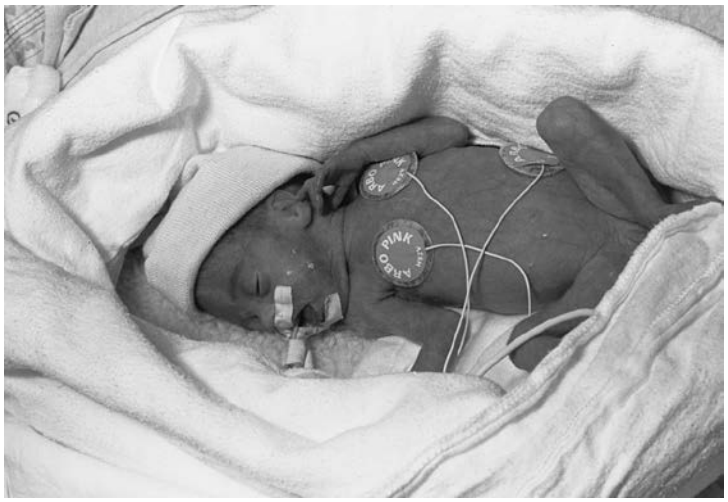

FIGURE 13.7 Very small premature infant resting quietly in a "nest" of pads and blankets.

Picking up the preterm infant from a supine position often produces startles, apnea, or head hyperextension. A better technique is to roll the infant prone, which flexes the head, and then flex the limbs onto the trunk and pick up the infant. If the infant has difficulty breathing in prone position, swaddle or contain the extremities before picking up the infant.

Prone positioning encourages the infant to work on using neck extension and promotes flexion of the extremities. Devices for prone positioning include a small hip roll or sling to assist in maintaining flexion, use of gel/water pillows for head support, and secure lower boundary for foot bracing. Use of a rolled cloth or gel pillow placed under the infant (from top of the head to the umbilicus) (1) provides elevation of the body to promote extremity flexion without placing excessive pressure on the knees and elbows, (2) enables the shoulders to round forward over the top of the roll, and (3) enables the legs to flex over the bottom edge of the roll. **Prone (versus supine) positioning has numerous benefits and is the position of choice for many NICU infants** (Box 13.11). The semi-prone position (¾ turn) decreases the variability of respiratory rate in preterm infants (median gestational age of 28.6 weeks) receiving nasal CPAP.[463] The quarter-prone position also has been shown to improve oxygenation of premature infants on CPAP.[420] **To improve sleep duration and quality, nurses are encouraged to assess each**

BOX 13.11 EFFECTS OF PRONE POSITIONING

1. Decreases heart rate variability
2. Improves oxygenation by 15% to 25%[39,159,357]
   a. Increased $TcPo_2$ values
   b. Increased Pao_2 values
   c. Decreased apnea, bradycardia, and periodic breathing
   d. Increased peripheral oxygenation and decreases cerebral blood flow[37]
   e. Decreases respiratory rate[69]
3. Improves lung mechanics and lung volumes[159,423]
   a. Increased lung compliance
   b. Increased tidal volume
4. Decreases energy expenditure[157]
   a. Increased quiet sleep; higher arousal threshold[194]
   b. Decreased awake time; more sleep time[69,77,194,284]
   c. Decreased caloric expenditure (median difference supine vs. prone: + 3.1 kcal/kg/day)
   d. Decreased heat loss[77]
   e. Less crying[77]
   f. Lower levels of activity[77]
   g. Lowers stress levels as measured by a reduction in salivary cortisol levels[69]
5. Decreases (by 50%) gastric residuals in the first 30 minutes after feeding[81]
6. Decreases gastroesophageal reflux[118]

individual preterm and more often use the position (prone vs. supine) that results in the least arousals.[284] Sleeping in the prone position does not improve oxygenation in preterms 32 weeks' PMA or older for infants without respiratory problems. The study concluded that **preterms older than 32 weeks' PMA and without respiratory difficulties should be placed supine and monitoring continued to ensure adequate oxygen saturation.** Use of a sheepskin or lambskin helps to further facilitate flexion and prevents skin abrasion, especially on the knees.

Sleep Position. The most recent American Academy of Pediatrics (AAP) position statement on infant sleep states that healthy infants should be placed *only* in the supine position for sleep beginning immediately after birth.[294] Infants should sleep in their own beds and in the same room with their parents for at least 6 months and preferably for the first year of life. Overheating sleeping infants; use of soft sleeping surfaces, stuffed toys, and positioning devices[418]; and inappropriate sleep environments (e.g., waterbeds, pillows, blankets, bumper pads, bed railings, bed sharing, and sitting/carrying devices)[88,148,355,375] should all be avoided in healthy infants.[294] Use of a pacifier for sleep and sleeping in proximity (same room) as parents is also recommended.[294] The Study of Attitudes and Factors Effecting Infant Care (SAFE) collected prospective data from a nationally representative sample of postpartum mothers about the intended sleep position and the actual positions infants were placed in for sleep.[88] Although approximately 70% of the mothers queried usually placed their infants to sleep supine, less than 44% who intended to use supine position actually placed their infants supine in actual practice. **African American mothers and mothers with less than a high school education were more likely to intend to use prone or side-lying position.** When advised by a doctor to use only supine positioning, mothers were less likely to use prone and side-lying for infant sleep.[88]

Use of side-lying and prone positioning, as well as containment with soft bedding for physiologically compromised term and preterm infants, is safe and appropriate in a NICU setting. Parents may question these practices; therefore, their physiologic base and rationale should be explained. **Parents should be taught that when their baby is medically stable, by 32 weeks' PMA,[294] he or she will be physiologically and developmentally mature enough to tolerate supine sleep position in preparation for discharge.[232] Many of the beneficial effects of prone positioning listed in Box 13.11 are no longer necessary[232] and become detrimental in increasing the risk for SIDS in the stable, mature preterm infant.**

Since the "Back to Sleep" campaign, the rate of SIDS has decreased by 53%,[294] but the SIDS rate in the United States (US) has minimally declined since 1999, and approximately 3500 sleep-related deaths occur in the US each year.[49,121] **SIDS rates are inversely associated with gestational age, and the risk of SIDS is three times higher in preterm infants.[168,315] VLBW infants (<1500 g), the group at highest risk for SIDS, have been found in one study to be more likely to sleep prone after discharge than larger LBW infants.[428]** Reasons cited by mothers included infant's preference and advice from professionals (NICU doctors, nurses) who may remain uncomfortable recommending supine sleep in this population[232,428] despite the AAP recommendations and the research that supports them[294] (Table 13.9). Among families with triplets and quadruplets, less than 80% of mothers used supine for sleep immediately after hospital discharge; use of supine positioning decreased over time, especially during daytime napping; 30% shared a bed with siblings; less than 50% slept in the parents' room; and use of a pacifier was low.[167]

Implementing "Safe Sleep" ("Back to Sleep") principles in the NICU remains a problem and influences parental behavior.[32,300,328] One study found that NICU nurses only followed safe sleeping practices 20% of the time before an evidence-based program promoting safe sleep began; after the implementation of the program safe sleep practices were used 90% of the time.[461] Nursing education with web-based learning and in-person teaching sessions improved compliance in safe sleep practices in two level III NICUs from 25.0% to 79.7%.[187] Another project to develop a safe sleep educational program and increase the percentage of eligible infants in a safe sleep environment in the NICU was conducted.[435] The process included a revised policy, educational updates for NICU staff, an educational packet and video for families, a wearable blanket, and an observation checklist. From a baseline of 21% of eligible NICU infants experiencing a safe sleep environment, safe sleep compliance increased to 88%.[435] Quality-improvement initiatives that

TABLE 13.9 SLEEP POSITION AS A RISK FACTOR FOR SUDDEN INFANT DEATH SYNDROME (SIDS): RESEARCH BASIS

SUPINE	PRONE
Preterm infants at 36–38 wk PCA[157] No significant difference in sleep organization based on body position More awakenings in supine vs. prone position Standard deviations of heart rate increase during quiet sleep in supine position; low frequency and high frequency of heart rate higher in supine vs. prone position in both active and quiet sleep states More sleep transitions, a lower arousal threshold, and higher heart rate variability while sleeping supine contribute to decreased vulnerability to SIDS	Prone position reduces spontaneous arousals from sleep in term infants,[322,356] which may be related to a decrease in cerebral oxygenation in prone sleeping[456] First quiet sleep after feedings significantly longer, fewer awakenings, and decrease in overall heart rate variability in prone vs. supine[157,356] Preceding characteristics of prone sleep constitute a higher arousal threshold, and thus increased vulnerability to SIDS in prone position[322,356,456] Decreased baroreflex sensitivity, which increases vulnerability to hypotensive events[459]
Full-term (n = 10) infants in prone/supine sleep positions given 0.4 mL water; instillation into the mouth resulted in airway protective responses of swallowing (95%) and arousal (54%)[195]	62 healthy, growing low BW infants (26–37 wk GA; 750–1600 g BW); sleeping position — a shift of EEG activity toward slower frequency, which may be related to mechanisms associated with a decrease in behavioral arousal in prone position[356,366]
Swallow rate rapid in supine position in response to small infusions of fluid, whereas respiratory rate remains largely unaffected When supine, term infants can coordinate rapid swallowing while maintaining breathing	A significant decrease in swallowing and breathing in active sleep in prone vs. supine position; airway protection is compromised in prone sleeping position during active sleep in healthy term infants exposed to minute pharyngeal fluid
Full-term (n = 3240) ≥37 wk GA evaluated in the first 24 hr of life for frequency/severity of spitting up incidents while asleep[400]: • 96.6% did not spit up during sleep. • 130 episodes of spitting up while sleeping supine (55% required no intervention; 37% brief bulb suction; 6% gentle stimulation; 2% wall suction). • <4% spit up while sleeping supine, and none required significant intervention or experienced serious sequelae.	Six episodes of spitting up while infants side-lying (66.7% no intervention; 33.3% bulb suction)

BW, Birth weight; *GA,* gestational age; *EEG,* electroencephalogram; *PCA,* postconceptual age.

identify barriers, change hospital policies, and provide safe sleep education for nurses and parents are needed to improve compliance with safe sleep recommendations for preterm infants.[300]

In term infants, supine sleep position may delay some motor milestones by 1 month but does not delay walking. Increased amounts of time in supervised prone play ("tummy time") encourage earlier motor milestone attainment in supine sleepers and helps prevent head molding. Head molding (i.e., bilateral flattening of the head and elongation of the face) is a significant problem in preterm infants; it results from flattening of the skull as the baby lies against the firm incubator mattress. To parents, this head flattening is concerning, and they may find the infant less cute and desirable than a term infant with a rounded head. **To prevent head molding, preterm infants are often placed on waterbeds, water pillows, air mattresses, or eggcrate-type mattresses, with varying results.** Preterm infants (<32 weeks' gestation with birth weight <1500 g) who are turned every 3 hours, repositioned in one of six positions, and never placed in the same position twice in 8 hours had significantly rounder head shapes from 9 to 13 weeks of life compared with infants repositioned according to a standard NICU procedure.[179]

Kinesthetic. A combination of vestibular and tactile stimulation increases quieting behaviors, decreases apneic and bradycardic episodes, entrains respirations, increases visual and auditory fixation, and increases brain growth.[210] Waterbeds provide contingent stimuli because

they move in response to the infant's movement; oscillating waterbeds provide rhythmic motion. Kinesthetic stimulation is provided by rocking chairs, hammocks, baby swings, and baby carriers, the effects of which have not been investigated. In Brazil, a combination tactile/kinesthetic stimulation program enrolling 16 clinically stable preterm infants under 2500 g was conducted and compared with a control group of 16 preterms.[133] Outcomes of the preterms receiving the tactile/kinesthetic program included (1) higher daily weight gain, (2) predominance of self-regulated behaviors (i.e., regular respirations, balanced tone, state of alertness, range of postures, coordinated movements, hand-to-mouth movement control, suction, grip, and support), and (3) a trend toward shorter length of stay.[133] An RCT of parent-administered physical therapy (promotion of head and postural control and midline orientation) to preterm infants from 34 to 36 weeks PMA resulted in improved motor performance at 37 weeks PMA when compared to usual care.[419]

Upright positioning in a car seat or infant seat encourages symmetry and spatial orientation. Soft rolls or foam padding maintains flexion; a rolled blanket in a horseshoe configuration around the infant's head and shoulders prevents lateral slouching. Carrying quiets the infant, provides sensory communication with the caregiver, changes the infant's environment, and provides visual, auditory, and tactile stimuli. A nasal cannula (see Chapter 23) and portable tank enable mobility for an infant receiving oxygen.

Rather than standardized protocols, tactile interventions must be individualized by assessing each infant's physiologic and behavioral responses before, during, and after touch (see Table 13.6). **While an infant is acutely ill, tactile intervention should include minimal handling, containment, and gentle touch (without stroking).** As the infant matures and becomes physiologically stable, stroking, rocking, and holding are integrated based on the individual infant's tolerance and preferences. In healthy preterm infants, a program of range-of-motion exercises with passive resistance is associated with an increase in weight gain and growth, bone mineral content and density, and muscle mass and a decreased risk for osteopenia.[239,430]

Cobedding. Cobedding, the practice of placing medically stable twins and higher-order multiples together in the same open warmer, incubator, or crib, was initiated after the observed stress response in separated siblings. **The practice of cobedding spread based on anecdotal information, because there is limited research to support or refute its use.**[219] Few differences between cobedded and noncobedded infants have been demonstrated. A study of 117 sets of twins randomized to cobedding or sleeping alone found that cobedding promoted self-regulation (i.e., more time in the same state, less time in opposite states, and less crying) and more quiet sleep without apparent increased risk.[175] Limitations of the research on cobedding include small sample size, short follow-up periods, lack of randomization, and blinding of evaluators.

Infection, safety, and parents continuing the practice after discharge are major concerns of cobedding. To date, increased infection rates in cobedded infants have not been reported. Infection concerns are addressed by good hand washing and color-coding of equipment. Other safety concerns include proper identification for medication administration and medical emergencies and maintenance of temperature stability for all cobedded infants.[13] Because parents continue care practices at home that they have witnessed and become accustomed to in the hospital, the possibility of continuing cobedding at home (and the lack of evidence as to its safety) must be considered.

The National Association of Neonatal Nurses (NANN) recommends that a decision to cobed be made with input from parents and should involve education of staff and parents about potential benefits/risks, the experimental nature of the practice, and the development of a clinical evaluation protocol to collect data on risks and benefits.[299] The AAP recommends separate sleep areas in the hospital and at home.[294] **Both NANN[299] and the AAP[294] have concluded that neither the safety or benefit of cobedding has been established by current research and that parents should be instructed to follow established safe sleeping practices at home.[294]**

AUDITORY INTERVENTION

The NICU is a noisy environment that has no diurnal rhythm or predictability; it is as noisy at night as in the daytime (Table 13.10).[102,158,269] An infant in the NICU is exposed to an onslaught of noise 24 hours a day for days, weeks, or months. At follow-up, preterm infants exhibit a lower threshold

for sound and a reduced responsiveness to auditory stimulation.[31] Assisted ventilation, severe asphyxia, drug therapies, and possibly acoustic insult account for the increased risk for sensorineural hearing loss in NICU infants. **The incidence of hearing loss decreases with an increase in gestational age. An increased risk of hearing loss is associated with being born very preterm and late preterm.**[180] Moderate to severe conductive hearing loss also occurs in 42% of VLBW infants. Conductive hearing loss is attributed to endotracheal intubation, poor eustachian tube function, increased otitis media, and CLD in preterm infants.

The first goal in auditory intervention is to assess the current level of noise in the NICU and decrease the noise decibel level wherever possible.[269,340] The noise environment of an individual infant depends on the type of NICU (single-family rooms or open-bay), ambient sounds in the nursery, the type of incubator and support equipment, and the baby's own behavior (e.g., quiet or crying). Noise measurement protocols must sample multiple noise sources and sites.[102,269] Some NICUs have installed decimeters that present a flashing or blinking light when the noise level exceeds a preset level (about 50–65 dB). Sources of noise include heating, ventilation, and air conditioner flow units (noise levels may decrease by 2.5–10.5 dB when these units are turned off). **The greatest contributor to loud noise in the NICU is talking and conversation by the staff.** Noise levels vary with type of room, location, time of day, and day of week within the NICU; therefore various locations or various times and days should be measured.[102,269,340]

Increased environmental noise levels are a stressor to all infants in the NICU—preterm infants and ill term infants (e.g., infants with persistent pulmonary hypertension of the newborn or drug withdrawal) (Box 13.12). The sudden, high-pitched, shrill, dysrhythmic noise of equipment alarms alerts the care provider, but it also results in infants manifesting an extreme hypersensitivity to sound (as a learned conditioned response). CNS-injured preterms are particularly vulnerable to sound stress in the NICU, are less able to habituate to NICU noise, and respond with exaggerated and prolonged physiologic responses (e.g., alterations in respiratory rate, bradycardia, desaturations). **Noise is stressful not only to the infants but also to parents and care providers in the NICU.**[38,176] Three years after their NICU experience, mothers recall the noise level in the NICU as a stressor. NICU noise is stressful to care providers and has the potential to damage hearing; cause physiologic responses (e.g., increased blood pressure, altered immune response, increased stress hormone secretion, disturbed sleep); cause fatigue, irritability, and "burnout"; interfere with communication with coworkers and parents; alter concentration; and increase errors.[405]

Although the AAP recommends that noise levels be less than 45 dB,[448] most NICUs' noise levels range between 38 and 90 dB, with higher noise bursts (see Table 13.10).* Recommended standards for noise criteria have been established to protect sleep, support stable vital signs, and improve speech

BOX 13.12 EFFECTS OF LOUD NOISE[368,436,452]

- Increase in stress behaviors:
  - State lability
  - Arousal state
  - Avoidance behaviors—more fussy, more startles, etc. (see Table 13.4)
  - Sympathetic nervous system arousal measured by noninvasive skin conductance, which was higher in male preterms
- Decrease in approach behaviors (see Table 13.4)
- Cardiorespiratory changes:
  - Increased heart rate
  - Increased respiratory rate
  - Increased apnea or bradycardia
  - Increased hypoxemia (decreased pulse oximeter)
  - Increased peripheral and arterial vasoconstriction:
    - Increased systemic blood pressure
    - Increased intracranial pressure
  - Increased sensory neural hearing loss
  - Abnormal auditory development and processing
  - Prevents habituation
- Alters development of sleep-wake cycles:
  - Disturbs sleep; interrupts light sleep
  - Even moderate noise disturbs sleep
  - Increases wakefulness and agitation
- Increased risk for intraventricular hemorrhage:
  - Increase in cerebral blood flow
  - No change in cerebral oxygenation when peak sound levels increased by 5 dB for short duration; cerebral oxygenation at higher sound levels for longer durations unknown[119]

*References 71, 102, 147, 269, 340, 341

TABLE 13.10 NOISE LEVELS IN THE NICU

LEVEL (DB)	COMMENTS
48–69	Humidifiers and nebulizers
50–60	Normal speaking voice
50–73.5[a,b]	Incubator (motor noise)
53	Median noise level on conventional ventilator
55–88	Bradycardia alarm
58–85[c]	Noise in NICU (talking, equipment alarms, telephones, radio)
59	Median noise level on high-frequency oscillator
65–80[b]	Life support equipment (ventilator; intravenous pumps)
66–76	Sink on/off
67	Incubator alarm
70	Background noise mean level should not exceed
72.8–71.7	Air conduction noise levels of jet ventilator, CPAP [201]
74–89.2	Bone conduction noise levels of jet ventilator, CPAP[201]
85[d]	Noise level at which hearing damage is possible for adult; (?) neonatal effects
90	Peak sound intensity in the NICU not to exceed
90[d]	Adult exposure for 8 hours requires protective device and hearing conservation program
92.8[b]	Opening incubator porthole
84–108	Placing a plastic bottle of formula on top of incubator
96–117[b]	Placing a glass bottle of formula on top of incubator
70–116[b]	Closing one or both cabinet doors
80–124[b]	Closing one or both portholes
120	Threshold for pain
130–140[b]	Banging incubator to stimulate apneic premature infant
160–165[d]	Recommendations for peak, single noise level not to exceed to prevent (adult) hearing loss; (?) neonatal effects

[a]Modern incubators generate less than 60 dB; exceeds hourly recommendation of 50 dBA (see Table 13.11).
[b]Measures from inside the incubator.
[c]Noise levels do not vary from morning to night.
[d]Occupational Safety and Health Administration (OSHA) standard. (No safety standards for neonates have been established.)
NICU, Neonatal intensive care unit.
Data from Thomas KA, Uran A. How the NICU environment sounds to a preterm infant: update. *MCN Am J Matern Child Nurs.* 2007;32:250.

intelligibility. Recent noise studies in NICUs have found the following★:

- Noise levels are still louder than recommended.
- Environmental changes to reduce noise must be monitored because they may increase rather than decrease noise.
- Nurses perceived their own NICU as "pretty quiet" when, in fact, noise levels were above recommendations.
- Noise levels have not significantly decreased in the NICU.
- Single-room NICUs attenuate noise; there is more silence. However, equipment noise and noise from medical interventions is not decreased in single-room units. Parent engagement and presence is related to more language exposure.

★References 4, 67, 71, 80, 102, 269, 340

TABLE 13.11 RATIONALE FOR SPECIFIC NOISE CRITERIA[448]

NOISE CRITERION	RATIONALE
Hourly Leq (equivalent sound level) of 45 dB in infant room; 50 dB in staff work areas	Preserves sleep for healthy term infants most of the time
Hourly L_{10} of 50 dB in infant room; 55 dB in staff work areas (sound levels may exceed 55 dB only 10% of the time or a total of 6 min/h)	Preserves sleep for infants; enables caregivers to speak at normal conversational levels and be clearly understood 12 feet away, approximately 90% of the time
L_{max} of 65 dB in infant room; not to exceed 70 dB in staff work areas (maximum decibel sound level ≤1 sec in duration—transient bursts of noise)	Minimizes rousing babies and causing startle responses

- Initial and continued staff education is necessary; monitoring and feedback every 2 to 3 months is necessary
- Quality-improvement initiatives including education and behavioral and environmental modifications decrease noise in the NICU; constant dialogue between champions and staff is required.

Table 13.11 **presents specific noise criteria and their rationale.** Parents and care providers must be involved in planning, developing, and being educated about quieter NICUs.[38,395]

Strategies to minimize external auditory stimuli include quieting alarms with suction (and remembering to reset them), not taking a shift report over or allowing medical rounds near the infant's incubator, having noisy equipment repaired immediately, emptying sloshing water in ventilator or nebulizer tubing, maintaining cardiac monitors in a quiet state with alarms on (decreasing the sound of alarms by 50%), and purchasing quieter equipment (e.g., plastic instead of metal trash containers; quieter incubators). Choosing heated humidifiers (48 dB) rather than nebulizers (69 dB) and keeping the containers full of water, rather than low, decrease noise from respiratory equipment. Nursery design changes[448] include smaller cubicles rather than one large room, soundproofing materials, lights for phones and alarm systems, and minimizing equipment noise. Placing a blanket on top of the incubator or using an incubator cover muffles the noise of equipment placement; gentle, considerate (to the infant) placement of equipment on or in the incubator muffles sound; and closing portholes and drawers gently decrease the structural noises of caregiving. Prohibiting placement of equipment (e.g., clipboards, stethoscopes, formula bottles) on top of the incubator prevents such noises.

Tapping (by parents or siblings) or banging (by medical, nursing, or ancillary personnel) on the incubator Plexiglas should *never* be permitted. This (along with a brisk startle reflex from the infant) is an opportunity to teach about the noise levels generated by such activity. Infants should be kept in incubators as long as necessary to maintain heat balance. **Older incubators do *not* protect the infant from noise. A well-managed NICU environment may be much quieter than the continuous noise of an incubator. Noise in modern incubators varies according to the model.** Sound sources within an incubator include its motor, infant sounds, equipment sounds inside the incubator, equipment sounds transmitted from outside the incubator, and ambient nursing noise (e.g., personnel, phones). **Modern incubator walls attenuate impulse noises from the NICU and may decrease the infant's noise exposure.** Inside modern incubators, motor noise does not exceed 60 dB, but this level exceeds the more recent recommendation of 50 dB. However, impulse noises from the incubator (i.e., doors, latches) are louder on the inside of the incubator (see Table 13.10). **Prolonged stays in an incubator not only expose the infant to repeated caregiving noises but also mean there will be a dearth of kinesthetic stimulation (e.g., carrying, holding, rocking, swinging, sitting upright in an infant seat) and socially relevant speech patterns.** Both the internal noise generated by the incubator and how well the incubator attenuates external noise should be considered in incubator purchases.

Noise levels in the NICU may interfere with development of other sensory systems and delay the development of hearing and language. Radios have been banned in most NICUs. **Day-night cycles (naptime, nighttime) when auditory stimulation**

is decreased should be established in the NICU. Institution of a quiet time or rest period—through reduction of (1) noise from talking, equipment, telephones, and so on; (2) light by dimming overhead light; and (3) procedures to only emergency treatment—has resulted in enhanced infant sleep (34%–85%), less crying (14%–2.4%), and less parental and caregiver stress.[395] A more recent study found **low noise levels during quiet time, with total sleep time highest during quiet time with longer awake periods after quiet time, prompting the researchers to recommend quiet time as a nursing intervention in all NICUs.**[347] At discharge, NICU infants often will not sleep in a quiet room. Softly playing a radio facilitates sleep, and the infant gradually is weaned from it. Signs such as "Quiet . . . baby sleeping" or "Do not disturb, I'm asleep (talk to my nurse)" ensure undisturbed sleep *if* they are heeded.

The "in-turning" premature infant (see Box 13.2) of less than 34 weeks' gestation probably receives enough auditory input from the NICU. Auditory enhancement at this stage is probably overstimulation. Just as high-frequency sounds arouse, low-frequency ones, such as the heartbeat, respiratory sounds, and vacuum cleaners, quiet and facilitate sleep.[110] One study showed less behavioral response and less salivary cortisol release by infants who were presented with a heartbeat sound or white noise (both at 85 dB) during and after heelstick.

Although music has been shown to soothe full-term babies, the use of music with preterm infants has been studied with inconsistent results. Two meta-analyses of music therapy show benefits to preterm infants in: (1) physiologic parameters (heart and respiratory rates, oxygen saturations, quiet sleep, and behavioral state), (2) feeding behaviors and length of stay, (3) pain management, and (4) reduction of maternal anxiety and parental stress.[40,316] The most recent analysis also found studies showing no significant differences between preterm infants exposed to various types of music therapy and no harmful effects, possibly due to the lack of measurement of the ambient noise in the NICU during music therapy.[316] A literature review of music therapy (more live music) and musical stimulation (more recorded music) found more individualized care with music therapists that resulted in more effects on premature infants' physiologic and behavioral responses.[321]

Presentation of in utero sounds and a female voice to agitated, intubated preterm infants has resulted in improved oxygen saturation and behavioral states. An RCT of the effects of live music replicating womb sounds was conducted at multiple sites with preterm infants (≥32 weeks' gestation).[240] Music therapists chose lullabies identified by parents as important to their cultural heritage and that were within the parents' vocal range, and parents were taught to entrain their singing to their infant's respiratory rate and activity. **Outcomes included (1) lower heart rates during lullabies and music with a rhythm, (2) increased caloric intake and sucking behavior with parent-selected lullabies, and (3) decreased parental stress.**[240] Using music by Mozart has been shown to lower resting energy expenditure by 7.7% in preterm infants.[203] Preterm infants have lower pain scores and better behavioral states during heelstick when they listen to the same music that their mothers listened to during pregnancy.[214] However another recent article by board-certified musical therapists who specialize in music in the NICU states that classical music, pop/rock music, and instrumental or nature sounds (preferred by nurses and parents) are all contraindicated for premature infants in the NICU (especially if music is meant for calming) because of musical complexity.[105]

Music therapists in the NICU concentrate on neurologic enhancement for sensory integration, pacifier-activated sound to enhance NNS and feeding readiness, live music to enhance physiologic stability and calming, and education and emotional support for parents in the NICU.[105,393] **Careful decision-making and consultation with music therapists is recommended prior to use of recorded music for premature infants in the NICU.[105] Evidence-based guidelines for the use of recorded music for premature infants are listed in** Box 13.13.[105] Music therapy should be individualized according to infant tolerance and cues, decibel levels monitored and maintained in appropriate ranges, and staff and parents educated about benefits.[316] Exposure of 20 healthy preterm infants to low-intensity recorded maternal voice over a 3-day period resulted in an increase in oxygen saturations and a decrease in heart and respiratory rates during the voice period that persisted into the after-voice period.[367] Recorded maternal voice enables premature infants 35 weeks' and later gestation to be awakened less frequently by noises in the NICU and to exhibit a sleep-wake pattern that responds increasingly with age to their mother's recorded voice.[382] However, premature infants less than 35 weeks' gestation did not have better sleep and less wakening in response to their mother's recorded voice.

BOX 13.13 EVIDENCE-BASED RECORDED MUSIC GUIDELINES FOR PREMATURE INFANTS IN THE NICU[105]

Eligibility Criteria
- At least 28 postmenstrual weeks[15,162,341]
- Daily nursing approval

Music Characteristics
- Initial use for very premature infants: music should be as simple and nonalerting as possible[393]
- Soothing, constant, stable and relatively unchanging[393]
  - Voice alone or voice with only one instrument
  - Light rhythmic emphasis and slow tempo
  - Constant rhythm and volume
  - Melodies in a high vocal range, which infants hear best
  - Female (mother preferred) or child vocalists
  - In the native language of the family
- Least alerting music for premature infants include:[305]
  - Three chords or less
  - Major chords
  - Lullaby style (repetitious: no separate melody for chorus/bridge)
  - Music played slowly and softly

When to Play
- State—awake or at beginning of sleep[162]
- During skin-to-skin care[218]
- Immediately after painful/stressful procedure
- Audio recordings should not be left unattended with the high-risk infant[161]

When to Stop
- If infant exhibits frequent/continuous signs of overstimulation (e.g., squirming, arched back, grimacing, increased heart/respiratory rates, irregular breathing pattern, changes in skin color, crying, splayed fingers, hiccoughing)
- During painful/ stressful procedures[393]

Duration and Frequency
- Maximum of 4 hours/day, alternating between 30 minutes of music and 30 minutes of no music[25,424]

Volume
- 65–75 dB, scale C[15] (measured at ear, not source)
- Music should be played with background noise not exceeding 50 dB[162]

Presentation
- Place speakers on each side of the infant's head or feet so sound stimuli are received binaurally[393]
- Music equipment must be tested to ensure it does not create electrical interference with medical equipment such as cardiac monitors and ventilators and is resistant (if used in the incubator) against high temperatures (~36°C) and humidity (~75%) levels[277,323]

Contraindications
- Musical toys and mobiles because of the highly repetitive nature of the sole music selection usually available with these toys, the inability to adjust sound levels, and the lack of research on their use[393]
- Radio, white noise, or nature sounds[393]
- Earmuffs[277]
- Headphones on the infant[161] or directly on the mother's abdomen while pregnant[162]
- Music played free field in an open bay because the volume is difficult to manage for each infant and it may not be appropriate because of the gestational age for those subjected[393]

Adapted from Detmer MR, Whelan ML. Music in the NICU: the role of nurses in neuroprotection. *Neonatal Network.* 2017;36(4):213–216.

The human voice is the most preferred sound. The preterm in an incubator may be isolated from important exposure to his or her mother's voice that would have occurred over months in utero. A systematic review of the effects of **maternal voice on preterm infant's development found that an infant's mother's voice is a non-noxious intervention that is consistent with developmental care and should be embedded in developmental care strategies.**[345] Parental talking to their preterm infant in the NICU has been shown to be a strong predictor of infant vocalizations at 32 weeks and conversational turns (i.e., infant coos and parent gives a vocal response) at 32 and 36 weeks.[72] This study found that **preterms begin vocalizing at 32 weeks and that the rate increases over time. When parents are present in the NICU, preterm vocalizations increased by as much as 129%, particularly at 32 weeks.**[72] Another study of **maternal talking and singing found greater oxygen saturation levels, fewer negative critical events, and a prevalence of calm alert state in the preterms who were reconnected to their mother's voice while in the NICU.**[137] An exploratory study of VLBW preterms (16 exposed to biologic maternal sounds [BMS] matched with 16 exposed to usual NICU

sounds) was conducted to measure weight gain.[464] **VLBW infants exposed to BMS (maternal voice and heartbeat) gained more weight and had a higher growth velocity compared with the control group.**[464] While in the NICU, parents reading to their newborns resulted in parental feelings of closeness to their infants, developing a sense of control, intimacy, and normalcy.[222,438] Follow up of **preterm infants who were read to by their parents shows better cognitive development at 2 years of age.**[54]

Increasing **preterm infant's language exposure (by parents talking to their infant) improves the infant's language development, enhances parent-infant attachment, and decreases parental stress.**[258] In the NICU, verbalizations to their preterm infant and positive affective involvement during feeding by mothers is associated with the same parental behaviors at 24 months.[150] **Teach parents the neonate's preference for high-pitched voices speaking in typical speech patterns (not baby talk). While in the NICU parents, can talk to the baby about their day, essentially conversing with the baby, and listening for responses. Parental talking to the baby in the NICU is associated with higher scores on language and cognition at 7 and 18 months corrected age.**[73] The degree of attenuation of the higher frequency of mother's voice by the lower frequency of incubator noise, the incubator walls, and the ambient noise of the NICU has not been measured. Role model and teach parents to gently talk to the infant while touching and giving care. Teach parents to talk to their infant while presenting their faces in the infant's range of vision. Watch for infant tolerance, and increase or decrease talk time to avoid overload. For older infants, imitate the infant's coos and babbles; this reinforces and encourages vocalizations.

For a neonate, hearing is more important than vision for attachment and bonding to the parents. Within seconds after birth, newborns are able to discriminate and prefer their mother's face. They have connected her familiar voice with her unfamiliar face. A high index of suspicion about hearing loss is warranted if caregivers do not observe normal responses to sound stimulation. **Hearing screening by high-risk factors alone identifies only about 50% of newborns with significant hearing loss; therefore, universal newborn hearing screening is the standard of care.**[17]

VISUAL INTERVENTION

The NICU is lit with bright, cool-white fluorescent lights 24 hours a day. Light levels vary between and within various NICUs. Early studies showed light levels in the low range, from 34 to 100 lux at night and 184 to 1000 lux during the day; more recent studies report light levels ranging from low levels of 1 to 25 foot-candles (ftc) to high levels of 235 ftc.[385] **The amount of light to which the preterm infant is exposed is influenced by (1) location in the NICU, (2) seasonal or climactic variations, (3) use of phototherapy, (4) ophthalmoscopic examinations (e.g., at birth and for retinopathy of prematurity [ROP] follow-up), (5) use of procedure lights,[317] and (6) infant-related factors (e.g., maturity and amount of eye opening, head position, or eye shielding).** Ambient light levels in the NICU should be adjustable through a range of 10 to 600 lux (approximately 1–60 ftc) at every bedside.[448] Other light recommendations for newly built NICUs are outlined in Table 13.12.

Although decreased light levels and response to bright light have not been shown to reduce the incidence of ROP, ophthalmic sequelae of preterm birth are common.[160] (See Chapter 31 for a discussion of ROP.) There are three broad categories of ophthalmic sequelae: (1) decreased visual function, (2) strabismus, and (3) decreased eye size (arrested growth) and abnormal refractive state (increased myopia). In addition, there is abundant animal, child, and adult research documenting negative biochemical and physical effects (e.g., change in endocrine function, increased hypocalcemia, cell transformations, immature gonadal development, chromosome breakage).[158] **Very preterm infants are able to detect and react to small variations in light levels.**[465] Exposure to bright lights in the NICU is associated with the following[158,317,465]:

- Decreased oxygenation (on pulse oximetry); decreased regional cerebral saturation
- Increased incidence of retinopathy
- Altered vital signs (increased heart and respiratory rates)
- Alteration in state organization (i.e., altered sleep patterns, poorer circadian rhythms; more wakefulness/less sleep[314])
- Skin changes (e.g., tanning, rashes)
- Alteration of nutrients in total parenteral nutrition (TPN) solution, formula, and breast milk

TABLE 13.12 LIGHT RECOMMENDATIONS IN THE NICU[448]

ILLUMINATION LEVEL	PURPOSE
High levels: 60 foot-candles (ftc)	Evaluate and assess skin color and perfusion
Lower levels: 10–20 ftc	Safe and adequate because of concerns over retinal/ocular damage from continuous exposure to high levels (60 ftc)
Nighttime levels: 0–5 ftc	Diurnal variation in light levels
Procedure light: 185 ftc	Available at every bedside to temporarily increase lighting for infant assessment/procedure without increasing light exposure to all other babies Prevent light from reaching infant's eyes
Support areas	For charting, medication preparation, etc., should provide adequate and separate light to accommodate sleeping babies and working health care providers Lighting should be located to avoid any infant's direct line of sight to the fixture
Daylight	One source visible from care areas for its psychological benefit for staff and families

NICU, Neonatal intensive care unit.

Rapid increase in the intensity of ambient light causes a decrease in oxygen saturation in younger, immature preterm infants; slower increasing of light levels enables easier adaptation.[317]

The first goal in visual intervention is to assess the current level of light and decrease it wherever possible. A very immature preterm infant is accustomed to the muted light of the uterus (light filtered through the abdominal and uterine walls) and has fused eyelids (if the infant is less than 26 weeks' gestational age). Draping blankets on top of the incubator or using a handmade or commercial incubator cover decreases the light at the infant's level during rest but allows immediate maximal illumination when the cover is pulled back. Using adjustable lighting at each infant's bedside enables every infant to have more or less light depending on the care and rest circumstances of the individual infant. Because infants are continuously monitored, not all infants need to be subjected to maximal illumination at all times.[158]

Cycled light—dimming the lights in day-night cycles—is associated with positive effects (Box 13.14). Randomized controlled studies show that the circadian clock of the preterm infant is entrained by cycled light.[160] Preterm infants exposed to low-level cycled light for 2 weeks before discharge showed night/day rest-activity patterns within the first week after discharge. Preterms

BOX 13.14 EFFECTS OF CYCLED LIGHT[a]

- Behavior:
  - Decreases/no change in movement or motor activity
  - Increases motor coordination
  - Increases sleep time
  - Decreases fussing and crying
  - More eye opening
- Cardiorespiratory changes:
  - Decreases heart rate
  - Decreases respiratory rate
- Feeding behavior:
  - Quicker progression to oral feedings
  - Feeds more efficiently and in less time
  - Increased weight gain and better growth
- Circadian rhythm development:
  - Melatonin level
  - Temperature
  - Heart rate
  - Rest and activity patterns
- Decreased cortisol levels
- Decreased incidence and severity of retinopathy of prematurity
- Decreased parental and/or care provider stress
- Decreased infant handling and noise levels
- Shortens length of stay

[a] References 55, 56, 224, 295, 359, 360, 426.

exposed to low-level uncycled light were delayed in their development of day-night differences in activity and rest till 3 weeks after discharge.[358-360] A recent randomized controlled **trial of early (28 weeks' PMA) versus late (36 weeks' PMA) introduction of cycled light to extremely preterm infants (<28 weeks' gestation) found improved weight gain and shortened hospital stay with early introduction of cycled light.**[56]

Visual attentiveness is correlated with birth weight and gestational age; the more mature the infant, the more the infant is able to fix and follow. An infant at 28 weeks' gestation fixes and follows but may become apneic, behaviorally disorganized, and stressed as a result. Visual stimulation is very tiring and taxing (increases the heart rate) for the immature infant. Those of less than 34 weeks' gestation probably receive enough stimulation from the NICU environment. Premature visual stimulation also may interfere with auditory neurosensory development. When these infants reach the "coming-out stage" (see Box 13.2), they may signal their readiness for visually enhancing activities.

Infants receiving phototherapy are deprived of visual sensory stimuli because of their protective eye pads. These should be removed during care and feeding and interaction with parents and professionals. Interesting visual stimuli include inanimate objects (e.g., toys, black-and-white faces and patterns, pictures of family members, artwork from siblings, mobiles) and animate objects (e.g., faces of parents, siblings, professionals) (Fig. 13.8). **Infants prefer the human face as a visual stimulus, especially the talking face, which stimulates both visual and auditory pathways.** Parents often need to be encouraged that their infant prefers to watch and listen to their faces and voices rather than toys.

Teach parents the abilities of the infant and appropriate methods of visual stimulation:

- Place mobiles, pictures, and faces of high contrast (i.e., black and white) within the visual range of the newborn: 8 to 12 inches for term infants, a little closer for preterm infants.
- Quiet alert is the best state for visual encounters after feedings, if awake; swaddle the infant to quiet or unwrap the infant to arouse; hold infant upright.
- Place the infant on the abdomen (called "tummy time") with objects of various sizes and shapes within visual range.

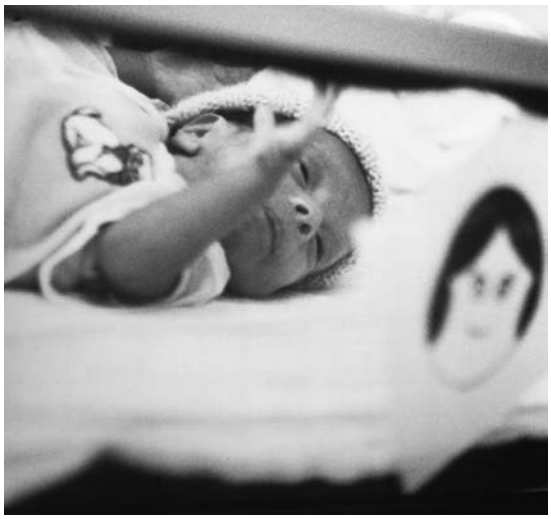

FIGURE 13.8 Premature infant fixing the gaze on a black-and-white face.

- Change toys and visual stimuli. Infants become bored with the same thing.
- When the preterm infant tolerates multiple stimuli, hold him or her in en face position (see Chapter 29) to feed, talk to, and rock. Whether the infant is nipple or gavage fed, alternate sides so the infant sees both sides of the care provider's face (especially important if the preterm infant exhibits the common preference for right-sided head turning).
- Place the infant at varied heights (in a baby carrier, crib, swing, infant seat, on the floor) so the infant sees the world from various angles.
- Place the infant so that he or she can bring the hands to midline and see his or her hands and fingers and eventually reach for toys.

Infants who exhibit gaze aversion should not be "pursued" by the face of the parent or professional, because this only potentiates the time "spent away" with their gaze to protect themselves from overload. Gaze aversion, flat facial affect, and absence of a smile may cast doubt on the ability of these infants to see because there is no eye "language" or caregiver feedback of preference, recognition, and delight. These infants do see, but they fix only fleetingly. **Minimizing the number of care providers is crucial for these babies so that they deal with as few caregiver cues, styles, and ways of being handled as possible. Most important, the caregiver must be sensitive and responsive to the infant's negative and positive cues.**

BOX 13.15 BENEFITS OF NONNUTRITIVE SUCKING (NNS) FOR PRETERM NEONATES

Physiologic

- Promotes physiologic stability[142]:
  - Better oxygenation
  - Decreased heart rate
  - Pain relief (see Chapter 12)
- Alters cardiac control during supine sleep (increased blood pressure during sleep from 2–3 months after term corrected age, which is peak occurrence of SIDS)[184]
- Increased insulin and gastrin secretion that may stimulate digestion and storage of nutrients[246]
- Better milk absorption and improved digestion related to better glucose utilization[142,246]
- Fewer gavage feedings, faster transition from gavage to oral feedings[42,142]
- Accelerated transition to full oral feedings (both breastfeeding and bottle feeding)[154]
- Shorter time to full transition to breastfeeding and to discharge; lower weight at full breastfeeding and at discharge; better sucking skills.[200]
- No effect on acid/nonacid GER—safe to use in premature infants with symptoms of GER[92]
- Better weight gain[20,42,142]
- Earlier discharge[142,154,200]

Behavioral

- Comfort, soothing, and self-consoling behavior[196]
- Improved behavioral organization that decreases energy consumption[246]:
  - Quieter, more restful behavior; more sleep
  - Less stress and tension
  - Improved self-consolation and soothing
  - Improved state modulation
  - Improved neurobehavioral organization and maturation
- Increased readiness for nipple feedings because of a more alert state (see Chapter 18)
- No negative effect on breastfeeding[87]

Neuromotor Development

- Acceleration of the sucking reflex[142,154,200]
- Improved muscle tone and coordination
- Accelerated neurologic maturation

SMELL AND TASTE INTERVENTION

Newborns, including preterms, can detect, discriminate, respond (e.g., facial expression, change in respirations, apnea), learn, and remember olfactory stimuli.[262,427] The neonate's well-developed sense of smell is not stimulated in the NICU with pleasant odors. A high-risk infant is stimulated by the smell of forgotten alcohol, skin prep, or povidone-iodine (Betadine) pads inside the incubator and the unpleasant taste or smell of oral medications.[262] Because a premature infant cannot respond by crying or moving away, **the infant responds to noxious smells by a decrease in respiratory rate, transient apnea, or an increase in heart rate.**[262] Removal of noxious odors from the incubator is as critical as removal of sharp instruments after a procedure. **Alcohol vapors from alcohol-based hand rubs that had not completely dried before touching the preterm was cited as the most common unpleasant smell to which the infants were exposed.**[213] Other unpleasant odors included cleaning solutions, detergents, soaps and skin care products, and wipes such as alcohol or adhesive removers.

Enhancing the olfactory environment includes having parents hold the infant or sit close if the infant cannot yet be held. **The smell of the mother's breast milk is especially pleasant and elicits more suckling than the smell of formula.**[45,427] Olfactory stimulation of sucking in preterm infants increases with increasing postnatal age. **Placing a drop of human milk on the infant's lips with a cotton ball or gauze sponge helps the infant recognize the mother's smell and associate that smell with food and feeding when the infant is able to nipple feed.**[45] An RCT of preterm infants **under 28 weeks' PMA exposed to the smell and taste of their own mother's milk prior to feeding found that those very preterm infants attained full oral feeding 2 days earlier and had better weight gain than very preterm infants who did not smell or taste their mother's milk.**[35]

The benefits of nonnutritive sucking (NNS) during gavage and between feedings are listed in Box 13.15. **Meta-analyses of NNS studies have found a significant effect on the transition to**

full oral feedings (from gavage feedings), transition from beginning to full oral feedings, and length of hospital stay.[142] Sucking on a pacifier satisfies the infant's sucking needs and may facilitate early learning that satiety and sucking are associated. However, nutritive and nonnutritive suckling are not alike (see Chapter 18). The fact that an infant vigorously sucks on a pacifier does not mean the infant will be able to suckle nutritively, because the expressive and swallow phases have not been present in nonnutritive suckling and coordination of suck, swallow, and breathing has not been necessary. This is confusing to most parents and many professionals and should be clarified for them.

High-risk infants often undergo prolonged periods during which a nil per os (NPO) status has been ordered, and during these times, their sensation of hunger is not relieved. Although pacifiers are soothing, these infants may learn that sucking and satiety are not related. **NICU infants also experience many aversive stimuli around and within the mouth** (e.g., oral intubation, oral and endotracheal tube suction, intermittent gavage) **that result in touch aversion of the mouth and a hypersensitive gag reflex.** Feeding difficulties may result from the following:

- Severity of illness[272,364]
- Neurologic damage (e.g., IVH)
- Structural abnormalities (e.g., cleft palate or submucous cleft, recessed chin)
- Prematurity: The infant is too neurologically immature and tires easily with "work" of feeding
- Aversive feeder (acquired or developmental: sucking defect; psychological: "hospitalitis," rumination) and aversive feeding experiences[380] that alter brain structure[386,389]
- A combination of these types

Neural maturation (34–35 weeks' gestation) is the developmental guideline for initiation of oral feedings (see Table 13.2),[154,384] although some infants are ready at an earlier age (30–34 weeks' gestation) (see Box 13.2). Maturation of feeding skills occurs because of developmental changes in the CNS, coupled with experiential learning.* So intimately interrelated are these indicators **that maturity depends on experience and experience depends on maturity; therefore, the more opportunities to nipple feed, the more improved the preterm neonate's feeding performance.** However, preterm infants may exhibit periods of apnea and tachypnea with bottle feeding, because consistent coordination of breathing with sucking and swallowing does not occur until 37 weeks' gestation (see Table 13.2). **In preterm infants with a PMA greater than 32 weeks who are ready to initiate oral feeding, delaying their start by 1 week has been shown to reduce physiologic distress (i.e., oxygen desaturations) with feedings.**[440]

The research basis for determining readiness for initiation of oral feedings is discussed in Chapter 18 **and in Box 13.2. *Cue-based or infant-driven feedings* are individualized feedings initiated and discontinued based on the infant's cues of readiness to feed and satiety, rather than on time or volume of feeding.**[206,207,380] Benefits of cue-based or infant-driven feedings are listed in Box 13.16. However, the most recent *Cochrane* review of **responsive (i.e., related to infant's cues) versus scheduled feedings found weak evidence to support benefits and overall no strong or consistent evidence that responsive feedings affect important outcomes for preterm infants or their families.**[441]

Coregulated feeds—the ability of parents to know their infant's cues and read and respond dynamically to changing needs of the infant—focuses on the feeding relationship rather than

BOX 13.16 BENEFITS OF CUE-BASED/INFANT-DRIVEN FEEDING

Physiologic
- Improved physiologic outcomes[223,409]
- Increased intake of nutrients[206,223,274]
- Increased weight gain[346]
- Fewer adverse events[206,346]
- Earlier discharge home[274,346,445,446]

Behavioral
- Enhanced behavioral maturity[206,223,409]
- Enhances the development of self regulation and reinforces sleep-wake cycles[343]
- Earlier achievement of full oral feedings[206,380,445,446]
- Safe, pleasurable experience for the infant and parents[408]

No additional workload[206,274,346]

Adapted from Lubbe W. Clinicians guide for cue-based transition to oral feeding in preterm infants: an easy-to-use clinical guide. *J Eval Clin Pract.* 2018;24(1):80.

*References 59, 278, 380, 384, 410.

the volume consumed.[408] Parents learn from professional care providers how to individualize every feeding encounter by (1) respecting infant cues, (2) seeing their infant as an active partner, (3) evaluating readiness to feed, (4) adjusting feeding to be contingent with the infant's breathing rhythm and other physiologic cues, (5) using proper positioning, and (6) decreasing physical and environmental stimuli that interfere with feeding.[365,380,408] A coregulated feeding intervention in which mothers of premature infants received five nursing intervention sessions during their **infant's transition to oral feeding identified the top five issues of concern for both mothers and nurses: (1) reading cues, (2) coregulating breathing, (3) providing motoric stability, (4) regulating milk flow and (5) providing rest periods.**[409] Both mother and nurse worked together on joint attention to infant's feeding challenges, auditory assessment of breathing and swallowing, review of feeding session by videotape, and planning for the next feeding session. Another study of preterm infants using a **coregulated approach to oral feeding found fewer apneic episodes and higher respiratory rate when compared to infants being fed by the standard feeding method.**[324] Although there were no differences in oxygen saturation, heart rate, or bradycardia between the groups, the infants fed by the standard method showed significantly higher SD12, a measure of heart rate variability indicative of randomness of the heart rate, a potential marker of increased stress.[320] These strategies enable a safe learning experience for both parents and their infant, provide a pleasant feeding experience, and lay the foundation for positive feeding outcomes and improved neurodevelopment.[380,408] **There is no one approach for feeding preterms; strategies in** Box 13.17 **are individualized to each infant and parent.**

BOX 13.17 STRATEGIES TO FACILITATE ORAL FEEDING

1. Minimize noxious stimuli to the mouth.
   a. Suction only as needed (not routinely).
   b. Consider indwelling gastric tube rather than intermittent gavage (e.g., an infant fed every 2 hours would have a gavage tube passed 12 times a day).
   c. Pass intermittent gavage tube down mouth through hole in pacifier nipple; if infant has hypersensitive gag, passing smaller tube down nose stimulates gag reflex less than passing tube down mouth.
   d. Perioral and intraoral techniques*
      i. These techniques are only more aversive, rather than therapeutic, on babies with touch aversion at mouth area; individualizing therapy is important.
      ii. When performing oral exercises, do so with care—do not stimulate aversion reflexes (e.g., gag reflex).
      iii. Use of a new motorized pulsating pacifier results in faster emergence of NNS and increase in proportion of oral nutrition.[30]
2. Enhance pleasant stimuli to mouth (first experiences with suckling have lasting neurobehavioral effects).[365]
   a. Have infant smell or taste breast milk; use colostrum/human milk for oral care.[35,45]
   b. Provide nonnutritive suckling[20,165] and NNS with mother's voice[84] while tube feeding[365] (see Box 13.15).
   c. Facilitate hand-to-mouth behaviors.
   d. Use nipple with proper flow rate.[153,267,379] If flow rate is too fast, increased flow stimulates anxiety and/or gag reflex and causes bradycardia—promotes incoordination. If flow rate is too slow, fatigue and frustration are increased and may result in inadequate consumption/growth failure.
   e. Perioral and intraoral stimulation—facilitates development of normal sucking behaviors.[26,165,229,237]
   f. Use Lact-Aid nursing supplementer (see Chapter 18):
      i. Never frustrate infant with dry breast.
      ii. Positive reinforcement for infant to nurse.
      iii. Calorically and energy efficient method.
      iv. Oral therapy—teaches infant proper nutritive suckle.
   g. For infants with difficulty in coordination of respiration with suck or swallow (prevents stress of apnea and hypoxia and enhances pleasure of feeding experience) (see Chapter 18)[97,406,407]:
      i. Assess feeding pattern (e.g., continuous or intermittent suck), pulse oximeter, muscle tone, breathing pattern, heart rate.[410]
      ii. Remove nipple from mouth to enable infant to breathe (pace feeding).[223]
      iii. Begin breastfeeding before bottle feeding.[396] (See Chapter 18 Critical Findings: Readiness for Initiation of Oral Feedings: Research Basis in Table 18.5.)
      iv. Use of orthodontic nipple results in physiologic stability and more effective feeding behavior in some infants.
      v. Use of soft-walled bottle system improves oxygenation and coordination and is more like breastfeeding than rigid-walled bottle[153]

Continued

BOX 13.17 STRATEGIES TO FACILITATE ORAL FEEDING—CONT'D

3. Positioning: Use proper position to facilitate swallow and improve suction—symmetric positioning with predominance of flexion.[410]
   a. Hold with feedings (even gavage) as much as possible.
   b. Consistent caregivers—parents, primary nurses, foster grandparents.
   c. Kangaroo care before feeding improves alertness; does not tire infant and should not be avoided before feeding; promotes breastfeeding.[89,152,365]
   d. Swaddle[380,410,454]:
      i. Decreases startles
      ii. Optimizes postural stability and control
      iii. Infant may become too warm and sleepy.[28]
   e. Facilitate swallowing:
      i. Position with chin tucked.
      ii. If breastfeeding, turn infant's whole body toward mother so head and trunk are in alignment (infant is not trying to swallow with head turned to one side).
      iii. Upright position with neck, shoulders, and back supported—slows gravitational flow of formula from nipple (as when infant is in semireclined position); restricted milk flow (e.g., milk flows only with active sucking, not with gravity) beneficial (e.g., more efficient; more volume obtained).
      iv. Head-elevated, side-lying position results in more physiologic stability (fewer and less severe bradycardia; slower, more relaxed breathing) for bottle feeding;[380] systematic review of side-lying position found conflicting results in studies and a large RCT with a diverse group of premature infants is recommended.[324]
      v. Cuddling, semireclined position increases flow of formula by gravity—may be too fast, regardless of nipple chosen; results in increased gags, choking, and bradycardia.
      vi. Prone with neck extended (slightly): Keeps tongue forward and airway unobstructed.
      vii. Good for aversive feeder who chokes.
      viii. Gentle, upward pressure under chin (chin support) or at base of tongue facilitates swallowing, because it mimics upward thrust of tongue with swallowing.
   f. Improve formation of suction:
      i. Semireclining (>45-degree angle) on lap of caregiver—frees both hands to work with infant on oral control.
      ii. Cupping both cheeks (check support) with fingers of free hand (i.e., hand not holding bottle) improves lip closure, suction formation, minimizes fluid loss, stabilizes the jaw, and organizes deglutition.[46,454]
      iii. Gentle tugging at nipple (as if to take it out of mouth) may smooth and strengthen suck; avoid prodding infant to suck.[380]
   g. Improve sucking organization[279]
      Multimodal intervention:
      Auditory (10 minutes of mother/female voice)
      Tactile (moderate touch stroking or massage)
      Visual (eye to eye) stimulation
      Vestibular (5 minutes of horizontal rocking)
4. Timing
   a. Do not allow infant to cry to exhaustion before feeding—infant will be too tired to eat.
   b. Keep external stimuli to a minimum in immature preterm infants (<34 weeks) for optimal intake and weight gain.[379,408]
   c. If or when satiated, infant will not suck:
      i. Feed by cue-based/infant-driven/coregulated feedings (see Box 13.16)
      ii. If feeding on schedule, note whether infant gives cue of hunger: fussiness and crying, hand-to-mouth behaviors or rooting, hiccups. Infants as young as 32 to 33 weeks can provide cues so that feeding can be individualized.[364,365,380]
      iii. If feeding on schedule, space time and see whether infant exhibits cues of hunger (as described earlier).
      iv. First, nipple what infant is able to feed; then tube feed (presence of an indwelling nasogastric tube may result in compromised respirations, oxygen desaturation, and bradycardia in the VLBW infant).[384]
   d. Try to nipple feed for no longer than 20 to 30 minutes (infant becomes too tired and uses up energy and calories to feed instead of to grow).[364]
   e. Infants of advanced age (around 6 months) may be unable to nipple if they have never had the opportunity. It may be more developmentally appropriate to cup feed or spoon feed infant, because normal infants begin cup drinking between 6 and 8 months of age.

* References 20, 24, 26, 46, 164, 165, 229.
NNS, Nonnutritive sucking; *VLBW,* very low birth weight.

Feeding difficulties at the beginning of life often lead to eating problems in infancy and later in life.[365,380] Severe behavioral eating difficulties are associated with prematurity, low birth weight, CNS injury, distress during feeding in the first 6 months of life, neurodevelopmental problems (cognitive, language, motor, socioemotional delays), and regular or frequent vomiting. Feeding difficulties are stressful to all family members, complicate parenting, and strain the parent-infant bond.[94,365,380]

Because criteria for discharge include full oral feedings with adequate weight gain, transition to full oral

feedings is a topic of ongoing research. A recent multicenter retrospective analysis of the **feeding behaviors of 6146 preterm infants born at 29 weeks' to 33 weeks' gestation found that the median PMA at first oral feeding was 33.9 weeks.**[59] This study also found that **for every week earlier that oral feeding was begun, full oral feedings occurred 4.5 days earlier and discharge occurred 3.4 days earlier.** Factors influencing earlier full oral feedings and earlier discharge included higher birth weight and black maternal race.[59] **Longer transition time to full oral feedings is significantly influenced by (1) apnea, (2) birth weight or gestational age, (3) younger age at first oral feeding, (4) BPD/CLD, (5) number of days being tube fed/receiving ventilatory therapy, (6) desaturations of oxygen with feeding and (7) location of the NICU.* Shorter transition time to complete oral feeding is associated with (1) earlier skin-to-skin care and oral feeding by parents[152]—first feeding at the breast before bottle feeding,[396] (2) greater weight, (3) older postconceptual age at initiation of nipple feeding,[63,278,336](4) use of oral stimulation (e.g., stroking, NNS, NNS with lullabies, NNS with mother's voice),† (5) use of oral colostrum,[35,45] and (6) a cue-based/infant-driven/coregulated feeding protocol (see Box 13.16).**

A randomized study of early introduction of oral (bottle) feeding (e.g., within 48 hours of full tube feeding) found the following[384]:

- Transition time to all oral feedings was significantly shorter.
- Oral feeding was introduced 2.6 weeks earlier.
- Total oral feeding was achieved at earlier postmenstrual age (e.g., 54% of 33 weeks' PMA infants versus 12.5% of control group).
- Weight gain and discharge weights were similar for both groups.
- Episodes of feeding-related bradycardia and desaturations were similar for both groups.
- Discharge was 10 days earlier for the earlier fed infants.

These researchers postulate that feeding opportunities in young infants provide them with practice and experiential opportunities to develop their oral motor skills and coordination of suck-swallow-breathe.[384] **A more recent study found that every 1% increase in the proportion of missed oral feeding opportunities extended the time to full oral feedings by 1.45 days and the time to discharge by 1.36 days.**[417]

For infants with BPD/CLD, the more days receiving positive-pressure ventilation and supplemental oxygen, the older (in postconceptual age) the infant when he or she is first fully nipple fed. For these infants, transition time to full nipple feeding may be lengthened because of the increased work of breathing, the precedence of breathing (at an increased rate) over feeding, and changes in heart rate variability.[97,273] However, a randomized study found that infants with BPD/CLD fed by an individualized, semi-demand method (using the infant's behavioral cues and cardiorespiratory state to determine frequency, length, and method) achieved nipple feeding earlier (5.9 days) compared with control infants (12.3 days).[272]

The goals of intervention include (1) a safe feeding (i.e., diminished risk for aspiration), (2) a functional feeding (i.e., adequate caloric intake for optimal growth and with minimal energy expenditure), and (3) a pleasant, social interactive experience for the infant and parents or caregivers.[165,342,380,410]

The use of individualized developmental care may assist VLBW and preterm infants with BPD/CLD in obtaining and maintaining an optimal condition for progression to oral feedings. **Use of skin-to-skin KC improves weight gain, supports and promotes breastfeeding, and shortens length of stay** (see Box 13.6). **Because KC improves alertness and does not tire the infant, it can be used as a strategy to facilitate oral feeding** (see Boxes 13.6 and 13.14). The use of developmental care enables VLBW preterm infants to initiate the first oral feeding and have the last gavage feeding at an earlier age compared with VLBW infants not receiving developmental care. Preterm infants successfully completing oral feeding spent significantly more time in awake states than did preterm infants who were unsuccessful in their feeding.

Using developmental principles, health care providers are able to facilitate both the preterm infant and parents in effective feeding experiences.[364,380] **A self-regulating preterm infant shows these signs of stability during feeding: (1) smooth, regular respirations (no or minimal increase in respiratory rate or effort); (2) consistent postural control—flexed, hands near face, maintains muscle tone, calm/organized behavior; (3) maintains optimal**

*References 192, 278, 384, 458.

†References 84, 164, 237.

color; (4) quiet, alert state, focuses on feeding; and (5) coordinates suck-swallow-breathe.[379,410] Coordination of feeding is facilitated by (1) imposing breaks/pacing (e.g., removing the nipple from the mouth; tipping the bottle so that the nipple is empty but remains in the infant's mouth), (2) limiting bolus size (limiting the number of sucks before a swallow results in smaller bolus size) by limiting the number of successive sucks before the infant becomes stressed, and (3) slowing the flow rate (e.g., using low-flow-rate nipples,[267] upright positioning to decrease hydrostatic pressure and gravitational flow).[379]

Signs of stress during nipple feeding, their significance, and appropriate interventions are listed in the Critical Findings in Table 13.13. **Stress can be avoided and oral feeding efficiency enhanced by ensuring that the preterm infant is awake and alert for feeding.**[165] **Even preterm infants who are near discharge still have oxygen desaturations when fed by their mothers; the incidence is decreased in infants receiving supplemental oxygen, beginning a feeding with a higher baseline oxygen saturation, and in those of an older postconceptual age.**[406,410] **Parents must be taught how to interpret their infant's cues of stability and stress so that they can modify their behavior and learn to intervene to help their infant safely and successfully feed.**[380,408] Skills parents need for effective feeding include (1) following the infant's lead about readiness to feed—preterms are able to root and open their mouths to the stimulus of a nipple; (2) assessing breathing cues, providing adequate rest (see Table 13.13), and not interrupting by "jiggling" or moving the nipple to stimulate sucking; and (3) recognizing that noisy swallowing and drooling indicate dysfunction[380,408] (see Table 13.13). Strategies that parents consider helpful in mastery of these skills are (1) being included in decision making about feeding and its success, (2) observing a nurse feed their baby, and (3) having a nurse spend time with them while they are feeding their baby to give them feedback, ideas, and tips about feeding.[380,408] For parents, learning to feed their infant is viewed as a significant symbol of parenting, as an opportunity to read and react to infant cues, and as a coregulator of feeding.[380,408]

Recent research shows that **maternal psychological well-being influences feeding of their premature infant.** Maternal depression, worry, and role stress were highest one week prior to the onset of the first oral feeding. **Maternal depression and role stress were associated with less use of developmentally supportive feeding behaviors such as minimizing tactile stimulation, providing steady tactile containment and stabilization, and regulating milk flow in response to neonatal cues.**[325] Additionally, maternal psychological functioning influences maternal presence in the NICU (distress associated with decreased maternal presence) and the length of stay.[82,163]

A feeding plan, developed with parents,[365,380,408] must be individualized for each infant and posted at the bedside (see Box 13.15 and the Case Study). All care providers must adhere to the plan for consistency and continuity of stimuli and to promote infant learning.[380] Evidence-based approaches to nipple feeding (for NICU preterms and sick term infants) have been developed that integrate contingent, developmental principles with more nurse autonomy and multidisciplinary collaboration and support. The Early Feeding Skills (EFS) Assessment checklist has been developed to assess a preterm infant's readiness for oral feeding, oral feeding skill, and ability to maintain physiologic stability and tolerance of oral feeding.[410] The Premature Infant Oral Motor Intervention (PIOMI) is an evidence-based, validated intervention that facilitates the development of oral feeding skills, improves oral feeding, shortens length of stay, and lowers costs.[229] The Preterm Oral Feeding Readiness Scale (POFRAS) evaluates aspects of physiology, behavior, and nonnutritive sucking and is moderately accurate in determining oral feeding readiness.[48] The Supporting Oral Feeding in Fragile Infants (SOFFI) method contains an algorithm to assist nurses in decision making, using specific evidence-based strategies and interpreting behavioral cues for bottle feeding preterm, sick, and fragile infants.[364] SOFFI is recommended to be used in conjunction with the National Association of Neonatal Nurses Guideline for Practice: *Infant directed oral feeding for premature and critically ill hospitalized infants.*[365] The Infant Driven Scale assesses feeding readiness in preterm infants and identifies infants at risk for delayed full oral feedings.[151] The Neonatal Eating Assessment Tool (NeoEAT) Bottle Feeding is a valid and reliable parent-report assessment of bottle feeding in infants younger than 7 months of age.[319] NeoEAT Bottle Feeding can be used in clinical practice to identify infants who need assessment and/or intervention and to measure their response to intervention. Three versions of the NeoEAT tool (NeoEAT Breastfeeding, NeoEAT Bottle Feeding, and NeoEAT Breastfeeding and Bottle Feeding) have been developed and tested for validity.[318]

TABLE 13.13 CRITICAL FINDINGS
STRESS* DURING NIPPLE FEEDINGS

SIGN	SIGNIFICANCE	INTERVENTION
Color change Pallor, dusky, gray, central cyanosis—perioral/periorbital	Oxygen desaturation[406,407] Feeding too rapidly with brief, shallow breaths Low hematocrit level Breath-holding	Assess baseline color before feeding Assess bottle-feeding delivery system: soft-walled system significantly improves oxygen saturation, coordination of suck/swallow/breathe, and more like breast feeding compared with rigid-walled feeding bottle[153,267,364,365] Periodic removal of nipple to facilitate deep breathing Monitor changes in color during feeding Use pulse oximeter during feeding to maintain saturation ≥92%[406,407]
Changes in state of alertness	Quiet alert state optimal for successful feeding Increased infant focus on feeding Increased organization of oropharyngeal muscle movements	Offer preterm opportunity to suck on pacifier before feeding—encourages awake/alert behavior[407]
	Increasing drowsiness, falls asleep: Respiratory fatigue resulting from rapid feeding, desaturation, increased respiratory rate, and/or work of breathing Fatigue resulting from behavior/energy expenditure (e.g., crying; bathing) before feeding	Pulse oximeter monitoring during feeding—give and/or adjust oxygen to maintain saturations ≥92% during nippling efforts Unwrap if sleepy
	Fussiness/restlessness—resulting from oxygen desaturation (e.g., hypoxia) because of the work of breathing (WOB) and nippling; disorganized behavioral state	Periodic rest periods and pace energy expenditure with nipple feeding Swaddle/rock if fussy
Breathing	Increased respiratory effort resulting from work/exercise of feeding,[266,406] especially in the infant with CLD/BPD[97,272]	PMA >32 weeks who are ready to initiate oral feedings: delay of start by 1 week reduces physiologic distress (oxygen desaturations) with feeding[440]
1. Respiratory fatigue: Falls asleep, ceases feeding before adequate volume obtained	WOB before feeding is increased further with effort of feeding Infants with poor endurance may be unable to feed or may demonstrate poor weight gain despite acceptable intake	Pulse oximeter monitoring with feeding to ensure adequate oxygenation; give oxygen PRN to keep saturation ≥92% Provide chin/cheek support (see Box 13.7) that decreases energy expenditure, enhances state organization and sucking activity
2. Tachypnea Respiratory rate >60/min	WOB increases with feeding; respiratory rate increased with work of feeding Increased incoordination of suck-swallow-breathe with feeding; predisposes to aspiration Increased risk for aspiration if gasping for breath	Brief and/or frequent breaks in feeding to enable deep breaths and reorganize breathing patterns[407]
3. Nasal flaring	Attempts to increase oxygen intake because of hypoxia or increased WOB	Pulse oximeter; supply adequate oxygenBrief breaks to reorganize breathing
4. Nasal blanching	Distress of breathing/hypoxia Incoordination of suck-swallow-breathe with possible aspiration if flaring/blanching occur	
5. Chin tugging/head bobbing/"catch-up" breathing/grunting	Attempting to increase air entry because of "air hunger"/hypoxia/WOB/decreased tidal volume Incoordination of suck-swallow-breathe; increased risk for aspiration	As for signs 1 through 3

Continued

TABLE 13.13 CRITICAL FINDINGS—CONT'D
STRESS* DURING NIPPLE FEEDINGS

SIGN	SIGNIFICANCE	INTERVENTION
6. Crowing sounds—high-pitched stridorous noise on inspiration	Incoordination of opening/closing of vocal cords that increases the risk for aspiration into the trachea[454]	As for signs 1 through 3
7. Swallowing	Primary swallow dysfunction predisposes to aspiration,[380] swallowing may be evaluated by videofluoroscopy	
A. Drooling	Loss of bolus control because of: Inability of tongue to collect and hold fluid that is flowing too fast Rapid respiratory rate, excessive WOB that shortens time for swallowing to occur, so that only part of bolus is swallowed	Give fewer sucks in a row, followed by brief break (pacing) so that bolus is smaller and easier to completely swallow[223]
B. Gulping	Use of prolonged sucking pattern or long sucking bursts (especially at the beginning of feeding) without deep breathing at the appropriate intervals Results in oxygen desaturation, bradycardia, apnea resulting from suppression of respiration Increases incoordination of suck-swallow-breathe and stimulates pharyngeal stretch receptors, resulting in vagally stimulated apnea	Give brief breaks (pacing) to assist the infant in slowing down the feeding[223]
C. Gurgling sounds in the pharynx (breathing sounds are wet/noisy)[380]	Fluid collecting in the throat, pharynx, or supraglottic space above vocal cords Noisy respirations caused by breathing through fluid in hypopharynx because bolus is too large or flow is too fast	Brief break from feeding to enable extra swallow/dry swallow to clear fluid from throat
D. Swallowing (several times) in succession	Deliberate swallows in succession to clear bolus (that is too large/flow is too fast) from pharynx Breathing is delayed with successive swallowing and may result in apnea/ bradycardia[268]	Break from feeding to clear throat and regain control of respiration
E. Coughing, choking, gagging, spitting up	Fluid has entered (or nearly entered) the airway[266] Changes in color, heart rate, respiratory rate suggest swallowing problems Occurrence toward end of feeding suggests gastroesophageal reflux; frequent or intense spitting up also may indicate reflux	Usually can be prevented by close attention and intervention to previous signs of feeding difficulty Breaks from feeding to clear airway, regain control of respiration and state organization Ability to cough enables infant to clear airway Inability to cough, color change, hypotonia, bradycardia, and apnea are symptoms of airway obstruction that may require suction and cardiopulmonary resuscitation Change nipple and/or bottle system

*Stress signals delay the transition to full oral feedings.[458]

BPD, Bronchopulmonary dysplasia; *CLD,* chronic lung disease; *PMA,* post menstrual age; *PRN,* as needed; *WOB,* work of breathing.

Modified from Shaker C. Nipple feeding preterm infants: an individualized, developmentally supportive approach. *Neonatal Netw.* 1999;18:15.

The latest *Cochrane* review found no RCT or quasi-RCT of instruments for assessing readiness to commence oral feedings in preterm infants.[95]

A case report has been published of the progress of one preterm infant's nutritive sucking and development of effective feeding skills using the nfant® Feeding Solution system.[70] The noninvasive assessment system measures tongue movements against a bottle nipple and streams the data to a tablet as the infant sucks. The real-time data is then used to evaluate not only sucking ability and progression but also the efficacy of interventions with a goal of providing safe, cue-based feedings that progress to full oral feedings quickly, resulting in earlier discharge and cost savings.

CASE STUDY

Tommy was a 28-week preterm infant with severe RDS, prolonged ventilation, and now BPD. He is now 38 weeks' postconceptual age, receiving hood and nasal cannula oxygen and trying to learn to nipple feed. In the morning report, the night nurse says that Tommy "has bradycardia with tube passage so that 24 hours ago he had a cardiorespiratory arrest that required resuscitation. He also has bradycardia and tachypnea with bottle feeding."

Tommy's nurse evaluated his initial attempts to bottle feed (after waiting for him to demand) and wrote the care plan (see Box 13.18) after feeding him 45 mL in 20 minutes without tachypnea, cyanosis, or bradycardia.

BPD, Bronchopulmonary dysplasia; *RDS,* respiratory distress syndrome.

BOX 13.18 TOMMY'S FEEDING PLAN

1. *Sit upright.* This decreases the flow of formula from the bottle and thus decreases:
   a. His gag reflex, which causes the bradycardia
   b. His anxiety, which is caused by a bolus of formula in his mouth
2. *Use a blue nipple.* This is the shortest nipple and decreases stimulation of his hypersensitive gag reflex, which causes his bradycardia. (All other nipples stimulated him to gag.)
3. *Gently push up under his chin when he gets a mouthful of formula.* This pushes his tongue upward against his palate, the same way the tongue moves during swallowing. (READER: Swallow and note your tongue motion.) He becomes frightened (i.e., eyes wide open and fearful; increased respiratory rate; arching and struggling) when he has a mouthful of formula, because he is used to sucking only on a dry pacifier and having nothing to swallow. His fear raises his heart rate, respiratory rate, and gag reflex, which causes bradycardia.
4. *Talk to him.* Softly and gently, tell him he can swallow, and praise him when he does.
5. *Nipple.* Have him do this as much as possible (he will only get better with practice) and supplement feeding with the indwelling nasogastric tube (no more intermittent tube passage).

CRYING OR SMILING INTERVENTION

Crying is the infant's innate care-eliciting behavior, a signal that he or she needs attention. The energy expenditure of a crying infant is increased by 7.5% compared with the resting state.[351] Immediate response decreases the infant's physiologic stress, increases the infant's trust in the environment, and enhances the sense of self and of control over the world.[249] The infant's need to escalate to "out-of-control" crying is decreased with immediate response so that infants are easier to soothe. Consoling the crying infant also helps the infant change states so he or she is able to attend to and interact with the environment.

Term infants vocalize, cry, and look at their caregiver more than do preterm and ill infants.[158] Although preterm infants are more irritable than full-term infants, preterm infants cry less throughout the day than do full-term infants. **NICU infants exhibit fewer care-eliciting behaviors (some preterm infants in one study never cried, vocalized, or looked at their caregiver).[158]** Preterm infants thus are less responsive to the caregivers (both parents and professionals), who receive less positive feedback from the infant and hence are less rewarded. In one study, those NICU infants who were able to cue the care provider (cry, look, vocalize) were consistently responded to 80% to 100% of the time.[158]

Intubated infants who cannot produce an audible cry signal their needs by agitation, heart rate changes, and changes in oxygenation. Preterm infants (<32 weeks' gestation) may recover better from agitation when left alone, because active consolation is overstimulating. How caregivers attempt to soothe a crying infant while giving NICU care includes (1) no response to cries (58.1% of the time), (2) response by talking (29.2% of the time), (3) response by social touching (5.5% of the time), and (4) response by talk and social touching (7.2% of the time).[158]

Parents and staff should use graduated interventions in quieting a crying infant by the following:

- Soothing with gentle, high-pitched talking (loud enough that the infant can hear it above his or her crying)
- Placing the palm of the hand across the infant's chest or holding arms on chest with the palm of the care provider's hand
- Swaddling with blankets to decrease self-upsetting startles
- Picking up infant, holding (upright is the most soothing position), and rocking
- Placing the infant skin-to-skin on the parent's chest
- Offering a pacifier

Most stimulation in the NICU is procedural. The lack of social stimulation in the NICU not only affects the infant but also teaches parents that their infant is too weak for, too fragile for, uninterested in, or incapable of social interaction. Again, social stimulation must be paced according to the stage of development and stability of the infant[115] (see the Critical Findings in Box 13.2). Enhancing the infant's social environment includes presenting the smiling, moving, talking care provider's face to the alert infant; touching and stroking; and soothing and consoling the distressed infant.

In many busy NICUs, parents and a foster grandparent program provide this sensory integrated social experience. If the infant has been transported to a referral center, parents may live some distance away and be unable to visit daily. A chronically ill 4- to 5-month-old infant who begins to recognize the foster grandmother may smile, relax, and feed better for her and is often fussier and more irritable on her day off. A foster grandparent program benefits both infants and seniors—the infant receives love and socialization, and the senior "has a reason to get up in the morning."

If possible, parents should be encouraged to perform the "firsts" with their infant (e.g., first nipple feeding, first bath, first time out of the incubator). Because parents are not always present, they will miss some important milestones for their infant (e.g., extubation). Many NICUs have developed baby diaries (or calendars) and/or use videotaping in which the nurses, physicians, and foster grandparents write or record important information about the infant's day (as if the infant were the author). The text is accompanied by self-developing pictures with humorous captions (e.g., "Look at me. I've got my tube out!"). Staff members are very creative in relating what's been happening so that the parents have not only a verbal report (that may be forgotten over time) but also a keepsake of NICU progress.

BOX 13.19 ADVANTAGES OF SINGLE-FAMILY ROOM NICU CARE[230,231,350,434,453]

Increased developmental and family-centered care
Increased parental participation in their infant's care:

- More skin-to-skin care
- More visits; more time in NICU
- Ability to stay overnight in the NICU
- Received more breastmilk
- Lower gestational age at full oral feedings
- Growth: faster weight gain; higher weight at discharge mediated by increased developmental support
- Increased parental satisfaction, reduced stress, more privacy, and fewer interruptions

Cost-effective:

- Shorter length of stay
- Less sepsis
- Fewer medical procedures due to enhanced maternal involvement

Improved neonatal outcomes:

- Better attention due to increased developmental support
- Less stress, hypertonicity, and lethargy due to developmental care
- Less pain and physiologic stress due to enhanced maternal/parental involvement
- Higher language and cognitive scores at 18 to 24 months of age

The pursuit of "humane,"[204] **relationship-based**[10,11] **developmental care continues** with redesign of NICU environments,[448] including single-room care and changing the attitudes and care practices among health care providers. Advantages of single-family room care are listed in Box 13.19.

A comparison study of single-family NICU rooms versus open-ward NICU was conducted in an urban NICU with low levels of parental visiting and holding and found poorer outcomes at 2 years—**rather than the room configuration, the presence and care-by-parents influences improved outcomes.**[337] More recent follow-up studies comparing the outcomes of preterm infants cared for in single-family rooms to open-bay NICUs also found **improved outcomes in those infants cared for in single-family rooms because of enhanced maternal involvement and better developmental support.**[230,231]

Creating an integrated, relationship-based, family-centered, developmental care philosophy requires the following:

- A commitment by individual care providers to alter practice for the benefit of neonates and families and to integrate family-centered developmental care into their individual practice
- Relationship building with neonates, families, and colleagues
- The use of effective change strategies within the institution's organizational climate
- Implementing the guidelines of national professional organizations[16,448] to satisfy ethical, legal, and professional standards of care
- Changing health care providers' knowledge base, which requires multidisciplinary educational opportunities (e.g., orientation, in-service, continuing education, consultation) and written resource materials[6]

Developmental care can no longer be considered "nice, but optional," especially with the evidence that not only brain function but also actual brain structure are positively affected by the early experiences of family-centered developmental care in the NICU.* A study **evaluating the effect of developmental care on the neurodevelopmental outcomes of preterm infants found less psychomotor delay (16.1%) at 2 years of age in those toddlers who received developmental care in the NICU than those toddlers cared for without developmental care (27.4%).**[205] Another recent study of toddlers who were born prematurely (75% very preterm; 25% moderate/late preterm) found those with a **longer stay in the NICU had the highest risk for behavioral problems.**[74] The level of prematurity or the presence of BPD/CLD and ROP did not affect temperament, whereas a longer stay in the NICU was associated with more pervasive developmental and emotionally reactive problems. Based on these findings, these researchers **emphasize the need for developmental care in NICUs to reduce stressful and painful experiences for premature babies and to provide protection from overwhelming stimuli in the NICU during the premature infant's initial development.** Developmentally appropriate care in the NICU must also be accompanied by "proactive developmental monitoring and implementation of timely therapeutic and educational early intervention services … to continue to support optimal outcomes for preterm infants."[238]

*References 7–9, 270, 271, 289–291.

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14 FLUID AND ELECTROLYTE MANAGEMENT

MICHAEL NYP, JESSICA L. BRUNKHORST, DAPHNE REAVEY, AND EUGENIA K. PALLOTTO

Advances in the management of specific neonatal disorders have contributed to a remarkable decline in morbidity and mortality rates in newborns. Fluid and electrolyte therapy, nutritional support, thermal regulation, and maintenance of oxygenation remain central features of modern, supportive neonatal intensive care. Fluid and nutrition data have accumulated over time, but opportunities remain for increasing knowledge in order to optimize clinical management and long-term outcomes. For example, the restrictive fluid policies of the 1950s were misguided efforts that caused hyperosmolarity, hyperbilirubinemia, and hypoglycemia. On the other hand, the degree to which initial fluid, electrolyte, and glucose administration should be "liberalized" remains uncertain—particularly in very-low-birth-weight (VLBW) infants (infants with birth weights less than 1500 g).[1,15,21] **Many high-morbidity outcomes, such as patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage, and hyperglycemia, in VLBW infants are associated with larger volumes of fluid, electrolyte, and glucose administration.[1,25,52]** At best, clinicians make approximations for therapy in many clinical situations, which is why good measures of fluid and electrolyte requirements are needed. Infants requiring neonatal intensive care commonly receive parenteral fluids, often for prolonged periods of time. The fluid requirements of both premature and term infants vary based on the underlying diagnosis and therapies used to treat these disease processes.

This chapter discusses the implementation of the following fundamental principles: (1) rapidly assessing the infant's initial condition; (2) developing a short-term, time-oriented management plan; (3) initiating therapy; (4) monitoring the infant; and (5) modifying the plan based on clinical and biochemical data.

PHYSIOLOGY

Neonates show physiologic differences when compared (on a per-kilogram basis) with older children and adults: (1) their basic metabolic rate is greater, even double; (2) their fluid requirements are four to five times higher; (3) their sodium excretion is only 10% that of older children and adults; and (4) their glomerular filtration rate is 5 to 10 times less than that of adults.[15] The subdivisions of total body mass (TBM) are illustrated in Fig. 14.1. Total body water (TBW) as a percentage of TBM demonstrates a curvilinear decline with increasing gestational age (Fig. 14.2). **During the early fetal period, the fetus's TBW is 95% of total weight and decreases to 80% at 8 months' gestation and then to 75% at term.**[15] Intracellular fluid (ICF) and extracellular fluid (ECF) as percentages of TBM change in opposite directions as gestational age advances, ECF decreases, and ICF increases with growth.

BLUE type highlights content that is particularly applicable to clinical settings.

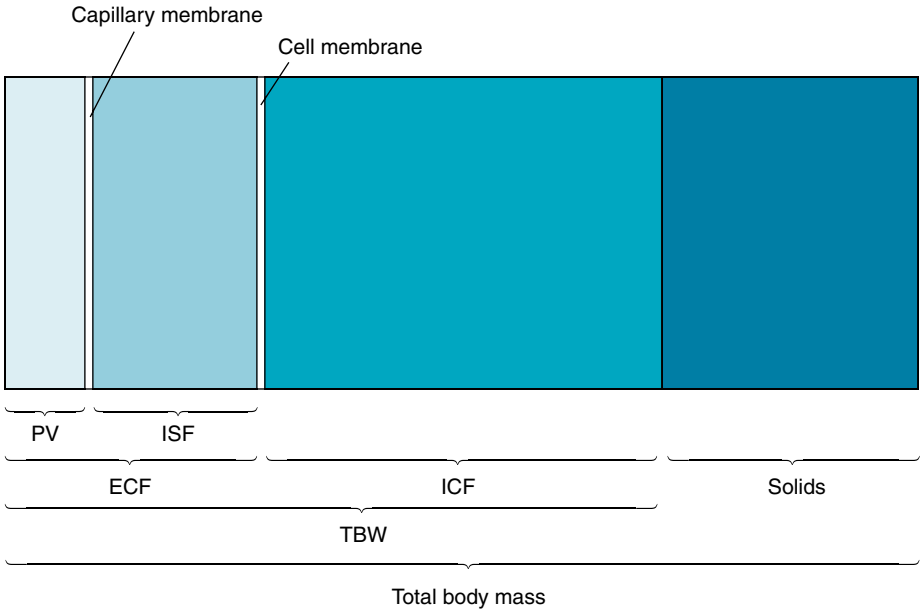

FIGURE 14.1 Major subdivisions of total body mass. *ECF,* Extracellular fluid; *ICF,* intracellular fluid; *ISF,* interstitial fluid; *PV,* plasma volume; *TBW,* total body water. (From Winters RW, ed. *The Body Fluids in Pediatrics.* Boston: Little, Brown; 1973.)

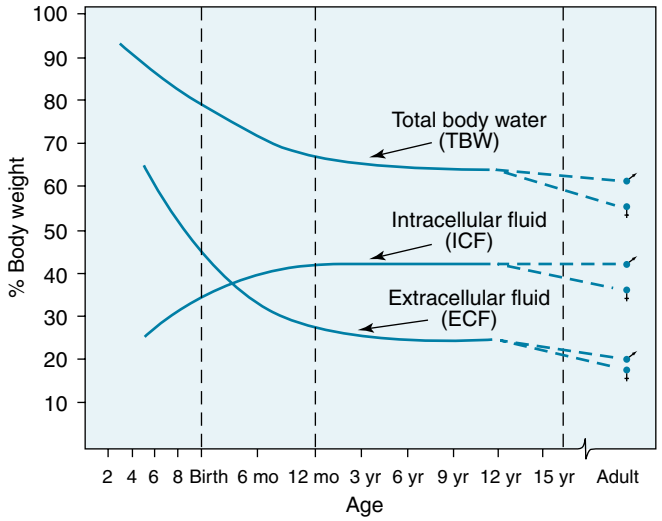

FIGURE 14.2 Effects of age on TBW, ICF, and ECF. Note curvilinear changes that are maximal during perinatal period. (From Winters RW, ed. *The Body Fluids in Pediatrics.* Boston: Little, Brown; 1973.)

An understanding of the physiologic and body composition phenomena is important to accurately calculate fluids and electrolytes for the neonatal patient. Caregivers should independently calculate all requirements and compare calculations with standard guidelines. **Intravenous (IV) fluid should be administered by a special infusion pump that can regulate fluid with a precision of at least 0.01 mL/hr. Intake should be measured hourly and all output measured. The balance of intake versus output should be assessed at least every 8 to 12 hours using a standard format** (Fig. 14.3).

Output

Times	Closed drainage system Δ _____ Chest tube # Site / Activity	cm H2O / Color	Pleurovac reading / Drainage in cc's		Urine: Type / Color	Specific gravity	pH / Glucose	Protein / Blood	Amt. / Cumul.	Stools: Last stool _____ Type	Hematest / Clinitest				Gastric: Tube Δ d _____ Amt.	Color / Irrig.	Cumul. total	Blood out: Balance forward _____ Reason	Amt. out	Cumul. total
0700																				
0800																				
0900																				
1000																				
1100																				
1200																				
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Chest tube activity
B - Bubbling
F - Fluctuating
D - Draining
C - Clamped
N - No movement

Chest tube color
BL - Bloody
S - Serosanguinous
Y - Yellow
W - White or milky
Other: _____

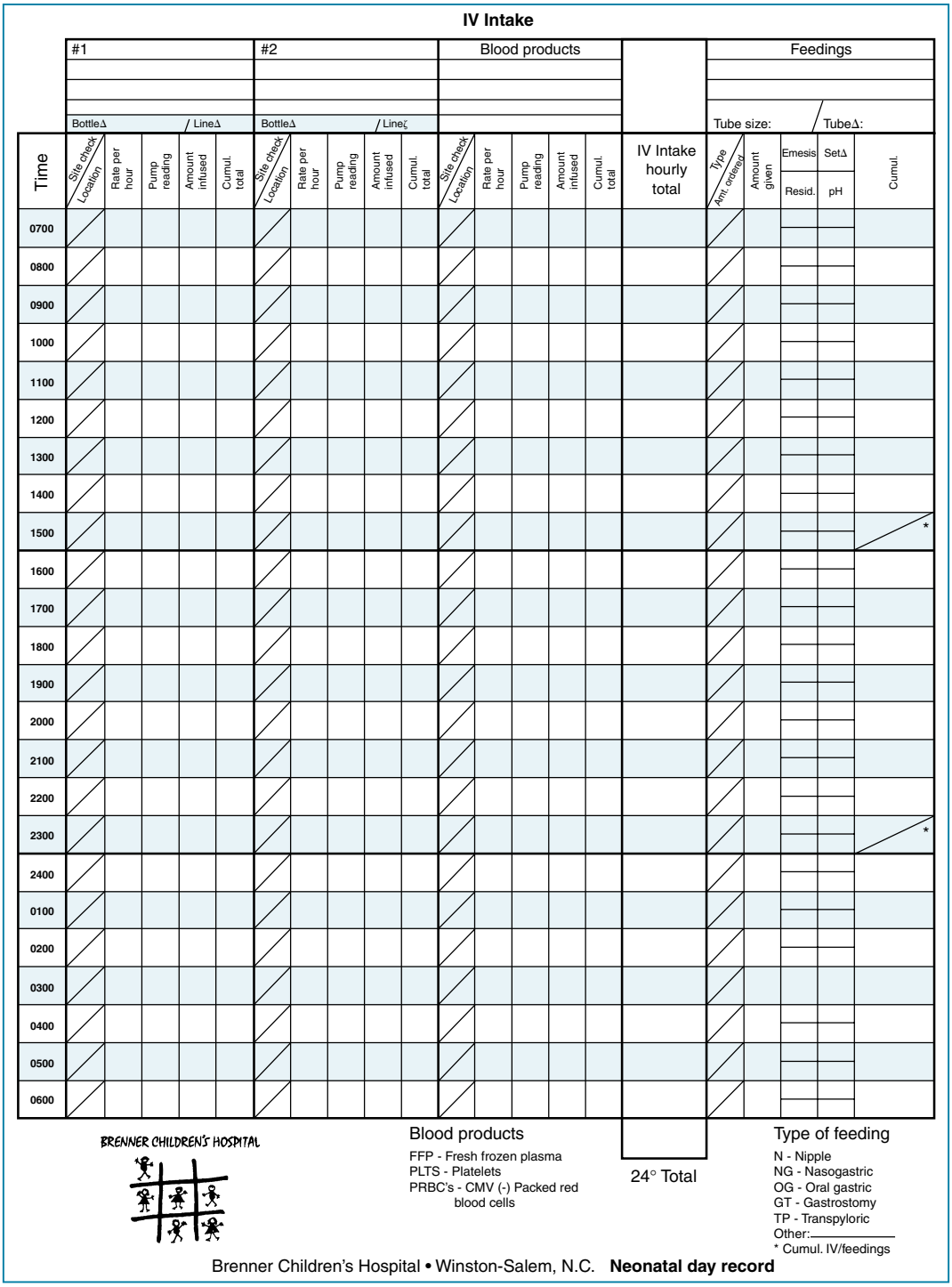
Urine type
VD - Void
CATH - Catheterized
CR - CREDÉ

Urine color
A - Amber
Y - Yellow
BL - Bloody
Other: _____

Stool type, size, and color
F - Formed
P - Pasty
LO - Loose
M - Mucus
MEC - Meconium
SDY - Seedy
SOF - Soft
W - Watery
LG - Large
MED - Medium
S - Small
T - Transitional
Y - Yellow
BR - Brown
BLK - Black
BL - Bloody
G - Green

Brenner Children's Hospital • Winston-Salem, N.C. **Neonatal day record**

FIGURE 14.3 Model intake and output sheet. (Courtesy Brenner Children's Hospital, Winston-Salem, North Carolina.)



IV Intake

Time	#1 Bottle Δ / Line Δ: Site check / Location	#1: Rate per hour	#1: Pump reading	#1: Amount infused	#1: Cumul. total	#2 Bottle Δ / Line ζ: Site check / Location	#2: Rate per hour	#2: Pump reading	#2: Amount infused	#2: Cumul. total	Blood products: Site check / Location	Blood products: Rate per hour	Blood products: Pump reading	Blood products: Amount infused	Blood products: Cumul. total	IV Intake hourly total	Feedings Tube size: / Tube Δ: Type / Amt. ordered	Feedings: Amount given	Feedings: Emesis / Resid.	Feedings: Set Δ / pH	Feedings: Cumul.
0700																					
0800																					
0900																					
1000																					
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BRENNER CHILDREN'S HOSPITAL

Blood products

FFP - Fresh frozen plasma
PLTS - Platelets
PRBC's - CMV (-) Packed red blood cells

24° Total

Type of feeding

N - Nipple
NG - Nasogastric
OG - Oral gastric
GT - Gastrostomy
TP - Transpyloric
Other:_____
* Cumul. IV/feedings

Brenner Children's Hospital • Winston-Salem, N.C. **Neonatal day record**

FIGURE 14.3, cont'd

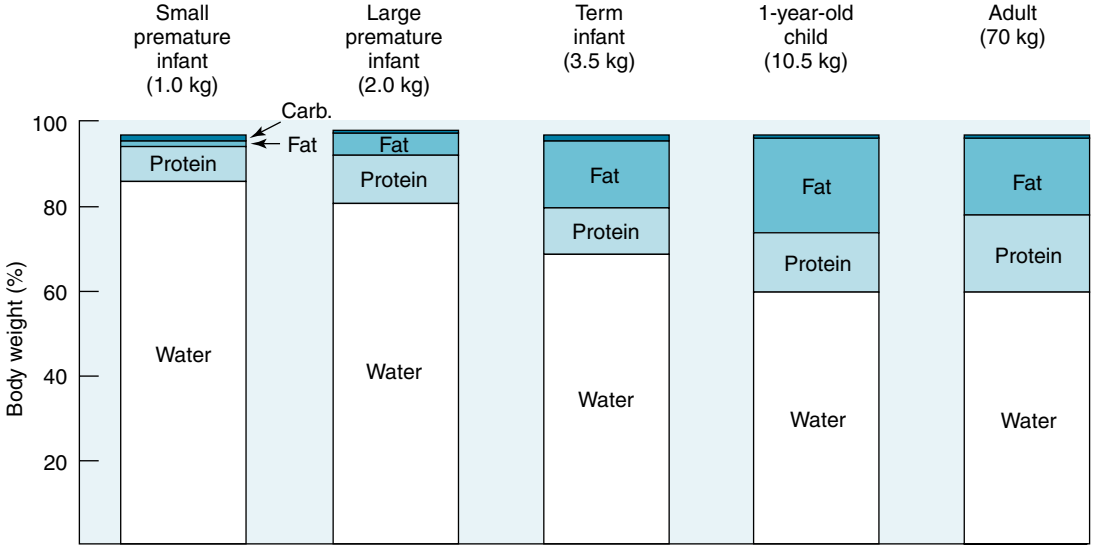

FIGURE 14.4 Effects of gestational age on body composition compared with older children and adults. (From Heird WC, Driscoll JM Jr, Schullinger JN, et al. Intravenous alimentation in pediatric patients. *J Pediatr.* 1972;80:351.)

The ability of infants, especially those who are **premature, to remove free water and/or remove a solute load is impaired. Once clinical signs of fluid overload or deficit occur, it may be difficult to regain balance**. Fluid balance should be managed prospectively; consistent assessments and laboratory evaluations should be a part of every initial care plan.

The effect of gestational age on body composition is striking (Fig. 14.4). Because gestational age is a determinant of the percentage and distribution of TBW, accurate assessment is important. In utero, fetal fluid and electrolyte balance occurs through feto-placental exchange. Changes in the distribution and percentage of body water will be influenced by intrauterine growth, maternal fluid balance, maternal medications, maternal health conditions, and placental blood flow. For example, a preterm infant born to a mother receiving magnesium sulfate may have elevated serum magnesium levels at birth, which may remain elevated for up to 3 to 5 days following birth. Small-for-gestational-age (SGA) infants have reduced amounts of fat, and their TBW (as a percentage of TBM) increases. Conversely, large-for-gestational-age (LGA) infants with an increased amount of body fat have a lower percentage of TBW.

The initial (first 3 to 5 days of life) weight loss of healthy term (up to 5% to 10% of TBM) and preterm (up to 10% to 15% of TBM) infants should be considered a normal physiologic loss of fluid. This loss is from the interstitial fluid (ISF). It is not a pathologic catabolism of body tissues but a result of the maturation of specific regulators of fluid and electrolytes. One such example, vasopressin (antidiuretic hormone), is secreted during the early stages of labor. This hormonal secretion contributes to renal maturation and has an antidiuresis effect at birth.[26]

After birth, contraction of the ECF compartment occurs, followed by natriuresis, diuresis, and weight loss.[15] **This weight loss is then regained over 7 to 10 days as muscle and fat, provided there is good nutrition. Neonates often demonstrate relative oliguria during the first 24 to 48 hours.** Disease processes, such as asphyxia, pneumonia, and respiratory distress syndrome (RDS), increase vasopressin release; thus, the fluid and electrolyte transition during the first few days of birth may be altered in these conditions.[22,42,59] Neonates with RDS will also have delayed postnatal contraction of the ECF compartment, further delaying diuresis. The onset of the diuresis, during the first few days of life, usually coincides with the initial stages of recovery from RDS.[27]

Despite the period of natriuresis after birth, infants usually do not require additional sodium during the first 24 to 48 hours of life. It is normal to have an initial negative sodium balance, but later it is necessary to retain sodium for appropriate growth; additional sodium supplementation may be required.[27] A review of maternal history and the intrapartum course may be helpful in calculating the infant's fluid

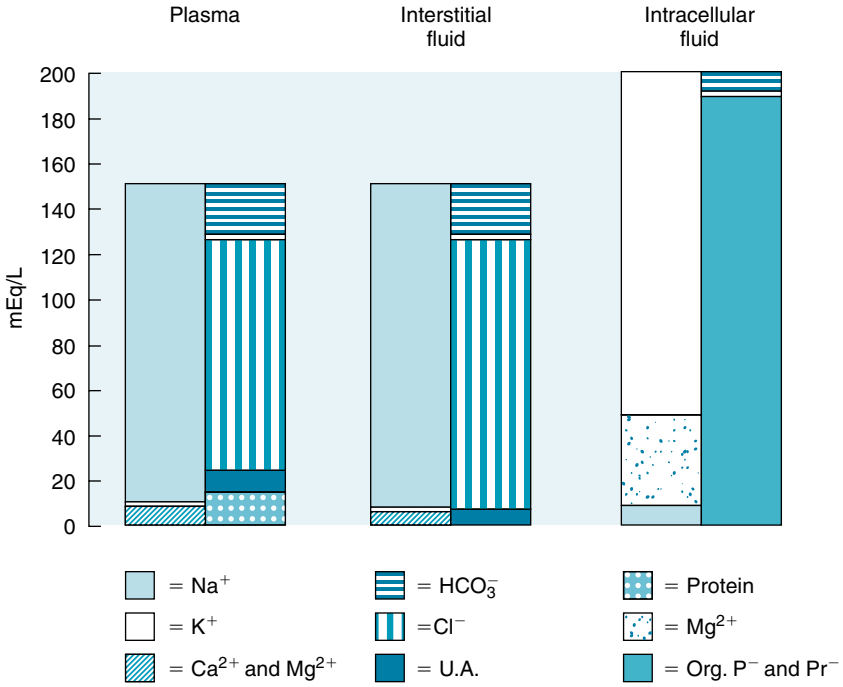

FIGURE 14.5 "Gamblegram" of plasma interstitial fluid and intracellular fluid. (From Winters RW, ed. *The Body Fluids in Pediatrics.* Boston: Little, Brown; 1973.)

and electrolyte requirements. For example, if the mother received large amounts of electrolyte-free fluids in the intrapartum period, the neonate may be hyponatremic and have an expanded ECF space at birth.[34,66]

Extracellular fluid comprises both intravascular fluid (plasma) and ISF. The electrolyte composition of ISF and plasma is similar, but it is strikingly different from ICF (Fig. 14.5). Sodium is the major cation in ECF (both ISF and plasma) and is easily measured. Potassium, the major cation in ICF, on the other hand, cannot be measured readily because ICF is not easily accessible. Because 90% of the total body potassium is intracellular, low levels of plasma potassium are assumed to reflect low total body potassium.

Maintaining appropriate fluid and electrolyte balance may be difficult due to the immaturity of the neonatal renal system: (1) inability to dilute urine secondary to lower glomerular filtration rate (GFR) and (2) inability to concentrate urine secondary to renal tubular immaturity. The neonatal GFR, a measure of renal function, is low in utero but increases rapidly within a few hours after delivery and throughout the first postnatal week as renal blood flow increases. This increased GFR is a result of increasing cardiac output and increasing glomerular permeability.[27]

GFR is independent of gestational age. It rises rapidly during the first 6 weeks of life, increases more slowly during infancy, and reaches adult values by 12 months of age. A VLBW infant in satisfactory condition at 6 weeks should have a similar GFR to that of term infants. The formation of nephrons is complete at 34 to 35 weeks' gestation, whereas maturation of the nephrons continues beyond 40 weeks' gestation.[15,21] **The GFR can be compromised in critically ill neonates.**

In addition to fluid balance, the renal tubules are responsible for mineral and electrolyte excretion and reabsorption. **Renal tubular function is influenced by gestational age.[27] At birth, immature tubular function is associated with sodium wasting and an impaired ability to reabsorb water.[28] These characteristics are exacerbated in premature infants.[62] Preterm infants with immature tubular function are more likely to experience electrolyte imbalance.**

The use of the urinary fractional excretion of sodium (FENa) [FENa = (Urine sodium × Plasma Cr)/(Urine Cr × Plasma sodium)] is an important

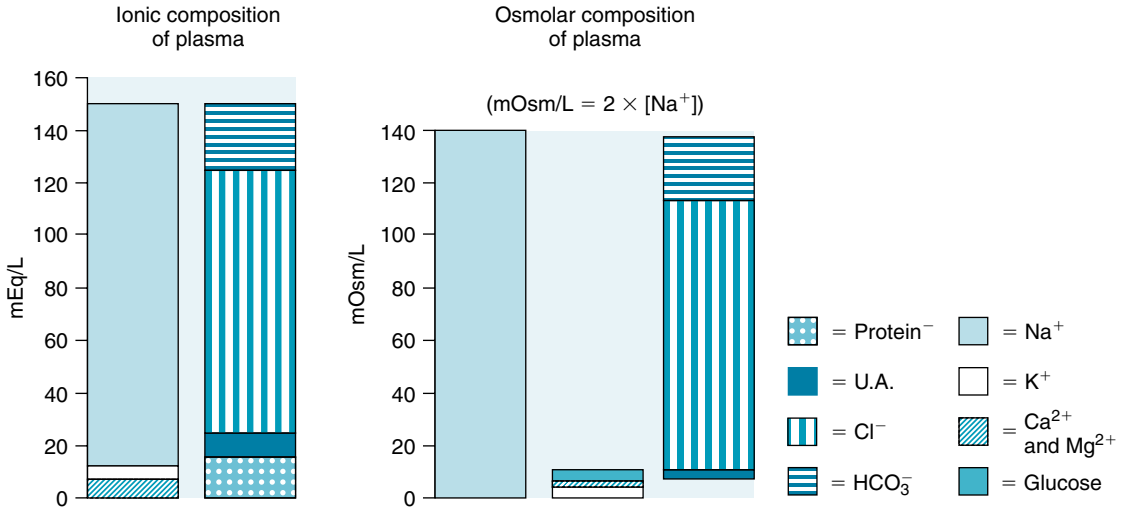

FIGURE 14.6 Ionic and osmolar composition of plasma. (From Winters RW, ed. *The Body Fluids in Pediatrics.* Boston: Little, Brown; 1973.)

tool in assessing sodium balance but must be interpreted cautiously, especially shortly after birth, due to the immaturity of renal tubular function. When using **FENa to diagnose the etiology of hyponatremia, a value greater than 3% reflects an intrinsic renal problem, whereas a value less than 2.5% reflects a prerenal problem** (e.g., volume depletion); both values are higher than that expected for an adult.[18] A falsely elevated FENa may be present when excessive sodium is lost in the urine due to prematurity or with diuretic use.[30,69]

The ability to excrete potassium is impaired at birth, especially in low-birth-weight infants, thus increasing their risk of hyperkalemia, particularly when given a potassium load before establishing stable renal function. **Calcium reabsorption is also reduced with immaturity and results in higher urinary levels of calcium; thus, early use of loop diuretics may lead to an increased risk of renal stones.**[31]

The capacity to concentrate urine in VLBW infants appears limited but can be influenced by gestational age and nutrient intake. The immature concentrating ability (maximum of approximately 600 mOsm/L) (Fig. 14.6) coupled with an inability to rapidly excrete an acute water or sodium load results in a narrow margin of safety when prescribing fluid and electrolytes, especially in the VLBW infant.[1,15,21]

In general, urea is the major component of urine osmolality (and hence specific gravity). When total parenteral nutrition is provided, urine specific gravity may rise because of a low renal threshold for glucose and amino acids. **Very preterm infants will have glucosuria despite serum glucose levels in the normal range. The renal protein and glucose threshold increase with advancing gestation.**

Neonatal urinary acidification is also limited, and the threshold for bicarbonate excretion is reduced, leading to both decreased bicarbonate retention and acid excretion. Both physiologic and pathologic factors can contribute to this urinary alkalinization. Acidemia develops in premature infants due to this limited capacity for hydrogen ion excretion. **Alkaline urine pH will precede the development of acidemia. Closely monitoring and replacing losses can prevent the development of severe acidemia.** In more mature infants, urinary alkalinization will occur in the setting of more acute illnesses, such as a urinary tract infection or bicarbonate-losing tubular necrosis that may occur in neonatal diagnoses associated with acute kidney injury or with nephrotoxic medications.[53] The ability to distinguish acidemia occurring from an acute illness versus a developmentally impaired urinary acidification system is important for proper treatment. The **anion gap (serum Na^+/[serum Cl^- + serum bicarbonate]) is a useful tool in this assessment. The normal anion gap typically is less than 8. A widened anion gap is suggestive of increased production of organic acid, in particular lactic acid (a pathologic condition),**

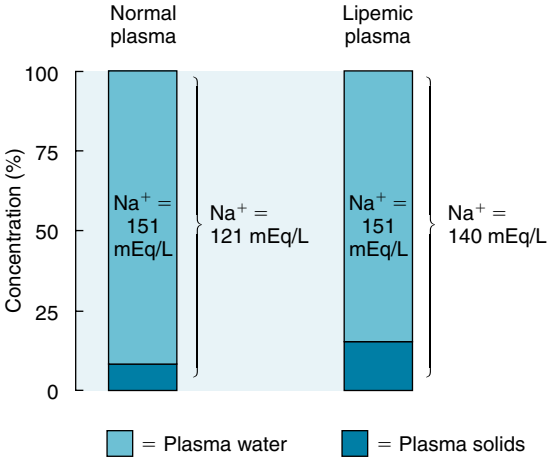

FIGURE 14.7 Effects of hyperlipidemia on plasma water and plasma sodium concentration. (From Winters RW, ed. *The Body Fluids in Pediatrics.* Boston: Little, Brown; 1973.)

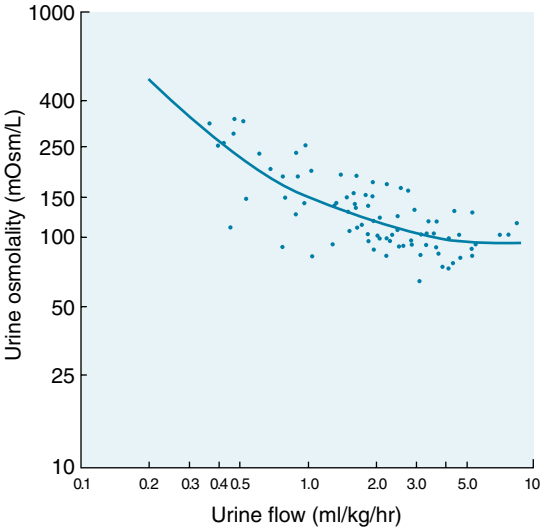

FIGURE 14.8 Normal urine flow rates. (From Jones MD, Gresham EL, Battaglia FC. Urinary flow rate and urea excretion rates in newborn infants. *Biol Neonate.* 1972;21:322.)

whereas a normal or narrow gap suggests bicarbonate loss due to the lowered threshold for bicarbonate excretion in the neonate. Further details are available in Chapter 8.

Hormones, including antidiuretic hormone, aldosterone, atrial natriuretic factor, and parathyroid hormone, are involved in regulating the neonatal fluid and electrolyte balance, yet the specific roles are not well defined. **Most hormonal effects occur by modifying renal function through a change in either GFR or renal tubular permeability. For example, the increased osmolality that occurs in dehydration is a trigger for antidiuretic hormone release, leading to changes in the permeability of the distal tubule and collecting duct. This change results in more water reabsorption and thus more concentrated urine.**

Osmolality can be satisfactorily estimated in many clinical settings by the following formula (Fig. 14.7):

$$\text{Osmolality} = \left[2\left(\text{Na}^{+}\right) + \text{Glucose (mg / dL)} \div 18\right] + \left[\text{BUN (mg / dL)} \div 2.8\right]$$

Osmotic forces are responsible for apparently low plasma electrolyte concentrations in some common clinical settings. For example, in hyperglycemia, the plasma sodium concentration reported by the laboratory is usually low, but the total effective osmolality may be normal. An analogous situation exists for the less frequent condition of hyperlipidemia, in which low laboratory plasma sodium values are reported with a normal osmolality (Fig. 14.8). **Low laboratory values for plasma sodium (pseudohyponatremia) can be present in the setting of hyperlipidemia or hyperglycemia.** This occurs because the increase in plasma solids (lipids) causes a lower plasma water content, resulting in water displacement and hence a lower sodium concentration per liter of whole plasma.

Osmotic forces largely determine shifts in the internal redistribution of water in hydration disturbances. An example of changes in osmolality occurs in preterm infants who undergo insensible water loss because of skin immaturity, decreased body fat, and a large surface-to-volume ratio leading to increased evaporation. This water loss from the interstitial space results in a hyperosmolar extracellular compartment exhibited by hypernatremia and occasionally hyperkalemia and hyperglycemia.[15]

Another key concept in fluid and electrolyte balance involves insensible water losses (IWLs) that occur via pulmonary and cutaneous routes and are influenced by the factors listed in Table 14.1. **However, IWL varies greatly depending on gestational age and birth weight** (Table 14.2). The neonate's environment also can affect the fluid balance. **Radiant warmer usage decreases the**

TABLE 14.1 EXAMPLES OF OSMOTIC FORCE

	mM	N	mOsm
NaCl	1	2	2
Glucose	1	1	1
$CaCl_2$	1	3	3

TABLE 14.2 FACTORS THAT INFLUENCE INSENSIBLE WATER LOSS (IWL)

DECREASE IWL	INCREASE IWL
Heat shield or double-walled incubators	Inversely related to gestational age and weight
Plastic blankets	Respiratory distress
Clothes	Ambient temperature above thermoneutral
High relative humidity (ambient ventilator gas)	Fever
Emollient use	Radiant warmer
	Phototherapy
	Activity

neonate's radiant heat loss but can increase IWL by 50% to 200%, resulting in hypernatremic dehydration.[40] Incubators reduce radiant heat loss via their double-walled Plexiglas design.

Modern incubators provide sterile humidity (80% or greater) and are very effective in decreasing IWL by reducing evaporative heat loss. Internal incubator humidification was discontinued in the 1970s when it was associated with *Pseudomonas* infections.[41] Presumably, the nature of *Pseudomonas* promoted its stability and growth in the water humidification reservoirs. However, present humidification designs provide for direct heating of water in an external reservoir to a temperature that kills most organisms. The water is transformed into vapor, rather than mist, and carried in a gaseous state by the incubator's convective air flow, thus reducing the possibility of airborne bacterial transfer.[41]

Because added environmental humidity reduces transcutaneous evaporative water loss, an extremely preterm infant managed in humidity needs less fluid than those managed without humidity to achieve the same water balance. A relative humidity of 80% can reduce water loss to one tenth of the water loss of a preterm infant receiving care in 50% humidity.[40] This reduction in evaporative water loss affects the management of fluid requirements and the electrolyte balance in premature infants. **For infants with a birth weight of less than 1000 g, the use of humidity at 70% to 80% in the first week of life results in lower fluid intake and improved electrolyte balance and growth velocity.** A decreased risk of severe BPD has also been reported in extremely low-birth-weight (ELBW) infants cared for in humidified incubators.[36] Despite these improvements, the optimal level and duration of humidification have yet to be determined.

The ability to provide the proper fluid and electrolyte balance is determined by assessing initial fluid status, renal function, and estimated insensible fluid losses. Frequent assessment of fluid balance remains essential in preventing fluid deficit or overload, which can be difficult to correct once it has occurred.

ETIOLOGY

The causes of common electrolyte problems and common clinical syndromes are discussed under Treatment later in this chapter.

PREVENTION

Prevention of fluid and electrolyte imbalance in neonates begins with knowing how to calculate fluid and electrolyte requirements correctly. **The estimated metabolic rate forms the reference base for all calculations. The metabolic rate (and hence oxygen consumption) normally increases steadily over the first weeks of life, so changes in water and electrolyte requirements should be anticipated.**

If the daily caloric requirement is approximately 100 *kcal/kg/day,* the physiologic basis of metabolic rate may be used to calculate needs; however, most institutions determine an infant's daily fluid need on a *milliliters per kilogram (mL/kg)* basis, which is modified by factors that influence IWL and is usually adjusted depending on body weight, clinical composition, serum chemistry results, and urine volume and composition (Fig. 14.9; see also Table 14.2).

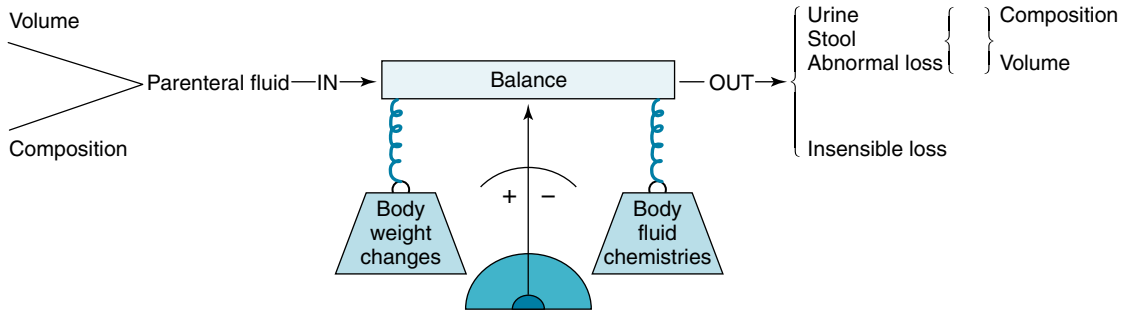

FIGURE 14.9 Basic scheme for monitoring and modifying fluid therapy.

Preterm infants have lower metabolic rates than those of term infants.[8] SGA infants may have higher metabolic rates than those of preterm infants of similar weight,[7] which may be because of their relatively large ratio of brain to body mass. Infants with congenital heart disease,[44] as well as infants in the immediate postoperative period,[48] also have higher metabolic rates compared with appropriate-for-gestational-age (AGA) infants. Both SGA and preterm infants, especially VLBW infants, should be expected to require more frequent assessment and modification of requirements.

Preterm infants, however, are subject to other problems that may diminish the influence of this metabolic rate when calculating fluid needs. SGA infants may require less water per kilogram than either preterm or term AGA infants due to their increased extracellular volume.[45] **Input should be recorded every hour. Output should be recorded hourly in critically ill infants but may be recorded every 4 to 6 hours in infants who require minimal stimulation.** The smallest infants require frequent fluid balance monitoring, so if output is unusually large, intake can be adjusted immediately. If fluid intake lags behind losses, critically ill infants may develop hypernatremia and may not tolerate "catching up." Continuous monitoring is necessary to ensure that fluid is administered in appropriate amounts. **Current infusion pumps can accurately infuse volumes of 0.01 mL/hr and must be used for the smallest, sickest infants.**

Requirements for fluid and electrolytes are divided into maintenance and deficit needs. ***Maintenance* indicates the infant remains in a zero-balance state** and can be subdivided into (1) normal loss, which consists of water and electrolyte loss through stool, urine, and insensible (lung and skin) routes; and (2) abnormal or increased losses, such as gastrointestinal/diarrhea, ostomy, and chest tube drainage.

All diapers should be preweighed using a gram scale and marked with dry/tare weight. After each stool or void, the diaper is reweighed; the difference equals the amount of loss. For example, if the dry weight is 20 g and the wet weight is 26 g, the difference is 6 g, or 6 mL of stool or urine. All losses should be calculated to the nearest milliliter.

The term *deficit* refers to previously incurred losses. These should be uncommon in the newborn but can occur when there are unrecognized losses, such as "third space" or interstitial losses with NEC (see later discussion). In older neonates, deficits may occur with disorders that have an insidious or delayed onset, such as renal tubular dysfunction or nonvirilizing congenital adrenal hyperplasia.

Deficits are best estimated by body weight comparisons. **Weight loss greater than 10% to 15% in 1 week should be considered excessive, although in VLBW infants it can be difficult to maintain within 10% to 15% of birth weight during the first week of life.[71] Infants who are SGA have less weight loss compared with AGA infants[72]** in the first 10 days after birth. Growth charts assist with calculations of weight loss and/or gain and help consider the normal physiologic weight loss that occurs during the first several days after birth when calculating an infant's fluid needs.

The initial choice of parenteral solution depends on the weight and postnatal age of the infant (Table 14.3). Also important is whether the infant is in an incubator with a heated humidified environment or under a radiant warmer without a plastic blanket or heat shield. **Uncovered VLBW infants under radiant warmers demonstrate IWLs of up to 170 mL/kg/day,[27] and the use**

TABLE 14.3 GUIDELINES FOR FLUID (mL/kg/day) AND SOLUTE PROVISION BY PATIENT WEIGHT AND DAYS OF AGE

WEIGHT (g)	RANGES OF WATER LOSS		DAY 1*	DAYS 2–3*	DAYS 4–7*
Less than 1250	IWL†	40–170			
	Urine	50–100			
	Stool	5–10			
	TOTAL	95–280	120	140	150–175
1250–1750	IWL†	20–50			
	Urine	50–100			
	Stool	5–10			
	TOTAL	75–160	90	110	130–140
More than 1750	IWL†	15–40			
	Urine	50–100			
	Stool	5–10			
	TOTAL	70–150	80	90	100–200

Increment for phototherapy: 20–30 mL/kg/day if patient is in open warmer and has radiant phototherapy. No adjustment if baby is in humidified environment and/or has fiberoptic phototherapy source.
Increment for radiant warmer: 20–30 mL/kg/day.
Maintenance solutes: glucose: 7–12 g/kg/day (4–8 g/kg in VLBW infants)
Na: 1–4 mEq/kg/day (2–8 mEq/kg/day in VLBW infants)
K: 1–4 mEq/kg/day
Cl: 1–4 mEq/kg/day
Ca: 1 mEq/kg/day

*Adjustment based on a urine flow rate of 2–5 mL/kg/hr and a stable weight.
†May be reduced by 30% if the infant is on a ventilator.
IWL, Insensible water loss; *VLBW,* very-low-birth-weight.

of radiant warmers should thus be avoided if possible. Maintenance of water and glucose needs in larger infants on the first day of life can usually be met by a 10% glucose solution infused at 60 to 80 mL/kg/day, which provides an acceptable glucose infusion of about 4.2 to 5.5 mg/kg/min. The infusion rate can be gradually increased over 4 to 5 days to 120 to 140 mL/kg/day using principles of monitoring discussed later in this chapter.[5]

All sick infants require IV access for fluid administration. Placement of an IV line is the most common procedure in the neonatal intensive care unit (NICU).[50] The IV equipment should include (1) a needle or catheter, (2) connecting tubing, and (3) an infusion pump.

Electrolytes such as sodium and potassium are usually omitted for the first 1 to 2 days of life and then added as the salt of acetate, chloride, or phosphate in amounts of 1 to 4 mEq/kg/day. Mildly acidotic and VLBW infants may be given their sodium requirements as sodium acetate.[5] **Potassium should never be added to IV fluid until urine flow and renal function have been assessed. The initial requirement for calcium is 1 mEq/kg/day (20 mg/kg/day), but this rises to a maintenance requirement of 3 to 4 mEq/kg/day (about 60 to 80 mg/kg/day) of elemental calcium, preferably given as calcium gluconate (about 600 to 800 mg/kg/day).**[65] This maintenance is most important in VLBW infants and those who are severely ill. **Careful observation of peripheral IV sites with the infusion of IV fluids containing calcium is critical due to the risk of tissue necrosis associated with infiltration.**[35]

Factors that influence IWL must be identified early and maintenance needs adjusted appropriately to prevent problems with water and electrolyte balance. Humidified incubators significantly decrease the IWL of ELBW infants. They require less fluid intake, have lower percentage of weight loss, and have fewer episodes of hypernatremia than infants cared for in a nonhumidified incubator.[36] **Management of VLBW infants presents special, complex problems, and continued research is needed.** The following observations may be helpful:

- **Total fluid requirements should typically start at 100 to 120 mL/kg/day at birth, although some authors suggest as low as 80 mL/kg/day,**[12,46,67] and often need to be increased by 20 to 40 mL/kg/day over days 2 to 6 of life, typically plateauing at 150 to 160 mL/kg/day. Higher fluid requirements may be necessary for VLBW infants managed on a radiant warmer or in nonhumidified incubation. **Careful restriction of fluids, without allowing dehydration, has been shown to decrease the risk of PDA and NEC.**[10] **A lower risk of BPD has also been associated with early appropriate weight loss in ELBW infants.**[36,72] Careful restriction of fluids allows for the normal contraction of extracellular fluid and appropriate weight loss while maintaining physiologic needs.[10,25,46]
- **Cumulative weight loss plateaus at 10% to 15% of birth weight by postnatal day 3 to 5.**
- **Sodium requirements (including medications) are 2 to 3 mEq/kg/day after 24 to 48 hours of age** and may reach a maximum of 4 to 5 mEq/kg/day during the first few weeks of life.[18]
- **Maintaining serum glucose concentrations (60 to 150 mg/dL) in VLBW infants may initially require relatively less glucose** than that of term or near-term infants because their own endogenous glucose production may not be effectively suppressed. **However, in order to preserve endogenous stores of glucose (e.g., glycogen) in clinical practice, the preterm infant may need up to 8 to 9 mg/kg/min of glucose, whereas the term infant requires about 6 mg/kg/min.**[19] **In VLBW infants, a gradual increase in the glucose infusion rate to 11 to 12 mg/kg/min by the end of the first week of life is usually well tolerated.**[5] The glucose concentration of the fluids administered may need to be changed, sometimes frequently, to maintain an appropriate serum glucose concentration. **With the larger initial fluid requirements of very tiny babies, lower glucose concentrations, sometimes down to D_5W (5 mg% or 5 mg/dL) in IV fluids, are often prescribed for ELBW infants as the initial fluid.** As anticipated, infants weighing less than 1000 g are the most difficult to manage without inducing excessive weight loss, hypernatremia, or hyperglycemia, especially those stabilized under radiant warmers. They may have greatly increased IWL with fluid requirements in the range of 175 to 200 mL/kg/day or greater. By the end of the first week of life, as the epithelium cornifies, their daily requirements decrease to 120 to 150 mL/kg/day. **When enteral caloric intake is low (fewer than 50 kcal/kg/day), neonates will require administration of IV fluids, which should be provided as parenteral nutrition**[43] containing glucose, amino acids, lipids, vitamins, and micronutrients in order to support growth (see Chapter 17).

DATA COLLECTION

Parenteral therapy should be based on the following principles: (1) assess the patient's clinical status for maintenance needs, factors that modify IWL, and confounding medical or surgical disorders; (2) calculate short-term (12 to 24 hours) fluid and electrolyte needs; (3) initiate therapy at the proper site and infusion rate; and (4) monitor and adjust the fluid infusion rate and content based on clinical and biochemical data.

History

Factors influencing IWL (see Table 14.2) include gestational age, birth weight, and postnatal age. When the patient's condition changes, it is important to detail the change to evaluate the potential effect of the new condition on fluid and electrolyte balance and requirements. Thus, NEC may be associated with an acute need for additional volume expansion–type fluids because of "third space losses," whereas with acute renal failure, anuria should prompt clinical reassessment and usually indicates the need for reducing daily fluid administration.

Signs and Symptoms

Weight, urine output (Box 14.1), and **serum sodium concentration** (Box 14.2) are the best overall clinical guides to assess whether therapy is

BOX 14.1 DATA COLLECTION

Clinical Evaluation of Fluid and Electrolyte Status

- Serial weight (sometimes two to three times per day)
- Heart rate
- Blood pressure
- Skin perfusion
- Urine output
- Other drainage (ostomies, gastric, chest tubes)

BOX 14.2 DATA COLLECTION

Laboratory Evaluation of Fluid and Electrolyte Status

Essential values are included in this box. Other measurements are routinely made but are less valuable in the rapid determination of fluid status and complications of imbalances.

- *Sodium* (most sensitive indicator of water loss in excess of electrolytes, as is insensible water loss)
- *Potassium* (may rise with decreased kidney perfusion and acidosis)
- *Hematocrit* (will rise with extracellular fluid contraction)
- *Blood urea nitrogen* (relatively insensitive indicator of dehydration in neonate)
- *Creatinine* (will rise slowly with renal failure)
- *Total CO_2* (low level indicates acidosis, either because of bicarbonate loss or metabolic acidosis from poor tissue perfusion and anaerobic metabolism)

adequate. **Weight is the most sensitive index of IWL and must be accurately determined at least every 24 hours.** Accurate daily weights in VLBW infants require special nursing efforts and may be facilitated with electronic bed scales.

Urine output should be 2 to 5 mL/kg/hr with a specific gravity of 1.005 to 1.012.[24] Blood pressure and peripheral perfusion may be used to reflect changes in vascular volume and cardiac output. **Normal capillary refill is typically less than 3 seconds and is more reliable when tested on the forehead or sternum.** However, its sensitivity and specificity have been questioned in infants and should be interpreted with caution as a sign of adequate hydration. **Blood pressure and heart rate should be evaluated in conjunction with capillary refill time.**

Loss of skin turgor is a late and variable sign and usually is not helpful in assessing therapy, but vital signs (heart rate, respiratory rate, and temperature) provide useful signs about metabolic rate and stress. However, temperature may be affected by many external factors. Drainage volume and content from ostomies, chest tubes, nasogastric tubes, and other sites should be quantitated accurately. Fluid samples can be submitted for laboratory analysis to improve the accuracy of the replacement fluids. The amounts of drainage represent maintenance requirements that must be added to the calculation of baseline daily maintenance needs (abnormal + normal = total maintenance).

Laboratory Data

Tests for concentrations of electrolytes (Na^+, K^+, Cl^-, Ca^{2+}), red blood cells (hematocrit), glucose, blood urea nitrogen (BUN) or creatinine, and acid-base status should be performed serially (see Box 14.2). Occasionally, serum osmolality and protein concentrations are helpful in assessing the neonate's condition. The anion gap may be calculated from the difference of the positive and negative ions, sodium, chloride, and bicarbonate: $[Na]^+ - ([Cl^-] + [HCO_3^-])$.

Urine volume must be recorded with every void. Measuring urine osmolality and glucose and electrolyte concentrations helps clarify fluid and electrolyte balance when amounts of glucose, protein, or other solutes appear in the urine. In a preterm infant, especially a VLBW infant, an elevated urine pH may signal bicarbonate loss due to renal function immaturity.[56]

All drainage must be collected and measured, with the concentration of solutes determined (see Box 14.2). Accumulations over 4 to 6 hours are preferable to a single "spot" collection, which may be misleading. Occasionally, determining the trace electrolyte elements, hematocrit, and protein content of urine or drainage can be crucial to management. However, there are no "normal" values for urine electrolyte concentrations because they must be interpreted with respect to the infant's clinical diagnosis, medications, and serum electrolyte concentrations.

Electronic health records allow for real-time evaluation of fluid balance. Data can be downloaded directly from IV pumps or entered manually on an hourly basis. The practitioner can review

actual intake and output (see Fig. 14.3), evaluate total fluid balance, and quickly make adjustments, if needed, to ensure optimal fluid balance in the neonate. Graphs are also available to provide further detail and trend changes over time.

TREATMENT

Techniques of IV Therapy

In modern neonatal intensive care, peripherally inserted central venous catheters (PICCs) have become an invaluable tool. Placement permits long-term administration of IV fluids, avoiding multiple painful procedures for peripheral IV placement and the need for surgical placement of a long-term central catheter. **This is particularly valuable for ELBW infants for whom the time to establish full enteral feedings may be prolonged.** This technique is also helpful for long-term parenteral nutrition. **Complications of long-term indwelling central catheters include infection, thrombosis, phlebitis, infiltration, effusion, occlusion, and catheter breakage.**[73] Some reports suggest that the risk for infection significantly increases after the PICC has been in place for longer than 2 weeks;[39] therefore, these catheters should be discontinued as soon as enteral nutrition is adequately established. **Thrombosis is more likely to occur when the flow rate of IV fluids is extremely low** (less than 1 mL/hr). Although the use of heparin in PICC-line fluids has been shown to prolong patency of the line, it does not decrease the incidence of thrombosis.[54] **Infiltration usually occurs at the site of the catheter tip.** This includes infiltration into the mediastinum, pleural space, or pericardium, depending on the location of the tip of the catheter (see Chapter 7).

Peripheral insertion of central venous catheters can be accomplished readily but requires clinical training and experience. Insertion sites include the saphenous, antecubital, axillary, basilic, cephalic, popliteal, posterior auricular, and external jugular veins.[55] Avoidance of upper extremity PICCs in infants with single-ventricle cardiac anatomy is recommended to prevent thrombosis or occlusion of upper extremity veins required in the eventual Fontan procedure.[2] The **catheter is advanced so that the tip is in the superior or inferior vena cava; suboptimal positioning is associated with increased risk of complications.**[14,33] **The position of the catheter tip must be confirmed radiographically.** Confirmation by lateral radiograph is recommended with saphenous insertion due to a risk of inadvertent placement in spinal vessels.[58] Cannulation of the subclavian vein of VLBW infants requires insertion by a pediatric surgeon. Venesection or cutdown of peripheral or central vessels can be performed with appropriate training.

Midline catheters can be used for infants who will require more than a few days of IV fluid administration. Midline catheters are longer than peripheral IVs and are inserted deeper into the vein, where blood flow is greater, but remain outside of central vessels. Because of their placement, **midline catheters can only be used to provide fluids appropriate for peripheral access.** The length of duration is an advantage of midlines compared with peripheral IV lines; catheters can last 1 to 2 weeks, with some reports of midlines lasting up to 3 months.[38]

Peripheral venous access continues to be a valuable approach to IV therapy when short-term vascular access is needed. The advent of extremely small catheter and introducer sets has permitted prolonged use of a single peripheral infusion site. "Butterfly" infusion sets are rarely used for IV access.

A rubber band is an effective tourniquet for the extremity of a small infant. Attention must be paid to antiseptic technique when acquiring venous access. Before puncturing the skin, prepare materials for placement. It is **important to recognize the significant risk for infiltration and skin necrosis with a peripherally inserted IV line. Calcium-containing solutions in parenteral nutrition present an additional risk, particularly for skin damage.** Prevention of such extravasation injuries is paramount because few treatment options are available. Although the needle or catheter must be taped in place, the tape should allow for adequate visualization of the site. **The fluid administered should be recorded at least every hour, and the site should be observed for signs of infiltration.** Although traditionally, splints/padded boards have been used to decrease movement and increase catheter duration, there are no studies to support the practice in neonates.[16] If splints/padded boards are used to stabilize an IV line, it should be **taped in a manner that allows visual inspection of the insertion site.** The most common complication of

IV therapy is infiltration, with rates as high as 70%.[74] **If extravasation occurs, the infusion should be stopped immediately and the IV catheter removed. The affected extremity should then be elevated to limit swelling.**[20] Hyaluronidase is an enzyme that degrades hyaluronic acid, a constituent of the normal interstitial barrier, which increases the distribution and absorption of locally injected substances.[9] By facilitating more rapid absorption of potentially damaging fluid, tissue necrosis may be lessened. A plastic surgery consultation should be considered when tissue necrosis is anticipated.

Umbilical vessel catheterization should be limited to several days' duration until a central catheter can be placed (see Chapter 7).

It is important to provide pain relief during the placement of peripheral IVs, midlines, and/or PICC lines. Methods that have been shown to decrease pain during venipuncture in infants include oral sucrose,[61] swaddling, nonnutritive sucking, breastfeeding, kangaroo care, and topical anesthetics.[4] The use of sucrose has been found to be superior compared with topical lidocaine in infants[64] (see Chapter 12).

The combination of pharmacologic and nonpharmacologic pain management modalities is recommended, but additional research is needed. When undergoing venipuncture, the use of topical lidocaine and sucrose was found to be superior compared with sucrose alone in preterm infants[11] but not in term infants.[64] IV morphine and the combination of morphine and topical tetracaine reduces the pain associated with peripheral central line placement in ventilated neonates; however, the use of morphine also increases the need for respiratory support,[63] so it should be used with caution. **At a minimum, nonpharmacologic pain treatments should be used for all venipuncture procedures in neonates.**

Common Problems

In NICUs, virtually all patients initially receive IV fluid therapy. Therefore, conventional rules of pediatric fluid therapy that estimate losses and project deficit replacement may not be appropriate. Weight, urine output and concentration, and the concentration of various solutes in serum and other body fluids are usually known. The correct diagnosis usually rests on clinical and laboratory measurements (not estimates). Attempts should be made to identify the etiology of the deficit or excess while these conditions are being corrected.

HYPOCALCEMIA (INFANTS WITH TOTAL SERUM CALCIUM LESS THAN 7 mg/dL)

Hypocalcemia is a common finding in critically ill babies. Clinical findings may correlate poorly with biochemical data (total or ionized calcium). **Jitteriness, irritability, and twitching are common, but nonspecific, initial signs. Both serum calcium and glucose should be measured.** Hypocalcemia is often a clinical concern in infants of diabetic mothers and in infants with asphyxia, prematurity, and delayed nutrition. **The risk for "early" hypocalcemia within 72 hours of birth is minimized by supplementing IV fluids with 35 or more mg/kg/day of elemental calcium or initiating parenteral nutrition with 60 or more mg/kg/day for preterm infants.**[32] Alternatively, early neonatal hypocalcemia may be prevented with oral calcium supplementation of 80 mg/kg/day of elemental calcium gluconate[32] (100 mg of calcium gluconate = 9.3 mg of elemental calcium).

The normal physiologic neonatal calcium nadir occurs at around 48 hours of neonatal life.[29] At birth, when the infant is disconnected from the maternal calcium supply, calcium levels begin to fall, and parathyroid hormone secretion is stimulated. The parathyroid gland's response is somewhat insufficient, leading to a **calcium nadir within the first 2 days of life.** During this nadir, ionized calcium typically remains within the normal adult range but undergoes a substantial decline from fetal levels.[29] **Early administration of calcium to the neonate may interfere with the anticipated natural history of calcium homeostasis.** Treatment during this physiologic nadir, in term infants, is often not necessary unless the infant has a confirmed low level of ionized calcium. This would typically be associated with other medical concerns, such as hypoxic-ischemic encephalopathy or in infants of diabetic mothers.

Confirmation of low serum calcium values with an ionized calcium level is necessary because the albumin level, acid-base balance, and other factors could affect serum calcium levels. **Attempts to rapidly correct hypocalcemia, using bolus infusions and slow infusions over 2 to 3 minutes, are not as successful and may induce dysrhythmias, compared with more gradual attempts to correct hypocalcemia.**

Either repeated slow infusions every 6 hours or a continuous infusion is best. Additional calcium should be given intravenously as 100 to 200 mg/kg/dose of calcium gluconate over 4 to 6 hours if seizures or biochemical abnormality persists. **"Late" hypocalcemia, occurring at more than 7 days of age, usually has a specific cause,** such as malabsorption, hypomagnesemia, hypoparathyroidism, long-term diuretic therapy, or rickets, and should be evaluated in detail.[32]

Care should be taken when administering IV calcium: (1) the infant should receive cardiac monitoring to detect bradycardia; (2) calcium administration should be discontinued immediately if bradycardia occurs; and (3) the peripheral IV site should be checked for patency before and during administration because of the potential for skin necrosis, sloughing, and dystrophic calcification caused by infiltrated calcium.

HYPERCALCEMIA (INFANTS WITH SERUM CALCIUM MORE THAN 11 mg/dL)

Hypercalcemia is typically asymptomatic but may present with nonspecific symptoms in the infant. **Symptoms can include poor feeding, emesis, lethargy, irritability, polyuria, and constipation.** Both serum and ionized calcium should be measured, along with phosphate and alkaline phosphatase. The most common presentation of hypercalcemia is iatrogenic in the setting of excessive vitamin D or calcium supplementation or in response to inadequate phosphorus supplementation during the administration of parenteral nutrition. Hypercalcemia may also be seen secondary to maternal hypoparathyroidism or increased maternal vitamin D intake. Neonatal disease such as hyperparathyroidism, hyperthyroidism, Williams syndrome, and hypophosphatasia can also present with hypercalcemia. Hypercalcemia has been reported due to subcutaneous fat necrosis and as drug-induced hypercalcemia with thiazide diuretics.[13,51]

Initial management is often directed at adjusting the calcium-to-phosphorus ratio in parenteral nutrition solutions. Hypercalcemia in the setting of inadequate phosphorus supplementation results from increased bone reabsorption of calcium, and therefore treatment should be aimed at providing appropriate phosphorus supplementation as opposed to decreasing calcium. If hypercalcemia is severe, furosemide can be given to facilitate calcium excretion in the urine. Electrolytes must be monitored carefully, as well as the infant's volume status, with careful avoidance of dehydration. Normal saline can be given if there is concern for dehydration. Hydrocortisone can also be used to decrease intestinal calcium absorption. If the etiology of hypercalcemia is not apparent, further evaluation with additional laboratory studies, such as parathyroid hormone, 1,25-dihydroxy-vitamin D, 25-OH-vitamin D, urine calcium, and urine phosphate, should be considered.[13]

HYPERNATREMIA (INFANTS WITH SERUM SODIUM MORE THAN 150 mEq/L)

Clinical signs of hypernatremia are rare, except for late-occurring seizures. The most common causes of hypernatremia are (1) dehydration, usually caused by too little "free water" administration; (2) injudicious use of sodium-containing solution, such as sodium bicarbonate bolus infusion and sodium-containing medications; and (3) congenital or acquired reduction in antidiuretic hormone resulting in excess loss of "free water," diabetes insipidus. Intracranial bleeding correlates strongly with hypernatremia.[40] **Management should be directed toward prevention, and infants with hypernatremia should have serum sodium reduced slowly to prevent seizures.** Infants who experience hypernatremic dehydration often appear better hydrated than they are because hypernatremia shifts fluid into the intravascular space.

HYPONATREMIA (INFANTS WITH SERUM SODIUM LESS THAN 130 mEq/L)

Hyponatremia is usually asymptomatic because it develops chronically rather than as an acute imbalance; however, **a late clinical sign is seizure.** The most common causes include (1) excess hydration as a result of administration of electrolyte-free solutions; (2) renal loss of sodium in neonates receiving diuretic therapy, especially in VLBW infants; and (3) the **syndrome of inappropriate antidiuretic hormone secretion (SIADH) that is suspected when decreased serum sodium and decreased urine output occur.** This syndrome is associated with central nervous system and lung pathologic conditions. Clinical criteria include (1) low serum sodium, (2) continued inappropriately high urine sodium loss, (3) urine osmolality greater than plasma, and (4) normal adrenal and renal function. Management is by volume restriction until diuresis follows, and treatment is directed toward resolving the etiology.

TABLE 14.4 HYPERKALEMIA (INFANTS WITH MORE THAN 7 mEq/L SERUM POTASSIUM)

CLINICAL SIGNS	ELECTROCARDIOGRAM CHANGES
Muscular weakness	Short QT interval
Cardiac dysrhythmias	Widening QRS
Ileus	Sine wave QRS/T

In the case of sodium deficit as the primary etiology, one can compute the amount of sodium required to correct a deficit using the following formula:

$$\text{Necessary sodium} = (\text{Sodium desired} - \text{Sodium observed}) \times 0.6 \times \text{Weight (in kilograms)}$$

The target goal amount and the replacement rate given are a matter of clinical judgment based on underlying diagnosis and treatments for individual patient situations. In practice, the clinician often prescribes a percentage of the calculated deficit, repeats the serum measurement, and modifies the IV solution.

HYPERKALEMIA (INFANTS WITH SERUM POTASSIUM MORE THAN 7 mEq/L)

Causes of hyperkalemia include (1) acidosis with or without tissue destruction, (2) renal failure (water overload may limit management), (3) adrenal insufficiency (relatively uncommon), and (4) iatrogenic secondary to inappropriate potassium administration. **Nonoliguric hyperkalemia may be seen in ELBW infants; even in the absence of potassium intake, it tends to occur more frequently in infants at a younger gestational age who did not receive antenatal steroids.** Other electrolyte imbalances, such as elevated phosphate, can also predispose ELBW infants to nonoliguric hyperkalemia. If potassium levels are low at birth, the infant is less likely to develop nonoliguric hyperkalemia. Careful monitoring for electrolyte disturbances must occur in this population.[37,68]

Table 14.4 outlines clinical signs and electrocardiogram (ECG) changes that may be seen in hyperkalemia. Management is directed toward resolving the causes and nonspecific treatment, depending on the severity of the hyperkalemia and the associated clinical signs:

- **Stop all potassium administration.**
- **Evaluate total and ionized calcium.**
- **If hypocalcemia is present, infuse 100 to 200 mg/kg of calcium gluconate** to lower the cell membrane threshold. This is transient therapy but may be lifesaving.
- **Infuse sodium bicarbonate 1 to 2 mEq/kg, slowly over 30 minutes or longer.** This is also a transient therapy designed to promote intracellular sodium and hydrogen exchange for potassium. It is particularly useful when the hyperkalemia is associated with acidosis. However, if hyperkalemia is associated with acute renal failure, the relatively large volume of fluid required to deliver the sodium bicarbonate may be concerning.
- **Administer 1 g/kg cation exchange resin (sodium polystyrene sulfonate [Kayexalate]) as an oral or rectal solution.** Little experience has been reported in neonates, and technical problems of retention can be substantial. Furthermore, this may not be an option if the infant is on nothing-by-mouth status or has an injured gastrointestinal tract. When this resin is used, sodium in the resin is exchanged for serum potassium, which may result in hypernatremia. Therefore, careful attention must be paid to serum electrolyte concentrations. Necrotizing enterocolitis has also been reported with this therapy.[17]
- **An insulin infusion given simultaneously with a dextrose infusion can help shift potassium to the intracellular space.** There are several challenges to this form of therapy. First, the actual dose of insulin administered to the patient varies unpredictably because the insulin adsorbs to plastic IV tubing. Second, significant hypoglycemia and seizures may occur. The serum glucose concentration must be monitored frequently and the glucose infusion adjusted accordingly.
- **Administer albuterol.**[17,57] Albuterol inhalation may be useful in rapidly lowering serum potassium. Albuterol and other beta-adrenergic agents induce the intracellular movement of potassium.
- **Administer furosemide.** The administration of furosemide, a loop diuretic, will result in renal excretion of potassium. This may be useful in patients who are not experiencing renal failure, although the amount of potassium excretion is not predictable.[17]
- **Perform peritoneal dialysis.** With neonatal hyperkalemic peritoneal dialysis, sodium bicarbonate frequently must be added to dialysate to prevent acidosis. Peritoneal dialysis is a complicated procedure in neonates, involving catheter

placement and dialysis monitoring. It may be technically impossible in VLBW babies and difficult or impossible when there is injured bowel, as with NEC.

HYPOKALEMIA (INFANTS WITH SERUM POTASSIUM LESS THAN 3.5 mEq/L)

About 90% of the body's total potassium is intracellular. Low serum potassium always implies significant intracellular depletion; most potassium is intracellular, and total body potassium can be low even with normal serum levels. Management is directed toward the cause. The most common causes of hypokalemia are (1) increased gastrointestinal losses from an ostomy or nasogastric tube and (2) renal losses from diuretic therapy. **Diuretic-induced hypokalemia can be treated with supplemental potassium chloride.** Caution is needed, particularly if sending the patient home on this medication, because incorrect dosing can have serious consequences. Caution must also be used in providing supplementation if the patient is treated with potassium-sparing medications such as spironolactone or captopril.

Clinical signs of hypokalemia are related to muscular weakness and cardiac dysrhythmias. Ileus may also occur. Electrocardiographic changes include decreased T waves and ST depression.

Common Clinical Syndromes

RESPIRATORY DISTRESS SYNDROME

Before the widespread use of surfactant, pulmonary function in RDS tended to improve following a period of brisk diuresis on the third or fourth day of life. It was hypothesized that increased endogenous surfactant production led to improved pulmonary capillary integrity and lymphatic drainage. As a result, hypotonic interstitial lung fluid was reabsorbed back into circulation, and a delayed physiologic diuresis occurred. **Although antenatal corticosteroids and routine use of exogenous surfactant have altered the natural history of RDS, the preterm infant remains at risk for a more severe course should excessive fluid overload occur. Daily fluid intake should be monitored closely and restricted** to allow for the natural contraction of extracellular volume to occur.

Because of the observation of improved lung function associated with diuresis, furosemide and other diuretics have been suggested for the treatment of RDS. Although short-lived improvements in lung function were seen, no long-term effects on morbidity or mortality rates were shown.[23] The use of diuretics shortly after birth could also lead to hypotension and compromised peripheral perfusion, as well as electrolyte disturbances. **Aggressive use of diuretics is not indicated in the setting of RDS.**

PATENT DUCTUS ARTERIOSUS

Excessive fluid overload can increase the risk of PDA in premature infants. Treatment of a PDA with nonsteroidal antiinflammatory drugs can lead to renal vasoconstriction, with a resultant decrease in renal blood flow and the glomerular filtration rate. Therefore, it is not uncommon to see an increase in serum creatinine, oliguria, and hyponatremia during PDA treatment. Nonsteroidal antiinflammatory drugs should be given in the lowest effective dose, and concomitant administration of other nephrotoxic drugs should be minimized. Once the drug effect diminishes, accumulated free water should be excreted rapidly, especially if the ductus has closed and cardiovascular status has improved. Fluid status and electrolytes must be monitored closely before, during, and after PDA treatment.

BRONCHOPULMONARY DYSPLASIA

Infants with BPD typically have increased metabolic needs and require higher caloric intake. **However, volume overload can potentiate the worsening of pulmonary disease.[21] It becomes a delicate balance to provide adequate nutrition while avoiding excess volume.** Diuretics are often used in this population, creating an additional set of complications, as discussed previously. Electrolytes must be monitored closely, and diuretic dose and duration should be minimized.

CONGENITAL HEART DISEASE

Knowledge of the underlying physiology associated with the infant's specific heart lesion will ultimately guide the infant's fluid needs and management. **Fluid restriction is typically indicated in lesions with left-to-right shunting to manage pulmonary overcirculation.** Diuretics are also commonly used in this population. Lesions with outflow tract obstructions will typically respond well to liberal fluid volumes.

Careful attention must be paid to meeting the nutritional needs of infants with congenital heart disease. Surgical outcomes can be improved by

providing optimal nutrition, but this can be difficult to achieve in the face of increased metabolic demands, poor mesenteric perfusion, and delayed enteral feeding.[70]

PERSISTENT PULMONARY HYPERTENSION

Fluid management in the infant with persistent pulmonary hypertension is crucial because hypovolemia can exaggerate right-to-left shunting, leading to worsening disease. Once euvolemia is achieved, there is no additional benefit to repeated volume boluses. Hypoglycemia and hypocalcemia should be avoided because these states can also exacerbate pulmonary hypertension.[60]

NECROTIZING ENTEROCOLITIS

Necrotizing enterocolitis often results in a shock-like state in the infant. Capillary integrity and lymphatic drainage are often compromised, leading to fluid accumulation in the interstitium and diffuse bowel or other tissue edema (the "third space"). As effective circulating volume is diminished, antidiuretic hormone is released, and the renin-angiotensin-aldosterone system is activated, leading to sodium and free water retention. **Management is aimed at maintaining adequate intravascular volume and perfusion with the use of volume expanders, vasopressors, and/or inotropes.** Corticosteroids may also be useful to mitigate the effects of capillary leak. Discontinue all potassium-containing fluids because the combination of oliguria and bowel necrosis can quickly result in hyperkalemia.

If an oral-gastric tube is placed to facilitate intestinal decompression, monitor output closely, and consider partially replacing this volume every 8 to 12 hours. Gastric fluid is typically sodium rich, so the sodium loss should be replaced as well. Strictly monitor fluid intake and output, and attempt to maintain adequate urine output.

CONGENITAL ADRENAL HYPERPLASIA

The most common form of congenital adrenal hyperplasia is caused by the absence of 21-hydroxylase, which is required to produce aldosterone. Whereas affected females typically present at birth with ambiguous genitalia, males classically present in crisis at 1 to 3 weeks of life with profound hyponatremia, hyperkalemia, and metabolic acidosis. Treatment is initially guided at correcting electrolyte abnormalities. **Sodium bicarbonate administration at 1 to 2 mEq/kg may be most useful in correcting hyperkalemia, hyponatremia, and acidosis.** Additional treatment strategies for hyponatremia and hyperkalemia are discussed earlier in this chapter. Long-term treatment is aimed at appropriate replacement of mineralocorticoids and glucocorticoids.

RENAL DYSFUNCTION/RENAL DISEASE

Acute renal failure is most often caused by (1) extrinsic factors such as perinatal asphyxia, shock, and heart failure; (2) intrinsic factors such as congenital or acquired lesions; and (3) obstructive uropathy, including urethral obstruction or extra-genitourinary mass. Oliguria or anuria usually occurs initially.

During initial oliguria, electrolyte-free glucose infusion should be limited to IWL and urine output. Frequently, this entails providing total fluids of 50 to 80 mL/kg/day. Recovery is usually associated with natriuresis (excessive urinary sodium loss) and osmotic diuresis. This may develop rapidly with sodium losses as high as 20 mEq/kg/day. **Body weight and fluid losses must be carefully and frequently measured, at least every 12 hours.**

Nonrenal losses, such as gastrointestinal drainage, must also be measured. **Ideally, fluid and electrolyte therapy is directed toward maintaining the current weight or a weight loss of 1% per day until recovery is nearly complete.** This may be accomplished initially by ordering replacement of IWL as a basal fluid order and replacing a percentage of additional fluid losses on a per-volume basis. The choice of fluid used for replacement depends on the electrolyte content of the fluid lost. Thus, it may be helpful to measure urinary sodium and potassium loss concentrations and urine volume, recognizing that any "spot check" of these electrolytes will not fully reflect the loss over a 24-hour period.

Serial determination of serum electrolytes will help refine the fluid orders. As the patient recovers and renal function normalizes, the transition to more standard fluids and electrolytes should occur. The renal ability of the patient to concentrate urine must be evaluated serially. **If the patient remains in high-output renal failure and fluids are restricted, dehydration may occur.** Dehydration will result in weight loss, increased serum electrolyte concentration, and hypernatremia with dilute urine. **Weight change during renal failure demands a careful reevaluation of the fluid plan.**

ASPHYXIA

Perinatal depression can result in renal insult and acute tubular necrosis, leading to decreased urine output. SIADH may also occur following perinatal asphyxia, further reducing urine output. Fluids must be restricted to avoid fluid overload. The use of therapeutic hypothermia for the treatment of hypoxic-ischemic encephalopathy may further worsen fluid retention and the risk of hyponatremia.[49] **Fluid restriction to as low as 30 to 40 mL/kg/day may be required because this amount should replace only insensible losses.** Potassium supplementation should be avoided. As the kidney recovers from acute tubular necrosis, a polyuric phase may ensue, with large sodium losses. **Urine output must be monitored closely, urinary sodium quantified, and fluid replacement adjusted accordingly.**

Major Surgery

Surgical trauma is superimposed on the normal metabolic responses of the neonate. The type and extent of surgery and the gestational and postnatal age of the infant determine the clinical impact. **In healthy term infants, a negative balance of water, electrolytes, nitrogen, and calories with associated weight loss occurs during the first 3 to 5 days, followed by a transition to a positive balance and weight gain by 7 to 10 days.** Parallel transition times for preterm infants vary enormously. Deficits may exist as a result of delayed diagnosis, with external loss or internal loss. **"Third space" losses can be significant, with peritoneal losses being a notorious source of deficit underestimation.**

Predicting the metabolic response to surgery is difficult, reflecting wide variation among individual patients, even patients with similar lesions. **Uncontrollable and immeasurable variables prevent a standardized postoperative physiologic response for neonates, especially those weighing less than 2 kg.** Thermoregulation is a particular challenge for operative procedures. The patient is draped and shielded from radiant heat sources. Measuring and managing the patient's internal temperature with evaporative heat and water loss complicating the situation is difficult once the incision is made. Transport incubators, prewarmed operating rooms, radiant warmers, warming pads, and prewarmed solutions may help achieve thermoneutrality.

Intraoperative fluid balance is rarely precise despite the clinicians' best efforts. Blood loss on sponges, drapes, and other objects should be measured, but IWL from open body cavities is difficult to estimate.

The principles of postoperative management are as follows:

- **Monitor clinical and chemical variables frequently,** at least every 4 to 6 hours; evaluate fluid balance and measure drainage.
- **Recognize that insensible water losses may include "third space losses."** These include water lost into the lumen of the bowel or into the peritoneum secondary to peritonitis, resulting in the loss of both water and electrolytes from the intravascular compartment. At least a proportion of the fluids used to anticipate these losses should contain high sodium content similar to plasma. **Clinical judgment is used to estimate the third space losses because they cannot be measured. Serial evaluations of blood pressure, heart rate, urine output, and skin perfusion together may help determine if the volume prescribed is sufficient.**
- **Gastric output in patients undergoing intestinal surgery should also be closely assessed** in order to provide adequate replacement of free water and electrolytes, particularly sodium and chloride.
- **Provide parenteral nutrition early if significant enteral feedings (less than 50 kcal/kg) cannot be achieved by 3 to 5 days postoperatively.** Gastrointestinal motility returns rapidly in term infants compared with adults. Almost all VLBW infants require parenteral nutrition after surgery.

Diuretics and Electrolytes

Diuretics represent one of the most common classes of drugs administered to sick neonates and infants. **Electrolyte disturbances are the most common adverse effects of diuretic therapy and can lead to a variety of consequences. Clinical indications for the use of diuretics in neonates and infants include BPD, congenital heart disease, and renal failure.** The classes of diuretics most commonly used in this age group include loop diuretics, thiazides, and potassium-sparing diuretics. A discussion of the mechanism of action, diuretic efficacy, and common side effects follows.

LOOP DIURETICS

Loop diuretics bind to one of the chloride binding sites on the $Na^+/K^+/2Cl^-$ transporter, thus

inhibiting the reabsorption of sodium and chloride in the thick ascending limb of the loop of Henle. Water passively follows the movement of sodium and thus allows for diuresis.

Furosemide **is the most widely studied diuretic in neonates** and is consequently the prototype loop diuretic. **It produces a 3-fold to 5-fold increase in sodium excretion and a 10-fold increase in urine flow.**[47,75] Therefore, **hyponatremia, hypochloremia, and hypovolemia are common with chronic use of furosemide. Hypokalemia is also of significant concern with chronic use of furosemide.** The mechanism of potassium loss is due to blockage of tubular reabsorption of potassium and increased aldosterone production in the presence of sodium losses.[65] In addition to potassium losses, furosemide also promotes urine calcium and magnesium excretion. The reabsorption of these cations is decreased because of furosemide's ability to eliminate the transepithelial potential difference. **Chronic hypercalciuria leads to hypocalcemia and the possibility of renal calcifications and nephrocalcinosis.** Compensatory mechanisms lead to increased parathyroid hormone secretion with associated bone resorption, bone demineralization, osteopenia, and possibly rickets.

Bumetanide is another loop diuretic commonly used in neonates and infants. **It is 40 times more potent than furosemide.** The side effects are the same as those seen with furosemide.

THIAZIDES

Hydrochlorothiazide and chlorothiazide are the most widely used thiazide diuretics in neonates and infants. Thiazides exert their effect by blocking the Na^+-Cl^- transporter at the distal convoluted tubule, collecting tubule, and early collecting duct. Because only a small portion of sodium reabsorption occurs in the distal tubule, thiazide diuretic efficacy is limited.

Chronic use of thiazide diuretics leads to electrolyte disturbances, although they usually are less severe than with loop diuretics. **Hyponatremia and hypokalemia are the most common side effects.** Hypokalemia is the result of greater sodium-potassium exchange that occurs secondary to a higher concentration of sodium found in the distal tubule.

Whereas loop diuretics promote calcium loss, thiazide diuretics can increase serum calcium concentrations by increasing renal calcium reabsorption both proximally and distally.[40] This decrease in urinary calcium can be used to reverse loop diuretic–induced renal calcifications.

POTASSIUM-SPARING DIURETICS

Whereas loop and thiazide diuretics directly alter sodium reabsorption via direct inhibition of sodium transporters, **potassium-sparing diuretics such as spironolactone competitively antagonize the aldosterone receptor.** The primary binding site is the principal cell of the cortical collecting tubule. Aldosterone enhances sodium reabsorption in the collecting tubule and promotes potassium secretion. Therefore, antagonizing aldosterone results in diminished sodium reabsorption with a consequent increase in serum concentrations of potassium and hydrogen. **However, spironolactone inhibits the reabsorption of less than 2% of filtered sodium and is thus not an effective primary diuretic.** The major use is to prevent urinary potassium loss induced by other diuretics.

Hyperkalemia is the primary electrolyte disturbance to monitor with the use of spironolactone. This side effect is usually not of great concern because spironolactone is frequently used in conjunction with other potassium-wasting diuretics. Spironolactone should be avoided in renal failure.

COMPLICATIONS

Excessive fluid administration has been associated with BPD and PDA and is increasingly being shown to demonstrate a negative effect on clinical outcomes in critically ill infants.[3,6,25] **Inadequate fluid administration may also have adverse effects, having been associated with dehydration, decreased urine output, hypernatremia, poor tissue perfusion, and potentially, tissue damage.**

PARENT TEACHING

The need for and presence of an IV line in a newborn may be frightening for the parents. Clear, medically and physiologically sound explanations (in nonmedical jargon) of the need for fluid and electrolyte support for their infant help allay parents' fears (Box 14.3). **Scalp vein IV lines are of particular concern because a common misconception is that the needle is positioned**

BOX 14.3 PARENT/CAREGIVER TEACHING

Parent Teaching About Fluid and Electrolyte Management

- Most babies cannot be fed immediately and will require intravenous (IV) fluids.
- Umbilical venous and arterial catheters must be removed in a few days.
- IV fluids will be given through percutaneous central venous catheters, peripheral IV lines, or surgically placed lines.
- Scalp IV lines go only into subcutaneous veins, not into the brain.
- Placing the IV line is painful, and analgesia will be provided during the procedure, but the IV line will be painless afterward, unless infiltrated.
- Peripheral IV lines are subject to infiltration, which may be serious if the fluid is hyperalimentation fluid or contains calcium. IV lines are checked every hour.
- Central venous catheters (percutaneously or surgically placed) carry the risks of thrombosis, infection, or infiltration into body cavities such as the pleura or pericardium.
- IV fluids will be discontinued as soon as enteral nutrition is sufficiently advanced.

in the infant's brain. Explain to parents that scalp vein IV lines are in the large veins of the head and not the brain and that an IV line in the head may stay in longer, thus decreasing the need for multiple vein punctures, and allows the infant mobility of all four extremities. In answer to the question "Does it hurt?" a truthful answer is "Yes, when it is put in, but not after it is in the vein." Explaining the strategies used to decrease pain associated with IV line placement may also help allay their concerns.

The concept of the use of central venous catheters should be presented to the parents early in the hospital course if a delay in enteral nutrition is anticipated. **The advantages are fewer painful procedures, increased mobility of the patient, and decreased risk for infiltrate.** These should be clearly explained in lay language. Explaining the potential complications—such as infection; thrombosis; and the specific risk for the extravasation of fluid into body cavities, pleura, and pericardium—is also necessary. **Potential infiltration of peripheral IV sites should be addressed *prospectively* with parents. Erythema and edema are expected. Sloughing of the skin occasionally occurs in VLBW infants and is more common on the feet and hands than on the scalp.** Well-illustrated parent education materials often are very helpful when explaining these situations to parents.

Including parents in the care of their sick neonate requires an explanation about the importance of measuring intake and output. Inadvertent disposal of diapers and giving fluids that are not recorded should be prevented, emphasizing the importance of saving diapers for the infant's nurse. "A little spitting up" after feeding may be inappropriately dismissed if parents are not instructed in the importance of telling the nurse and saving it for evaluation.

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15 GLUCOSE HOMEOSTASIS

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During intrauterine life, the fetus depends on the constant transfer of glucose across the placenta to meet his or her glucose requirements. After birth, neonates must maintain glucose homeostasis by producing and regulating their own glucose supply. This requires activation of a number of metabolic processes, including gluconeogenesis (synthesis of glucose from nonglucose precursor substrates) and glycogenolysis (release of glucose via breakdown of glycogen stores) and intact regulatory mechanisms for glucose metabolism and an adequate supply of metabolic substrates.

FETAL PHYSIOLOGY

Throughout gestation, maternal glucose provides the principal source of energy for the fetus via facilitated diffusion across the placenta. Fetal glucose uptake varies directly with maternal glucose concentration; **fetal glucose concentration usually is about 70% of the maternal value.** Changes in maternal metabolism, including increased carbohydrate and lipid intake and decreased sensitivity of the maternal tissues to insulin, augment maternal glucose production and provide the additional glucose necessary to meet fetal energy demands.[9] **With normal maternal glucose concentrations and rates of glucose supply to the fetus, the fetus produces little, if any, glucose,** although the enzymes for gluconeogenesis are present by the third month of gestation.[124] **If fetal demand exceeds maternal supply, however, the fetus is capable of adapting by using alternate substrates provided from the maternal circulation, such as ketone bodies, for energy production.** This may be the case when maternal fasting or even starvation is severe enough to produce maternal and fetal hypoglycemia. In addition, data from animal models suggest that there may be fetal glucose production under these conditions.[92] Even in the basal state, the fetus relies on fuels such as lactate and amino acids to meet up to 25% to 30% of his or her energy demands, whereas lipids are used primarily for fat production.

Fetal glycogen synthesis begins as early as the ninth week of gestation, but the majority of fetal glycogen is produced in the third trimester. The major sites of glycogen deposition are skeletal muscle (greater than 90% of body glycogen), liver (the only organ whose glycogen can be released for use by other organs), lung, and heart.[131] By 40 weeks of gestation, hepatic and skeletal muscle glycogen contents are several times adult levels. By contrast, lung and cardiac muscle glycogen stores decrease as the fetus approaches term, although these stores are still sufficiently large to be of physiologic significance. Survival in animals exposed to anoxia and human infants after asphyxia, for example, is directly related to cardiac glycogen content. The decrease in lung glycogen, which begins at 34 to 36 weeks' gestation, may be related to ongoing developmental processes, such as the synthesis of surfactant.

In addition to glycogen, **the human fetus also stores energy as fat in adipose tissue.**[128] Most triglyceride synthesis occurs during the third trimester. **By 40 weeks' gestation, the human fetus has a body fat content of about 16%,** making it the fattest of all terrestrial newborn mammals. The human placenta transports some free fatty acids, although the amount transported to the fetus is not sufficient to account for the amount of adipose tissue present; therefore the fetus also must synthesize triglycerides,

BLUE type highlights content that is particularly applicable to clinical settings.

using glycerol derived from glucose, as well as fatty acids transported across the placenta. **Conditions in which fetal glucose supply is reduced will result in less adipose tissue accumulation and reduced glycogen stores.**

In addition to increasing glucose utilization, insulin also stimulates cellular hypertrophy and hyperplasia and thus is an important stimulus for fetal growth.[52] Fetal pancreatic insulin content and glucose-stimulated insulin secretion increase over the second half of gestation to levels comparable to those found in neonates.[85] **Fetal insulin secretion is augmented by higher glucose concentrations;** increased concentrations of amino acids add to this effect.[53] Increased concentrations of insulin increase fetal glucose and amino acid utilization and glucose oxidation rates without increasing total fetal oxygen consumption.[45,68] This implies that other substrates, primarily amino acids, become available for nonoxidative metabolism when glucose and insulin are plentiful; such conditions promote tissue accretion and growth.

Fetuses of diabetic mothers who have very unstable plasma glucose concentrations during late gestation have an increased islet cell response to hyperglycemia compared with normal fetuses of nondiabetic mothers, releasing more insulin than normal fetuses at any given blood glucose concentration. The **higher insulin levels in turn lead to increased growth consisting primarily of adipose tissue, producing the *macrosomia* typically seen in infants of diabetic mothers (IDMs).**

In contrast, **fetuses with intrauterine growth restriction (IUGR) have reduced numbers of pancreatic islets and beta cells and produce less-than-normal amounts of insulin in response to glucose and amino acid stimulation.**[21,112,160] In IUGR fetal sheep, hepatic insulin resistance develops,[153] augmenting hepatic glucose production. Such conditions can lead to postnatal hyperglycemia. In some neonates this propensity for postnatal hyperglycemia may be counterbalanced by other factors. Recent studies in IUGR fetal sheep show increased insulin sensitivity in peripheral tissues (e.g., heart and skeletal muscle) that persists into the neonatal period.[12,25,123,153] Furthermore, islet cells obtained from IUGR fetal sheep when removed from the environment with elevated catecholamines and adrenergic signaling in response to placental insufficiency and reduced fetal oxygen supply and blood oxygen content show insulin secretion at greater than normal levels.[25,30,93,98] These observations may account for the **apparent hyperinsulinemia that occasionally occurs in such IUGR infants several days after birth when oxygenation is restored and norepinephrine concentrations diminish, contributing to their common risk of hypoglycemia.**[8,91] Not surprisingly, therefore, **glucose homeostasis in IUGR neonates is highly variable.**

It also is important to note that although correction of acute insulin deficiency promotes growth, exogenous insulin appears to have little effect on growth in human newborns or animal models with chronic insulin deficiency, suggesting that **insulin infusion to promote growth in growth-restricted infants is unlikely to be beneficial and may lead to additional complications.**

The related pancreatic hormone glucagon, **which, like insulin, does not cross the placenta, has been detected as early as 9 to 16 weeks of gestation.**[117] In postnatal life, glucagon is a potent inducer of gluconeogenic enzymes, the opposite of insulin, which suppresses gluconeogenesis.[124] In fetal life, glucagon plays a much less important role in regulating glucose metabolism than insulin, reflecting the developmental insensitivity of fetal glucagon receptors. As a result, the insulin-to-glucagon effectiveness ratio in the fetus is high, which is important in preferentially maintaining glycogen synthesis and suppressing gluconeogenesis.

NEONATAL PHYSIOLOGY

At birth, the newborn infant is removed abruptly from his or her placental glucose supply, and blood glucose concentration falls. Several hormonal and metabolic changes occur at birth that facilitate the adaptation necessary to maintain glucose homeostasis. **Catecholamine levels increase markedly right after birth,** possibly as a response to the decrease in environmental temperature and to the loss of the placenta, which is responsible for as much as 50% of the clearance of circulating fetal epinephrine.[152] **Glucagon concentrations and receptor sensitivity also increase,** reversing the relatively high insulin/glucagon effectiveness ratio characteristic of fetal life.[136] **The increased glucagon and norepinephrine concentrations activate hepatic glycogen phosphorylase, which induces glycogenolysis.** Simultaneously, the decreasing glucose concentration and perinatal surge in fetal cortisol

secretion stimulate hepatic glucose-6-phosphatase activity. **Together these changes lead to an increase in hepatic glucose release.**[40] **Increased catecholamines also stimulate lipolysis, releasing fatty acids that can be metabolized to provide precursors for gluconeogenesis** and providing energy in the form of adenosine triphosphate (ATP) and cofactors such as nicotinamide adenine dinucleotide phosphate that enhance the activity of gluconeogenic enzymes. **Catecholamine release also activates brown fat triglyceride turnover, producing heat necessary for postnatal thermoregulation.** The normal postnatal decrease in insulin, augmented by the acute postnatal increase in catecholamines, combined with the increase in glucagon, induce synthesis of phosphoenolpyruvate carboxykinase (PEPCK), which is considered the rate-limiting enzyme in hepatic gluconeogenesis. The concentrations of PEPCK and other gluconeogenic enzymes continue to increase over the first 2 weeks of life, regardless of gestational age. These changes act in concert to provide glucose produced by the neonatal liver to replace the supply previously received via the placenta.

Maintenance of glucose homeostasis in the newborn infant depends on the balance between hepatic glucose output and glucose utilization by the brain and peripheral tissues. Hepatic glucose output is a function of rates of glycogenolysis and gluconeogenesis. Peripheral glucose utilization varies with the tissue- and organ-specific metabolic demands in the neonate. Studies in normal human newborn infants using several different methods have estimated that the steady-state glucose production/utilization rate in a term neonate ranges from 3 to 5 mg/kg/min, approximately twice the weight-specific rate measured in adults.[43] As in the fetus, approximately half of this glucose is oxidized to CO_2 during normal metabolic processes, whereas the remainder is used in nonoxidative pathways, such as glycogen and fat synthesis. **Neonatal glucose utilization increases (1) during hypoxia, because of the inherent inefficiency of anaerobic glycolysis**[97]**; (2) in the presence of hyperinsulinemia, which increases glucose uptake by insulin-sensitive tissues**[82]**; (3) in newborns with respiratory distress, because of increased respiratory muscle activity**[116]**; and (4) during cold stress, which leads to increased sympathetic nervous system activity with subsequent release of norepinephrine, epinephrine, and thyroid hormone, which increase metabolic rate.**[32] If rates of glycogenolysis and gluconeogenesis do not match the rate of glucose utilization because of insufficient or excessive hormonal control mechanisms or variability of substrate supply, disturbances of glucose homeostasis occur. These disturbances are recognized clinically by the presence of hypoglycemia or hyperglycemia.

Data Collection

HISTORY

The history of any neonate must include a detailed prenatal and family history. The most important information to be obtained from the infant's history is gestational age, fetal growth, Apgar scores, and details of events in the delivery room, especially any findings that suggest the presence of significant perinatal compromise. **An infant with a history of any of the conditions listed in** Box 15.1 **or** Table 15.1 **should be considered at high risk for developing a problem with glucose homeostasis.**

BOX 15.1 INDICATIONS FOR ROUTINE MONITORING OF BLOOD GLUCOSE FOR PREVENTION OF NEONATAL HYPOGLYCEMIA

Maternal Conditions

- Presence of diabetes or abnormal result of glucose tolerance test
- Preeclampsia and pregnancy-induced or essential hypertension
- Previous macrosomic infants
- Substance abuse
- Treatment with beta-agonist tocolytics
- Treatment with oral hypoglycemic agents
- Late antepartum to intrapartum administration of intravenous glucose

Neonatal Conditions

- Prematurity
- Intrauterine growth restriction
- Perinatal hypoxia-ischemia
- Sepsis
- Hypothermia
- Polycythemia-hyperviscosity
- Erythroblastosis fetalis
- Iatrogenic administration of insulin
- Congenital cardiac malformations
- Persistent hyperinsulinemia
- Endocrine disorders
- Inborn errors of metabolism

TABLE 15.1 NEONATAL HYPOGLYCEMIA: ETIOLOGY AND TIME COURSE

MECHANISM	CLINICAL SETTING	EXPECTED DURATION
Decreased substrate availability	Intrauterine growth restriction	Transient
	Prematurity	Transient
	Reduced glycogen stores	Transient
	Reduced fat stores	Transient
	Reduced ketogenesis	Transient
	Glycogen storage disease	Prolonged
	Inborn errors	Prolonged
	Carbohydrate metabolism defects • Fructose 1,6-diphosphatase deficiency • Pyruvate carboxylase deficiency • Phosphoenolpyruvate carboxykinase (PEPCK) deficiency • Galactosemia	
	Amino acid metabolism defects • Propionic acidemia • Methylmalonic academia • Glutaric aciduria • Maple syrup urine disease (branched-chain alpha-keto acid dehydrogenase deficiency)	
	Fatty acid metabolism defects	
Endocrine disturbances		
Hyperinsulinemia	Infant of diabetic mother	Transient
	Persistent hyperinsulinism of infancy	Transient
	Congenital hyperinsulinism (HI) • Recessive K_{ATP} HI • Focal K_{ATP} (focal adenomatosis) HI • Dominant K_{ATP} HI • Dominant glucokinase (GCK) HI • Dominant glutamate dehydrogenase (GDH) HI • Short-chain 3-hyroxyacyl-CoA dehydrogenase (SCHAD) HI	Prolonged
	Beckwith-Wiedemann syndrome	Prolonged
	Erythroblastosis fetalis	Transient
	Exchange transfusion	Transient
	Islet cell dysplasias	Prolonged
	Maternal beta-agonist tocolytics	Transient
	Improperly placed umbilical artery catheter	Transient
	Inadvertent insulin administration	Transient
Other endocrine disorders	Immaturity of hepatic enzymes necessary for glucose production	Transient
	Reduced or failed counterregulation	Prolonged
	Hypopituitarism	Prolonged

TABLE 15.1 NEONATAL HYPOGLYCEMIA: ETIOLOGY AND TIME COURSE—CONT'D

MECHANISM	CLINICAL SETTING	EXPECTED DURATION
	Growth hormone deficiency	Prolonged
	Hypothyroidism	Prolonged
	Adrenal and cortisol insufficiency	Variable
Increased utilization	Increased brain weight to body weight and liver weight ratio with increased brain consumption of glucose	Prolonged
	Perinatal asphyxia	Transient
	Hypothermia	Transient
Miscellaneous/multiple mechanisms	Sepsis	Transient
	Congenital heart disease	Transient
	Central nervous system abnormalities	Prolonged

HYPOGLYCEMIA

Definition

The absolute blood or plasma glucose concentration that defines hypoglycemia as a pathologic condition remains difficult to establish and has not been determined. Furthermore, there is no absolute correlation between blood or plasma glucose concentrations, clinical signs or symptoms, and either short-term or long-term outcomes. Instead, "reference" glucose concentrations generally reflect the lower limit of the normal range in a specific population of newborn infants, determined by statistical analysis of data collected in that population. Thus there is no consensus about threshold glucose concentrations below which diagnostic evaluation or treatment is mandated or that identify those infants likely to have adverse neurodevelopmental outcome.

Published definitions of hypoglycemia range from a blood glucose concentration of less than 20 mg/dL in preterm infants and less than 30 mg/dL in term infants to **a plasma concentration of less than 45 mg/dL.**[33-35] **Some sources have even suggested raising the lower limit of normal to 50 to 70 mg/dL,** although others have emphasized that such higher concentrations should be used primarily as target values during treatment for relatively severe and symptomatic hypoglycemia rather than thresholds for instituting treatment.[33] Published reports fail to distinguish between threshold glucose concentrations below which physiologic responses may occur (and below which clinical monitoring may be indicated) and those below which pathologic consequences are likely to develop (thus requiring aggressive treatment). In 1992 the majority of pediatricians in one survey in the United Kingdom defined a safe glucose concentration to be at least 36 mg/dL in blood or 45 mg/dL in plasma.[83,84] Fig. 15.1 shows that 95% of normal term infants have a blood glucose concentration of more than 30 mg/dL in the first 24 hours after birth and more than 45 mg/dL after 24 hours of age.[137] **A number of current references use 40 to 45 mg/dL as the lower limit of "normal" plasma glucose concentrations in the first 72 hours of life. By 72 to 96 hours of age mean plasma glucose concentrations in normal infants are very similar to those seen in older children and adults.***

Using these definitions of hypoglycemia, the overall incidence has been estimated at 1.3 to 4.4 per 1000 live births. Differences in incidence figures probably reflect variable inclusion of data from symptomatic versus asymptomatic infants. **In preterm infants, the incidence of hypoglycemia is increased; estimates range from 1.5% to 5.5%** (Fig. 15.2). **The incidence of hypoglycemia in term infants with IUGR may be as**

*References 3,33,76,101,102,134,146.

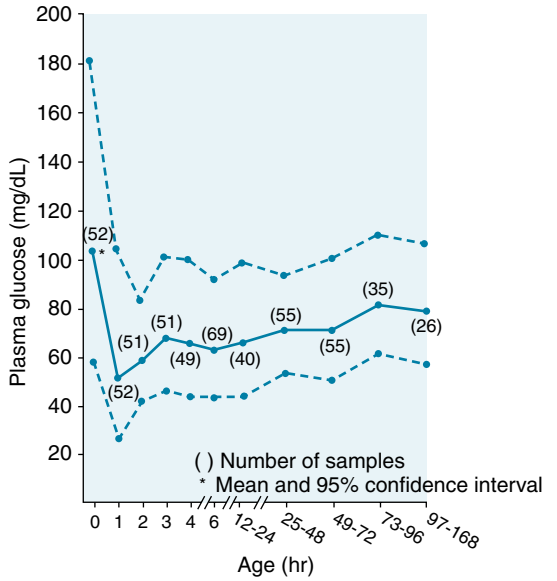

FIGURE 15.1 Plasma glucose concentrations during the first week of life in healthy appropriate-for-gestational-age term infants. (From Srinivasan G, Pildes RS, Cattamanchi G, et al. Plasma glucose values in normal neonates: a new look, *J Pediatr.* 1986;109:114.)

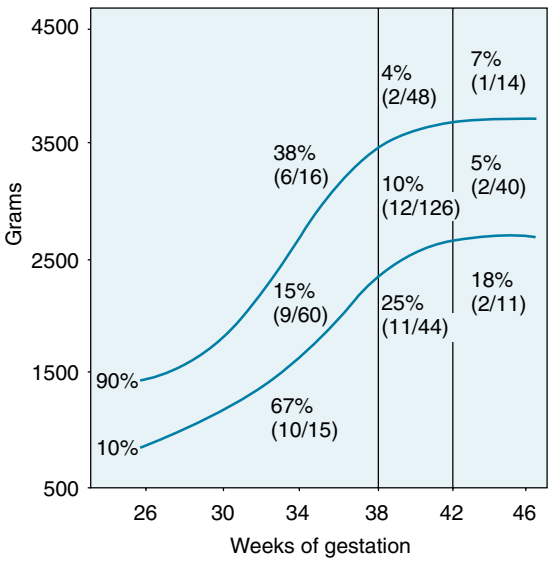

FIGURE 15.2 Incidence of neonatal hypoglycemia (blood glucose less than 30 mg/dL) by birth weight and gestational age. (From Lubchenco LO, Bard H. Incidence of hypoglycemia in newborn infants classified by birth weight and gestational age, *Pediatrics.* 1971;47:831.)

high as 25% to 50%, with an even higher rate seen in preterm small-for-gestational-age (SGA) infants.[62,95]

Hypoglycemia also may be defined clinically as the glucose concentration in a neonate that is associated with clinical signs that resolve when glucose is administered ("symptomatic" hypoglycemia), fulfilling Whipple's triad: (1) low blood glucose concentration; (2) signs consistent with neonatal hypoglycemia; and (3) resolution of signs and symptoms after restoring the blood glucose concentrations to normal values. This value is difficult to determine, however, because the clinical signs of hypoglycemia are nonspecific and may not be noticed initially. **From a physiologic point of view, an infant may be said to be hypoglycemic when glucose supply is inadequate to meet demand.** Unfortunately, no method is available to establish this value in a given infant. Infants with increased glucose utilization demand or limited capability to alter glucose delivery (which is a function of both blood supply and glucose concentration) are at increased risk for impaired organ function at low blood glucose concentrations. Specifically, animal studies have shown that insufficient glucose supply for relatively long durations (hours rather than a few minutes) may contribute to neuronal death, augment functional deficits, and increase the risk for long-term neurologic injury in the presence of cerebral hypoxia and/or ischemia. Clinical studies suggest that this may be true also in newborn infants. However, it is not clear whether the low glucose concentrations in cases of hypoxia and ischemia contributed directly to worse outcomes or were simply a marker for those infants with more severe and prolonged metabolic compromise during hypoxia-ischemia who were, therefore, more likely to have worse outcomes. Furthermore, it remains unclear whether earlier detection of hypoglycemia, such as in the delivery room, in this population could improve subsequent neurologic outcome.

Rather than defining hypoglycemia as an absolute blood glucose value, some investigators have suggested using specific glucose concentrations as an indicator that further management of low glucose concentrations is warranted. Threshold values are based on evidence available in the literature (see further discussion under Treatment later in this chapter).[33] **This approach considers the overall metabolic and physiologic**

status of the infant when determining what constitutes an acceptable blood glucose concentration. Some infants may undergo metabolic derangements at glucose concentrations above the hypoglycemic threshold, whereas others may be able to tolerate lower concentrations of blood glucose without developing metabolic stress. An infant with polycythemia, for example, may have a normal blood glucose concentration but decreased cerebral delivery of glucose because of reduced brain plasma flow. In contrast, breastfed infants have normal substrate delivery to the brain even with "hypoglycemic" blood glucose values, because they have increased plasma concentrations of ketone bodies compared with formula-fed infants, though these concentrations are still lower than what is observed in fasting children.[65,79] **Concentrations of ketones are even lower in preterm and IUGR/SGA infants than in term infants who are feeding normally, suggesting that preterm birth and IUGR are associated with less capacity to generate alternate brain energy substrates.** This decreased capacity might increase the vulnerability of such infants to cerebral energy deficits when plasma glucose concentrations are decreased.[65,66]

In summary, **the definition of the blood glucose concentration at which intervention is indicated must be tailored to the clinical situation and the particular characteristics of a given infant. Further investigation and treatment should be instituted in the symptomatic infant at blood glucose concentrations of less than 45 mg/dL, whereas asymptomatic term infants with known risk factors should be treated if their blood glucose concentration is less than 36 mg/dL.**[76,77] Several authors suggest that these thresholds for intervention should be higher in preterm infants and lower in breastfed full-term infants.[33,64] **The American Academy of Pediatrics' Committee on the Fetus and Newborn has recommended different guidelines for late preterm infants and term SGA, large-for-gestational-age (LGA), and IDM infants, emphasizing initial screening, feeding if tolerated, and prompt (within 1 hour) reassessment for clinical signs and repeat measurement of glucose concentrations.**[1] **The Pediatric Endocrine Society also has issued a set of guidelines that focus on targets for glucose concentrations once an infant has been identified as having hypoglycemia.**[155] However, it is important to recognize that there have been no systematic studies to demonstrate the risks or benefits of using any specific blood glucose concentration as a threshold for intervention in neonatal hypoglycemia. Given the apparently wide range of glucose values associated with normal neonatal outcomes and the inherent inaccuracies in measuring glucose concentrations and the absence of a specific level below which injury inevitably occurs, any individual blood glucose measurement should be considered a one-point-in-time-only representation of the balance between glucose supply and utilization rather than as an absolute indicator of glucose sufficiency or insufficiency.

Hypoglycemic Neuronal Injury and Neuropathology

A schema of how hypoglycemia can contribute to neuronal injury is presented in Fig. 15.3. **Hypoglycemic brain damage in the newborn infant occurs predominantly in gray matter structures, although severe hypoglycemia in newborn infants may also be associated with white matter injury, particularly when the hypoglycemia occurs simultaneously with hypoxic-ischemic injury.**[125,162] Pathologic studies of such severely hypoglycemic newborn infants have shown widespread neuronal injury in the cerebral cortex, hippocampus, basal ganglia, thalamus, brainstem, and spinal cord. Late neuropathologic lesions associated with severe and prolonged low glucose concentrations include microcephaly associated with cortical atrophy and diffuse neuronal loss, as well as astrogliosis. Abnormalities may also be seen in white matter, whereas the cerebellum is generally spared. Such severe outcomes are extremely uncommon and are very seldom seen in normal clinical practice.

Neuroimaging of Hypoglycemic Injury

Magnetic resonance imaging (MRI) performed 2 to 3 weeks after such severe but very infrequent hypoglycemia demonstrates abnormal signals in the cortex, often most apparent in the occipital lobes.[10] More recent neuroradiologic investigations have shown a much **wider variety in the pattern of injury involving both white matter and gray matter as a consequence of severe neonatal hypoglycemia.**[23,148] MRI-defined lesions after severe hypoglycemia in the newborn period

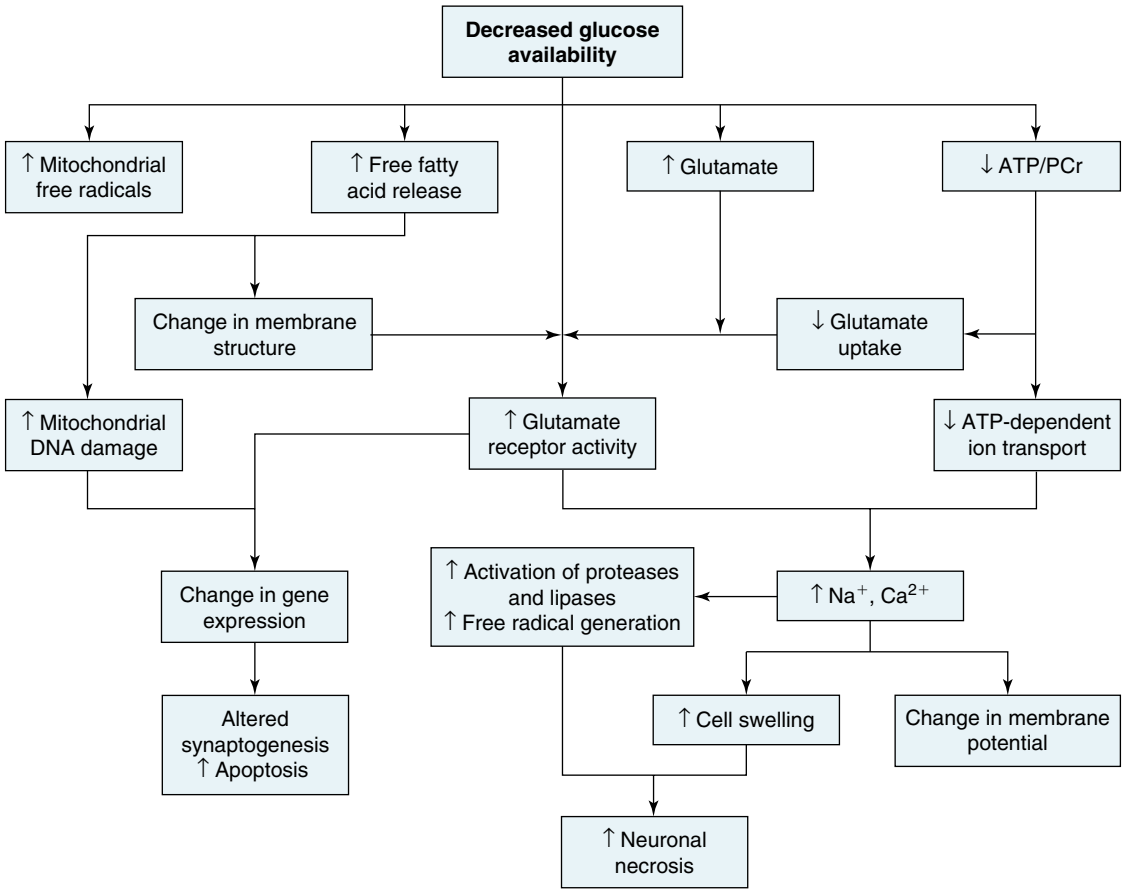

FIGURE 15.3 Proposed mechanism for the pathogenesis of hypoglycemic brain injury in the newborn. *ATP,* Adenosine 5′-triphosphate; *DNA,* deoxyribonucleic acid; *PCr,* phosphocreatine. (McGowan JE: Role of glucose in cerebral function. In Hay WW Jr, editor: Semin Neonat Nutr Metab 1997; 4:2-3. Columbus, OH: Ross Products.)

can be transient and not associated with long-term neurologic consequences, indicating that follow-up MRI scans should be considered to determine the permanency of the lesions.

Etiology of Hypoglycemia

The causes of hypoglycemia can be grouped into several broad categories based on the mechanisms producing the hypoglycemia (see Box 15.1[121];Table 15.1). These categories include inadequate substrate supply, abnormal endocrine regulation of glucose metabolism, and increased rate of glucose utilization. There also are several proposed causes for which mechanisms are not well defined.

INADEQUATE SUBSTRATE SUPPLY

If substrate availability is inadequate, hepatic glucose output will not meet metabolic demands. Most often this results from subnormal fat and glycogen stores that consequently do not provide sufficient energy to maintain glucose homeostasis until gluconeogenesis reaches adequate levels. **Because most hepatic glycogen is accumulated during the third trimester, infants born preterm have diminished glycogen stores.** In the past, infants with IUGR secondary to placental insufficiency also were considered to be at risk for decreased glycogen accumulation, presumably because of diminished transfer of glycogen precursors (e.g., glucose, lactate) across the placenta. In these infants, relative hypoxemia

caused by placental dysfunction also could stimulate increased production of adrenaline and noradrenaline, leading to increased glycogen breakdown and further compromising substrate supply. Evidence from more recent animal studies and human observations, however, suggest that **because of increased glucose uptake mechanisms in response to glucose deficiency (e.g., increased expression of cell membrane glucose transporters), muscle and hepatic glycogen stores are normal or even increased in IUGR infants.**[26,92,109,122,154]

Postnatally, catecholamine- and glucagon-stimulated glycogenolysis rapidly depletes glycogen supplies at a time when gluconeogenesis may be insufficient to provide enough endogenous glucose, resulting in hypoglycemia. **After the first few postnatal days, preterm infants may still be at risk for hypoglycemia even though glycogen stores are adequate**, because of low levels of hepatic microsomal glucose-6-phosphatase activity. Activity of this enzyme in preterm infants is low before birth and can remain low for several months after birth in some infants.[124,142,145] Because this enzyme catalyzes the dephosphorylation of glucose-6-phosphate to glucose and regulates the final step in hepatic glucose production, the decreased activity could contribute to diminished glucose production from both glycogenolysis and gluconeogenesis. Infants with low hepatic glucose-6-phosphatase activity may not be symptomatic with the initial episode of hypoglycemia but can become symptomatic if the hypoglycemia persists.

Up to 18% of preterm infants have problems maintaining normoglycemia at the time of discharge if a feeding is omitted or delayed.[59] Inadequate cortisol secretion in very preterm infants, particularly during periods of stress, also has been cited as a cause of limited activation of gluconeogenic enzymes. The underlying mechanisms for cortisol deficiency are not clear but may be related to a lack of adrenal stimulation as a result of limited hypothalamic-pituitary axis activity.

ABNORMALITIES OF ENDOCRINE REGULATION

Hyperinsulinemia is the most common endocrinologic disturbance producing neonatal hypoglycemia and may be the leading cause of the infrequent cases of persistent hypoglycemia in infants. Excessive insulin secretion in the newborn increases glucose utilization by stimulating cellular glucose uptake in insulin-dependent tissues, including muscle and liver. Brain glucose uptake, however, does not appear to be significantly altered by increased insulin levels. At the same time, the high circulating insulin concentrations promote continued glycogen synthesis and inhibit both glycogenolysis and gluconeogenesis, impairing the infant's glucogenic response to the increased glucose demand and decreasing plasma glucose concentrations. Suppression of ketone body production from free fatty acids by high levels of insulin also might limit the availability of alternative fuels for cerebral metabolism, thereby contributing to the increased risk for adverse long-term outcomes in this patient population.

The most common clinical condition in which hyperinsulinemia occurs is in the infant of a diabetic mother (IDM). In utero, the fetus becomes hyperglycemic because of increased transfer of glucose across the placenta during episodes of maternal hyperglycemia. **The fetal pancreatic beta cells are stimulated by the increased fetal glucose concentration to produce increased quantities of insulin. The pancreatic islet beta cells also appear to become abnormally sensitive to increases in glucose concentration after repeated hyperglycemic stimuli.** Before birth, the increase in cellular glucose uptake in response to the increased insulin secretion is matched by the increased availability of glucose from the mother. **After delivery, the maternal source of glucose is abruptly removed, whereas the hyperinsulinemia persists, producing hypoglycemia.** The decrease in glucose concentration after birth is a result of insulin-stimulated peripheral glucose uptake and inhibition of gluconeogenesis and glycogenolysis by the high insulin concentrations. Although some studies have reported other abnormalities in glucose metabolism in IDMs, Cowett and colleagues[37] found no difference in glucose kinetics in IDMs versus controls, perhaps because maternal diabetic control was well maintained during pregnancy in the group studied. A large review of pregnancies in diabetic mothers found no association between the incidence of neonatal hypoglycemia and the number of episodes of maternal hyperglycemia (a reflection of the degree of control) late in pregnancy.[67] **The incidence of neonatal hypoglycemia in IDMs correlates better with intrapartum, rather than antepartum, maternal glucose concentrations.** The results of these studies emphasize that it is a sudden increase

in glucose concentration that stimulates insulin secretion after a longer period in utero during which the fetal pancreatic beta cells have been sensitized to hypersecrete insulin as a result of repeated episodes of hyperglycemia.[38]

The incidence of hypoglycemia in IDMs is approximately 50%[62]; these infants usually are asymptomatic. The large and comprehensive Hyperglycemia and Adverse Pregnancy Outcome study has shown (1) that the complications typically associated with IDMs, including neonatal hypoglycemia, may be seen in women without overt gestational diabetes but with values at the upper end of the "normal" range on formal glucose tolerance testing; and (2) that the incidence correlates with the elevation in glucose values. This suggests that there is a continuum of abnormal glucose tolerance during pregnancy that is associated with increased fetal insulin secretion and that gestational diabetes represents the most severe degree of disturbed glucose homeostasis.[108]

Other causes of islet cell hyperplasia and resultant hyperinsulinemia include (1) severe erythroblastosis fetalis,[11] possibly resulting from inactivation of insulin by glutathione released from hemolyzed red blood cells; (2) exchange transfusion,[127] in which insulin release is stimulated by the high dextrose content of commonly used blood preservative agents; and (3) in utero exposure to drugs such as beta-agonist tocolytics.[115] In utero exposure to valproate and postnatal exposure to indomethacin also may result in hypoglycemia, but the mechanisms responsible are not known.

Idiopathic hyperinsulinism (i.e., increased, persistent insulin secretion without a known predisposing factor) may occur as a result of altered regulation of insulin secretion in pancreatic beta cells.[59,72] Two general forms of persistent idiopathic hyperinsulinism are recognized: prolonged neonatal hyperinsulinism and congenital (genetic) hyperinsulinism. Prolonged idiopathic neonatal hyperinsulinism appears to be common although not well recognized or understood. Affected neonates usually have some evidence of stress before or during delivery, such as low birth weight (LBW) with IUGR (this disorder may affect 10% or more of IUGR/SGA infants), birth asphyxia, or maternal preeclampsia. **Prolonged neonatal hyperinsulinism usually manifests in the first days after birth and often may be severe, requiring high dextrose infusion rates of 15 mg/kg/min of glucose or more.** Prolonged neonatal hyperinsulinism also may last several weeks to months and does not respond well to glucocorticoids but can be treated with diazoxide at doses of 5 to 10 mg/kg/day.[8,71]

Congenital (genetic) persistent hyperinsulinism is the most common form of persistent hypoglycemia in neonates and infants and is the most difficult to diagnose and treat.[77] The pancreatic abnormalities observed may be diffuse or focal, depending on the mutation present. Although the overall incidence of *persistent hyperinsulinemic hypoglycemia* (PHIHG) is low (approximately 1 in 50,000 births), the incidence of the inherited forms may be as high as 1 in 2500 infants in certain genetically homogeneous populations.[60] Depending on the degree of hyperinsulinemia in utero, these infants also may be macrosomic at birth. Most often, **infants with PHIHG present with repeated episodes of hypoglycemia in the immediate neonatal period, followed by severe, recurrent hypoglycemia after the first few days of life, often after discharge from the newborn nursery.** Recognizing such infants requires prolonged evaluation of an infant's capacity to maintain normal blood glucose concentrations between feedings after initial episodes of hypoglycemia are noted.

Several different genes have been associated with congenital hyperinsulinism.[119] Mutations in several regions on the short arm of chromosome 11 occur in many of infants with PHIHG; these mutations most often are inherited in an autosomal recessive pattern. Abnormalities of either the SUR1 or the Kir6.2 component of the K_{ATP} complex are most common. Because the K_{ATP} complex—the site of diazoxide action—is disrupted by the mutations, these infants usually do not respond to diazoxide treatment. Octreotide (long-acting somatostatin) can be more helpful in the short term, but near-total (95% to 98%) pancreatectomy usually is necessary. Pancreatectomy often requires continuous feedings and even insulin therapy[119] and replacement of pancreatic enzymes. Infants who have this form of hyperinsulinism typically are LGA, present with early neonatal hypoglycemia, and often require high rates of IV glucose infusion.

Hyperinsulinism resulting from a focal pancreatic lesion *(focal adenomatosis)* may occur in 50% of patients with congenital hyperinsulinism.[135] The adenomas are small—3 to 5 mm in diameter—and represent a localized clone of beta cells expressing a paternally derived mutation in the gene for either

SUR1 or Kir6.2 because of loss of heterozygosity for the maternal allele. The clinical course of these infants is similar to that of infants with hyperinsulinism due to widespread mutations of the pancreatic K_{ATP} channel. Localization of the focal adenomatous region of the pancreas via positron emission tomography (PET) with ^{18}F-fluoro-L-dopa may allow definition of the abnormal region of the pancreas, thereby guiding limited resection and avoiding more extensive, often near-total pancreatectomy.[20,86]

Several other mutations lead to genetic forms of PHIHG, including mutations in genes coding for glucokinase *(GCK HI),* glutamate dehydrogenase *(GDH),* hexokinase *(HK1),* hydroxyacyl-CoA dehydrogenase *(HADH),* and the nuclear transcription factors *HNF1A* and *HNF4A.*[119] These different genetic disorders are much less common and have variable presentations, usually later in the neonatal period or even in early infancy.

In addition to hyperinsulinemia, **global endocrine disturbances also can result in hypoglycemia.** These disturbances include a range of abnormalities of the hypothalamic-pituitary axis, the most severe being *panhypopituitarism.* Such infants frequently have growth hormone deficiency and hypothyroidism in addition to severe hypoglycemia. If pituitary dysfunction has resulted from a structural central nervous system (CNS) lesion, other neurologic problems may be present, including abnormal muscle tone and neonatal seizures. Adrenal failure and hypoglycemia can occur as a result of adrenal hemorrhage, often in association with neonatal sepsis. Isolated endocrine defects, including primary hypothyroidism and cortisol deficiency, also may be associated with hypoglycemia.

Infants with *Beckwith-Wiedemann syndrome* also are macrosomic and hyperinsulinemic; in addition, they have other associated anomalies, including macroglossia, which may cause airway obstruction, and omphalocele.[49] Asymptomatic hypoglycemia may occur in 30% to 50% of infants with Beckwith-Wiedemann syndrome and usually resolves in the first 3 days of life. However, up to 5% of affected infants may have persistent, frequently symptomatic hypoglycemia.[41] Infants with Beckwith-Wiedemann syndrome have abnormalities with a specific region on the short arm of chromosome 11, the same region in which mutations associated with other hyperinsulinemic syndromes have been identified.

ENZYMATIC AND GENETIC DISORDERS (TABLE 15.1)

Hypoglycemia can result from a wide variety of hormonal and enzymatic deficiencies.[75] Growth hormone and cortisol are counterregulatory hormones (i.e., they oppose the actions of insulin) and increase blood glucose concentrations by reducing glucose uptake in muscle tissue and stimulating lipolysis and gluconeogenesis during hypoglycemia. **Hypoglycemia is a common complication of growth hormone and cortisol deficiency. Thyroid hormone deficiency is another situation in which hypoglycemia can develop.** Deficiency of one or all of these hormones can be seen in cases of panhypopituitarism. Appropriate hormone replacement is the treatment of choice.

Hereditary disorders associated with deficiencies of specific enzymes that regulate substrate mobilization, interconversion, or utilization of carbohydrate, fat, or amino acids individually are rare disorders but collectively are frequently associated with hypoglycemia. These disorders are almost always inherited as autosomal recessive traits. Many infants with these disorders can be identified on routine and expanded neonatal screening, and early dietary interventions can be critical in the long-term management of their condition.

Glycogen storage disorders cause hypoglycemia from one of several enzyme deficiencies that prevent or limit glycogenolysis and release of glucose into the circulation.

INCREASED GLUCOSE UTILIZATION

Some term infants may have normal energy stores at birth and intact regulating mechanisms but may be stressed by one of several conditions so that the available supplies do not meet their energy requirements. An asphyxiated newborn is one common example. **During and after asphyxia, when tissue oxygen supply is limited, the neonate relies largely on anaerobic metabolism for energy production.** Anaerobic metabolism utilizes more glucose than aerobic metabolism to produce a given amount of energy. As a result, glucose produced by lipolysis and glycogenolysis is rapidly consumed. **Hypoxic-ischemic damage to the liver may further impair synthesis of gluconeogenic enzymes and thus delay the normal postnatal onset of gluconeogenesis. Elevated insulin concentrations also may be present, providing an additional cause for the hypoglycemia.**[39] **Other**

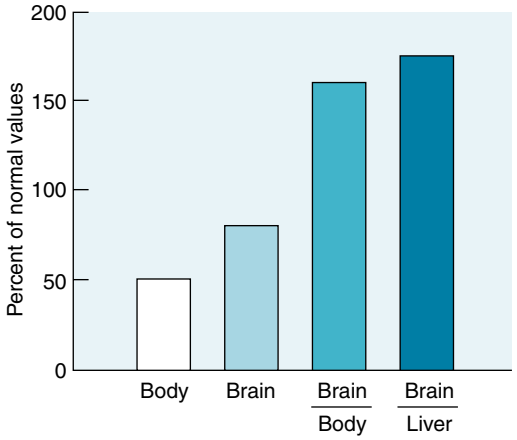

FIGURE 15.4 Differences in organ/body weight ratios in small-for-gestational-age infant compared with appropriate-for-gestational-age counterpart. (From Lafeber HN, Jones CT, Rolph TP. Some of the consequences on intrauterine growth retardation. In Visser HKA, editor: *Nutrition and Metabolism of the Fetus and Infant.* Boston: Martinus Nijhoff; 1979.)

conditions in neonates that lead to a shift from aerobic to anaerobic metabolism, thus predisposing the infant to hypoglycemia, include hypotension, severe lung disease with hypoxemia and hypoventilation, and septic shock.

Hypothermia may result in hypoglycemia through rapid depletion of brown fat stores for nonshivering thermogenesis and secondary breakdown and exhaustion of glycogen stores. Hypothermia is most often seen in infants born at home, but milder degrees may occur in the delivery room. **Hypoglycemia also has been observed in some infants with sepsis.** A study done in several such infants found that they had an increased rate of glucose disappearance in response to an IV glucose infusion, suggesting an increased rate of glucose utilization.[87] Stimulation of glucose utilization may be a result of circulating endotoxins, which increase the rate of glycolysis.

Several other factors also contribute to the risk for hypoglycemia in infants with other identified risk factors. **Preterm infants with respiratory distress syndrome (RDS), for example, have increased metabolic demands because of the increased work of breathing. Chronic hypoxia in IUGR fetuses stimulates catecholamine secretion, which can deplete glycogen stores.** Infants with IUGR and hypoglycemia may have increased rates of glucose disappearance when receiving an IV glucose infusion and reduced fat mobilization in response to hypoglycemia compared with normoglycemic SGA newborns. Because of the **increased brain weight/liver weight and brain weight/body weight ratios in all newborns (12% in term newborns for the latter comparison vs. 2% in adults), cerebral glucose requirements are markedly higher relative to the liver's capacity to respond than in the adult, even if glycogen stores are normal for size** (Fig. 15.4).[85] This is especially true in infants with asymmetric growth restriction. In addition, **increased insulin sensitivity has been reported in SGA newborns within the first 48 hours of life.**[14,130] These observations indicate that disturbances in glucose metabolism in addition to lower-than-normal energy stores may be present in some growth-restricted infants.

PREVENTION OF HYPOGLYCEMIA

Recognition of those infants at risk for disturbances in glucose homeostasis is the most important step in preventing both hypoglycemia and hyperglycemia. In infants with conditions predisposing to hypoglycemia, such as preterm infants, infants with IUGR, or IDMs, **early feeding and frequent monitoring of blood glucose concentrations may prevent a decrease in blood glucose concentration or allow early detection of decreased blood glucose levels. Maintenance of a neutral thermal environment is especially critical to minimize energy expenditure in those infants at risk for hypoglycemia.** Other conditions associated with hypoglycemia, such as asphyxia and hypothermia, may be avoided through appropriate obstetric and neonatal intervention. As many as 70% of infants requiring transport may not have had appropriate glucose evaluations documented in the referring centers.[44] A prompted intervention (STABLE Pretransport Stabilization Self-Assessment Tool [PSSAT])[44] may result in significant improvement in glucose monitoring.

DATA COLLECTION

History

The history of any neonate at risk of hypoglycemia must include a detailed prenatal and family history.

Important maternal risk factors associated with neonatal hypoglycemia are listed in Box 15.1. Other important data include a history of family members with atypical diabetes or other abnormalities of glucose homeostasis, family history of metabolic disease, and previous unexplained stillbirths.

The most important information to be obtained from the infant's history is gestational age, Apgar scores, and details of events in the delivery room, especially any findings that suggest the presence of significant perinatal compromise. **An infant with a history of any of the conditions listed in** Box 15.1 **or** Table 15.1 **should be considered at high risk for developing a problem with glucose homeostasis.**

Physical Examination

Careful measurement of birth weight and head circumference in combination with accurate gestational age assessment will establish whether the infant is preterm, LBW, SGA, or LGA and thus at increased risk for hypoglycemia. IDMs frequently have small heads relative to their general macrosomia and have been described as having "tomato facies" because of plethora and increased buccal fat. The physical findings associated with Beckwith-Wiedemann syndrome have already been described. The presence of midline facial defects, such as cleft lip or hypertelorism, may indicate the presence of a CNS malformation with associated pituitary dysfunction. Glycogen storage diseases should be considered in infants with hepatomegaly.

Clinical Signs

Signs of neonatal hypoglycemia are nonspecific and extremely variable (Box 15.2).[121] They include general findings, such as abnormal cry, poor feeding, hypothermia, and diaphoresis; neurologic signs, including tremors and jitteriness, hypotonia, irritability, lethargy, and seizures; and cardiorespiratory disturbances, including cyanosis, pallor, tachypnea, periodic breathing, apnea, and cardiac arrest. These features also occur in preterm infants and in neonates with sepsis, intraventricular hemorrhage, asphyxia, hypocalcemia, congenital heart disease, and structural CNS lesions, among other causes. **In the presence of any of the preceding signs, however, hypoglycemia always should be considered, because the diagnosis can be made relatively easily and prompt treatment is essential.**

BOX 15.2 CLINICAL SIGNS OF HYPOGLYCEMIA

- Mild to moderate changes in level of consciousness*
- Stupor or lethargy
- Tremulousness
- Irritability
- Coma
- Seizures (depend on duration, repetitive occurrence, and severity of hypoglycemia)
- Respiratory depression or apnea, leading to cyanosis
- Hypotonia, limpness, inactivity
- High-pitched cry
- Poor feeding (after previously feeding well)
- Hypothermia

* Most frequent and should be alleviated with correction of low glucose concentrations.

If a problem with glucose homeostasis is suspected, documentation of the aforementioned data, history (see Box 15.1**), physical examination, and clinical signs (see** Box 15.2**) must reflect ongoing monitoring and measures taken. The use of risk assessments, guidelines, or protocols that consider the data just mentioned helps systematize detection (**Fig. 15.5**).**

Laboratory Data

When hypoglycemia is suspected, the plasma or blood glucose concentration must be determined promptly. **Ideally, this determination should be made with one of the laboratory enzymatic methods, such as the glucose oxidase or hexokinase method, but even bedside reagent test strip glucose analyzers (i.e., glucometers) can be used if the test is performed carefully and with awareness of the more limited accuracy of these devices.** Although more expensive, some blood gas analyzers have the capability of measuring glucose concentrations as accurately as laboratory enzymatic methods. If present in the nursery or as a portable device, these instruments may offer the optimal combination of short turnaround time and accuracy.[73] In the clinical setting, early and rapid determination of glucose concentrations in the high-risk or symptomatic neonate is essential.[54] **Prompt detection of hypoglycemia permits early treatment and potentially helps prevent**

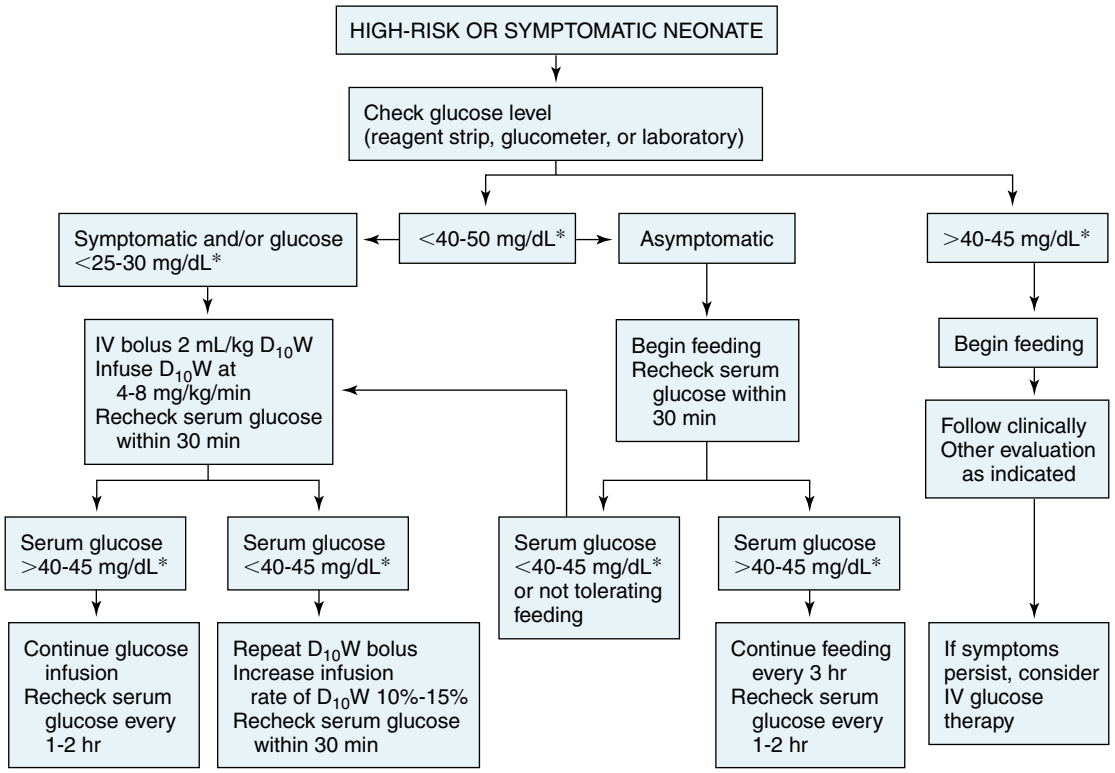

FIGURE 15.5 Decision tree for management of neonate with acute hypoglycemia. *IV,* Intravenous.

long-term neurologic sequelae.[34] Although laboratory measurements of glucose concentrations are the most effective methods for detecting hypoglycemia, requests for confirmatory glucose concentration measurements by the laboratory must be requested and accomplished STAT (15 minutes or less). Routine requests are often not available for up to 1 hour—far longer than appropriate for diagnosing hypoglycemia and thereby delaying the initiation of critically important treatment. The sample of blood can be obtained from a warmed heelstick or venipuncture specimen.

These methods can be useful in screening infants in whom abnormal glucose concentrations are suspected if the user is aware of their limitations. The accuracy of test strip results depends in part on the technique used. An adequate sample must be placed on the test strip pad, and the timing of reading the result is critical. Recently developed devices automatically read the result at the appropriate time, reducing one source of error. Hospital personnel should be trained and certified in the use of test strip methods and the bedside instruments used to quantify glucose concentration. With proper technique, test strip results demonstrate a reasonable correlation with actual blood glucose concentrations, but the variation from the actual blood glucose value may be as much as 10 to 20 mg/dL. A number of studies have compared the results obtained with specific commercial products with results obtained with laboratory methods.[6,57,99] Regardless of the test strip or instrument used, correlations with actual blood glucose concentrations are lowest at the lower glucose concentrations at which neonatal hypoglycemia must be accurately determined. Several studies have shown that use of test strips alone may fail to detect from 11% to as many as 67% of infants with statistically defined hypoglycemia.[56,57,88] There also is a significant incidence of false-positive results.

Because of the limitations of these methods, whenever a diagnosis of hypoglycemia is

suspected by test strip or glucometer results, the blood glucose concentration should be confirmed by a specimen sent to the chemistry laboratory for rapid (STAT) determination and reporting. Although laboratory results are more accurate and reliable than screening methods, a long delay in processing the specimen can result in a falsely low level as the erythrocytes in the sample metabolize the glucose in the plasma. This problem can be avoided by transporting blood in a tube containing a glycolytic inhibitor. ***Treatment of suspected hypoglycemia, however, should not be postponed until confirmation is obtained from the laboratory. Also, if hypoglycemia is suspected on the basis of clinical symptoms, initial treatment should be instituted even if the test strip result is "normal."*** If the actual value is abnormal, a delay in therapy could be harmful; if the actual value is within the normal range, therapy can be stopped without serious side effects.

Most cases of neonatal hypoglycemia have an identifiable cause (e.g., maternal diabetes or IUGR). In a term infant with no known risk factors for hypoglycemia, sepsis must be considered as the most likely cause of hypoglycemia and an appropriate evaluation should be performed. Of those infants without an identifiable cause, most have idiopathic hypoglycemia, which resolves spontaneously within 2 to 5 days, and no further evaluation is needed. However, in rare cases, hypoglycemia persists beyond the first week of life with no obvious cause, requiring a logical and rapid approach to diagnosis of the particular form of persistent hypoglycemia.[70,155] The diagnostic evaluation of these infants should include (1) simultaneous determination of glucose and insulin concentrations and alternate substrates, such as ketones and FFAs; (2) evaluation of pituitary function, including measurement of thyroid-stimulating hormone (TSH), thyroxine (T_4), adrenocorticotropic hormone (ACTH), cortisol, and growth hormone levels; and (3) appropriate studies to diagnose inborn errors of metabolism, such as lactate and pyruvate concentrations. Ideally, these studies should be obtained during an episode of hypoglycemia. Once hypoglycemia is identified in a neonate as persistent, a fasting study should be performed to measure plasma insulin concentration when plasma glucose concentration drops below 45 to 50 mg/dL. If this fasting study demonstrates hyperinsulinism, treatment should be immediately instituted.[77]

TREATMENT OF HYPOGLYCEMIA

Early identification of an infant at risk for developing hypoglycemia and institution of prophylactic measures to prevent its occurrence provide the best treatment for this disorder. The goals are to recognize at-risk infants, evaluate early and frequently for decreasing glucose concentrations, treat when indicated, and provide glucose and enteral feeding as needed to achieve and maintain glucose concentrations in the range that most normal infants achieve via their own homeostatic mechanisms within 6 to 12 hours after birth.

A decision tree suggesting guidelines for management of infants with hypoglycemia is shown in Fig. 15.5. **Most asymptomatic infants can be managed with early and frequent feedings (by breastfeeding or with expressed milk, with donor milk when appropriate as for very preterm infants, or with formulas). All symptomatic neonates should receive treatment with IV dextrose infusion to provide glucose at an initial rate of 4 to 6 mg/kg/min.** These suggested infusion rates cover the range of hepatic glucose production in normal term newborns. **In some circumstances (neonates with glucose concentrations of 20 mg/dL or less and/or with very severe clinical signs, such as seizures and/or coma), it may be useful to use a minibolus of 200 mg/kg dextrose (2 mL/kg of $D_{10}W$) plus the dextrose infusion regimen** originally described by Lilien and colleagues.[90] **Rapid normalization of blood glucose may be particularly beneficial in such severely symptomatic infants,** although no data confirm this assumption. **However, in asymptomatic newborns it may not be necessary to use the 200 mg/kg dextrose minibolus.[120] In IDMs or other infants suspected of having hyperinsulinism with asymptomatic hypoglycemia, the initial minibolus can be eliminated and the infusion rate kept at the minimum necessary to produce and maintain normal blood glucose concentrations (3 to 5 mg/kg/min).[120]** This practice helps prevent an excessive insulin response to the sudden increase in glucose concentration produced by the minibolus. When glucose infusion rates are being calculated, it is important to remember that commercially prepared glucose solutions actually contain glucose in its hydrated form (molecular

weight [MW] 198, versus MW 180 for anhydrous glucose), which lowers the actual glucose content of the solution by approximately 8%. **Thus $D_{10}W$ contains approximately 9.2 g of glucose per deciliter.**

Once the infant's glucose requirement has been determined, **the glucose infusion should be maintained at that level until blood glucose concentrations are stable and in the desired range. The target blood glucose concentration during IV therapy should be above the "hypoglycemic threshold" defined for that particular infant.** For example, if the hypoglycemia threshold is defined as 40 mg/dL, glucose concentrations should be maintained at or above 50 mg/dL.[33]

Adjusting therapy to maintain a blood glucose concentration higher than the "symptomatic" threshold allows a margin of safety in the absence of any data establishing a correlation between specific glucose concentrations in this range and long-term outcome. There is no evidence that diagnosis or treatment thresholds for preterm infants should differ from those for term infants.

If the infant was being fed before IV therapy was instituted, feedings may be continued. However, the calculated minimum glucose requirement should be provided by the IV infusion alone rather than by the combination of glucose infusion and feedings. In infants who were not previously fed, feedings can be instituted when clinically indicated. There are several advantages to feeding a hypoglycemic infant during treatment with IV glucose. In the hyperinsulinemic infant, galactose (one of the components of lactose) stimulates less insulin release than glucose and therefore helps stabilize blood glucose concentrations. **Continuation of oral feedings also aids in the process of weaning the infant off IV glucose. When feedings are well tolerated, the IV infusion generally can be slowly tapered if the glucose concentration and clinical status remain stable.** Although enteral feeding has the theoretical risk for augmenting insulin secretion and subsequent hypoglycemia as a result of the food-stimulated release of gut peptides that may potentiate insulin release from the pancreas, there is no evidence that withholding feedings actually prevents this potential problem. **It probably is better to continue breast milk or formula feedings using smaller, more frequent amounts or even continuous gastric infusion than to stop enteral feedings and try to maintain normoglycemia exclusively with IV glucose.**

Additional consideration should be given to the use of buccal dextrose gel.[120] In a large placebo-controlled, randomized trial, **40% oral dextrose gel, 200 mg/kg, placed on the buccal mucosa, restored normal glucose concentrations, reduced the recurrence rate of low glucose concentrations, and allowed enteral feeding, particularly breastfeeding, to continue or even advance. This therapy also decreased rates of NICU admissions for hypoglycemia and increased rates of continued successful breastfeeding.[63] Such therapy seems appropriate for the term or late preterm infant with transient hypoglycemia and probably for SGA, LGA, and IDM infants who are otherwise clinically stable.**[120] When buccal dextrose gel is utilized and these infants are managed outside the NICU, nursing staffing must allow for additional observation and monitoring. **Parental teaching regarding the signs of hypoglycemia and the need to avoid hypothermia must be provided and documented.**

In rare cases, such as infants with severe, refractory hyperinsulinemic hypoglycemia or infants with other morbidities such as hypoxic-ischemic encephalopathy or heart failure, enteral feedings might be contraindicated. In these infants, once glucose concentrations are stabilized and/or the other adverse clinical conditions have resolved, then enteral feedings can be used to treat hypoglycemia.

Adjunctive Therapy

Table 15.2 offers a summary of adjunct therapies for hypoglycemia.

GLUCAGON

Glucagon, 30 mcg/kg IV or intramuscular (IM), releases glycogen from hepatic stores when insulin concentrations are normal. However, IDMs and other infants with hyperinsulinemia may require much larger doses, up to 300 mcg/kg IV or IM, to produce a response. **Administration of glucagon may be useful diagnostically, because failure to respond to glucagon administration with an increase in serum glucose concentration suggests depletion of hepatic glycogen stores or a glycogen storage disorder. Glucose infusion should be maintained after injections of glucagon are administered, because**

TABLE 15.2 ADJUNCT THERAPIES FOR HYPOGLYCEMIA

THERAPY	EFFECT	DOSAGE
Corticosteroids	Decrease peripheral glucose utilization Enhance gluconeogenesis	Hydrocortisone 5–15 mg/kg/day or Prednisone 2 mg/kg/day
Glucagon	Stimulates glycogenolysis Releases glycogen from hepatic stores when insulin concentrations are normal	30 mcg/kg IV or IM 300 mcg/kg if hyperinsulinism is present
Diazoxide	Inhibits insulin secretion	15 mg/kg/day
Somatostatin (long-acting: octreotide acetate)	Inhibits insulin and growth hormone release	5–10 mcg/kg every 6–8 hr
Pancreatectomy	Decreases insulin production/secretion	

IM, Intramuscular; *IV,* intravenous.
From McGowan JE. Neonatal hypoglycemia, *Pediatr Rev.* 1999;20:6–15.

there is a risk for rebound increased insulin secretion in response to the glucagon-produced surge in glucose production. Some have suggested using continuous IV glucagon infusions, but this practice is not universal.[109] In addition, the rapid but transient increase in glucose concentration immediately after glucagon injection may produce a false sense that the hypoglycemia has resolved, even though the underlying cause still exists. Continuous infusions of glucagon have been used to treat refractory hypoglycemia.[26]

OTHER AGENTS

Glucocorticoids (hydrocortisone), somatostatin, and diazoxide have been used to treat hypoglycemia in refractory cases. **Glucocorticoids can be used to reduce peripheral glucose utilization and increase gluconeogenesis, particularly when glucose infusion rates of 12 to 15 mg/kg/min or more are needed to maintain normal glucose concentrations.** Somatostatin and diazoxide, which suppress insulin release, are most often used in infants with islet cell dysplasias.[77]

MISCELLANEOUS THERAPIES

In infants with hypoglycemia caused by a specific medical problem, therapy should be directed toward alleviating the underlying illness. This includes administration of antibiotics to treat sepsis, partial exchange transfusion to reduce hyperviscosity, hormone replacement in cases of hypopituitarism, and dietary intervention for metabolic disorders. A trial of diazoxide should be initiated in infants who have been identified as having hyperinsulinism. If diazoxide is not effective at a maximum dose of 15 mg/kg/day divided into two doses per day for 2 to 3 days, it may be stopped and octreotide could be tried. However, medical therapy alone fails to control hypoglycemia in 40% to 90% of infants with severe PHIHG.[42] If octreotide is not successful, surgical management is generally necessary. Before surgery, imaging procedures should be performed to determine whether the pancreatic abnormalities are focal or diffuse. Focal disease generally is cured with partial pancreatectomy, whereas diffuse disease requires near-total pancreatectomy and then treatment of the exocrine and endocrine deficiencies that invariably result.[51]

COMPLICATIONS OF HYPOGLYCEMIA

The outcome for infants with neonatal hypoglycemia appears to be related to the duration, repetitive occurrence, and severity of the hypoglycemia and the underlying etiology. Those with *asymptomatic hypoglycemia* usually have clinically normal neurodevelopmental outcomes, though in research outcomes assessments **there may be an association between low glucose concentrations and impaired neurodevelopment.[103] Furthermore, there is no evidence yet that treatment prevents**

such abnormal outcomes. *Symptomatic hypoglycemic* infants (primarily those with severe, protracted, and recurrent neurologic abnormalities such as seizures and coma associated with plasma glucose concentrations below 20 to 25 mg/dL for several hours or more) have a **poorer prognosis, with abnormalities ranging from learning disabilities to cerebral palsy and persistent or recurrent seizure disorders, as well as mental retardation of varying degrees.**[50] Prompt initiation of treatment is thought to be associated with a more positive outcome, although this has not been well documented.

In preterm infants, data indicate that hypoglycemia may adversely affect long-term outcome.[47,80,96] A follow-up study of more than 600 former preterm infants found significantly lower mental and motor indices in those with five or more documented episodes of moderate hypoglycemia (defined as a blood glucose concentration less than 45 mg/dL) during the neonatal period. This difference remained significant even when confounding factors such as intraventricular hemorrhage (IVH), need for ventilator support, and asphyxia were considered. However, not all comorbidities can be controlled for in this type of study. Furthermore, differences in cognitive function were less apparent at school-age follow-up in the same cohort of patients, and **newer studies have not confirmed any adverse outcomes associated with hypoglycemia in preterm infants.**[61,157] It may be that because nearly all preterm infants receive early IV dextrose infusions separately or as part of parenteral nutrition, low glucose concentrations—particularly repeated low values—are less likely to occur.[69,166] These discrepant results indicate the need for further long-term studies in preterm infants.

The incidence of neurodevelopmental abnormalities in IDMs ranges from 0% to 35%; the lower figures are from more recent studies and may represent improvement in obstetric and neonatal care. Some studies have been able to detect causes other than hypoglycemia that may have contributed to the overall outcomes.[67,129] These causes include such factors as prematurity, presence of congenital anomalies, congenital iron deficiency, and degree of control of maternal disease. However, Stenninger and colleagues[139] found that **IDMs who were hypoglycemic as newborns (glucose less than 27 mg/dL) had an increased frequency of deficits in attention, motor control, and perception at 8 years of age compared with both IDMs without hypoglycemia and normal newborn controls.** This association was also documented in a more recent study.[103] A number of other neonatal complications are associated with maternal diabetes, including polycythemia, which may add to disturbances of glucose homeostasis; hypocalcemia secondary to maternal hypoparathyroidism; dystocia secondary to macrosomia; and congenital anomalies. Infants of mothers with severe diabetic vasculopathy, in contrast to most IDMs, may have IUGR caused in part by decreased placental blood flow, with hypoglycemia resulting from inadequate glycogen and fat stores as occurs in all cases of IUGR rather than hyperinsulinemia alone.

Adverse neurologic outcomes have been reported in as many as 40% to 50% of infants with PHIHG, possibly because these infants cannot effectively generate ketone bodies, which could serve as an alternative source of energy for cerebral metabolism during periods of hypoglycemia.[105-107] In addition, infants with PHIHG who require a greater than 95% pancreatectomy often develop glucose intolerance or even frank diabetes mellitus later in life.[94] Hypoglycemia secondary to hypopituitarism also is associated with a poor outcome; often this results from other CNS or endocrine dysfunction rather than from the hypoglycemia itself.

PARENT TEACHING

Parent teaching should begin before delivery, with emphasis placed on good nutrition and early and regular prenatal care. Teaching also should include information about those conditions that increase the risk for hypoglycemia (e.g., IUGR associated with maternal cigarette smoking and poor maternal nutrition). Regular prenatal care ensures the early detection of potentially serious problems, including preeclampsia, gestational diabetes, and abnormal fetal growth.

Prenatal teaching is especially important in the woman with known diabetes mellitus, because overall outcome (although not necessarily the incidence of hypoglycemia) is directly related to the degree of control before and during pregnancy. Breastfeeding information and encouragement to breastfeed must be included in the prenatal education. In addition, the possibility of neonatal hypoglycemia and requirement for

IV therapy can be discussed with the parents before delivery so that they will be aware that the infant may require a longer hospital stay even if delivered at term.

If IV therapy is needed to treat neonatal hypoglycemia, regardless of cause, a thorough explanation of the treatment plan must be given to the parents at the time therapy is instituted. Frequent progress reports should be provided to resolve unanswered (and often unasked) questions and relieve parental anxiety. **When buccal dextrose gel is utilized and infants are managed outside the NICU, parental teaching must include the need for additional observation and monitoring, the signs of hypoglycemia, and the need to avoid hypothermia. Parents of children with islet cell dysplasias need to be aware of the clinical signs of hypoglycemia and emergency treatment measures that can be instituted,** because recurrent hypoglycemia may occur in these cases. Parents of infants with inborn errors of metabolism also need counseling with regard to prognosis and genetic counseling about risks for recurrence in future pregnancies.

HYPERGLYCEMIA

Definition of Neonatal Hyperglycemia

Hyperglycemia in newborns is usually defined, based on population data, as a blood glucose concentration of more than 125 mg/dL (greater than 150 mg/dL plasma) in a term infant or more than 150 mg/dL in blood in a preterm infant. In fetal life, the upper limit of the normal range of glucose concentrations is 108 mg/dL.[100] Unlike neonatal hypoglycemia, however, there are no reported "clinical" definitions of hyperglycemia (i.e., the appearance of physiologic disturbances associated with a specific high blood glucose concentration). The incidence of statistically defined neonatal hyperglycemia is difficult to determine; estimates range from 5.5% of all infants receiving intravenous (IV) infusions of $D_{10}W$ to as high as 40% in infants weighing less than 1000 g who are receiving IV dextrose infusions. Dweck and Cassady[48] noted that 86% of infants with birth weights under 1100 g were hyperglycemic, and of these infants, 84% had one or more serum glucose concentrations greater than 300 mg/dL. In 2006, Blanco and colleagues[19] found that 88% of infants with birth weights less than 1000 g had at least one blood glucose concentration greater than 150 mg/dL in the first week of life. **Neonatal hyperglycemia has been increasing in recent years in preterm infants as IV nutrition has become universal**[140,159] but has been balanced more toward energy with relatively high IV infusion rates of dextrose and lipid.[163]

Etiology of Hyperglycemia

Hyperglycemia is most common during the first week after birth (Box 15.3), although more recent studies have shown that hyperglycemia in very-low-birth-weight (VLBW) infants can persist well after birth, even after weaning off TPN or IV dextrose infusion and well beyond the immediate postnatal "stress" period when hyperglycemia is most common.[140,146]

Typically, **a neonate with hyperglycemia is an LBW infant (less than 32 weeks' gestation and less than 1200 g birth weight)—often one with IUGR—who cannot tolerate an IV glucose infusion at the usual rate of 4 to 8 mg/kg/min (i.e., $D_{10}W$ at 60 to 100 mL/kg/day).** This relative glucose intolerance appears to be caused by general immaturity of the usual regulatory mechanisms. In immature infants, especially those with IUGR, these differences include fewer pancreatic islets and beta cells and decreased pancreatic insulin secretion in response to glucose, a direct result of suppression by catecholamines both before and after birth.[89] After birth, persistence of

BOX 15.3 ETIOLOGIC FACTORS IN NEONATAL HYPERGLYCEMIA

- Iatrogenic (e.g., during intravenous glucose infusion)
- Decreased insulin production (e.g., with increased catecholamine production in very-low-birth-weight or intrauterine-growth-restricted infant; catecholamine infusion side effect)
- Decreased insulin sensitivity (e.g., with increased catecholamine production in very-low-birth-weight infant or transient diabetes mellitus; catecholamine infusion side effect)
- Sepsis
- Methylxanthine side effect
- Glucocorticoid side effect

catecholamine secretion can continue to suppress insulin secretion.[31] Catecholamine excess also can lead to insulin resistance, both peripheral (leading to decreased glucose utilization) and hepatic (leading to increased glucose production), and peripheral glucose intolerance.[48] Stress-induced production of cortisol and glucagon promote hepatic glycogen breakdown and gluconeogenesis with release of glucose into the circulation. These infants also have relatively decreased insulin-sensitive tissues (e.g., skeletal muscle and heart) as a fraction of body weight. There also is some evidence of abnormal insulin processing by the pancreatic beta cells such that more immature forms of insulin (proinsulin and proinsulin split products) are released. Because these immature forms of insulin are much less active in stimulating the insulin receptor, they may contribute to a relative insulin resistance in these infants.[110] Some investigators also have reported that, unlike adults, **most preterm and term infants fail to suppress endogenous glucose production despite the administration of an adequate exogenous supply (e.g., IV infusion),[27,36,28] but other investigators did not measure any glucose production in premature infants receiving IV glucose at a rate of more than 2 mg/kg/min.[168]**

Hyperglycemia is most commonly iatrogenic in extremely low-birth-weight (ELBW) infants (less than 750 g) who require excess water to replace fluid lost through insensible water losses and who receive excess glucose along with the infused water because it is necessary to provide an isotonic IV solution. The risk for developing hyperglycemia is significantly increased with decreasing birth weight (up to 18 times greater in infants with birth weights <1000 g than among those weighing 1000–2000 g) and with an increasing rate of glucose infusion, even if the absolute infusion rate remains within the accepted range.

Delay in initiating enteral feedings may be an additional risk factor. The incidence of **hyperglycemia is higher in LBW infants receiving all of their nutrition parenterally than in those who receive at least a part of their nutrition enterally, and prolonged intravenous nutrition may contribute to insulin resistance, particularly when hyperglycemia is present.[110,141] Enteral feeding increases gut secretion of incretins (GLP-1 and GLP-2) that stimulate endogenous insulin secretion.[7]**

The rate at which the glucose concentration is increased in IV solutions, including intravenous nutrition, also may contribute. **Hyperglycemia is increasingly common at glucose infusion rates greater than 6 to 8 mg/kg/min (normal basal glucose utilization rates are 4 to 6 mg/kg/min).** The presence of illness (e.g., sepsis), treatment with corticosteroids, and RDS that requires mechanical ventilation are associated with increased risk for developing hyperglycemia, most likely because of increased circulating catecholamine and cortisol concentrations that lead to increased lipolysis and glycogenolysis and inhibit pancreatic insulin secretion and insulin action.

Several other etiologic factors must be considered in infants with hyperglycemia. **Increased blood glucose concentrations have been reported in association with sepsis.[16] Intravenous lipid infusions also contribute to hyperglycemia by simple mass action of competitive lipid carbon supply to the mitochondria[144] and by glycerol that is a component of IV lipid emulsions.[143] Such effects are worsened if given rapidly at rates of more than 0.25 g/kg/hr,** but current practice is to administer lipids at a slower rate.[164] Lipid oxidation in hepatocytes also produces cofactors (e.g., ATP, NADP, NADPH, acetyl Co-A) that activate and fuel gluconeogenesis.[58,113] **Methylxanthines are frequently used to treat apnea in preterm infants and may be a cause of hyperglycemia.** This problem has been well documented after theophylline overdose but may occur also with appropriate administration. One study, for example, found that blood glucose concentrations in infants with therapeutic theophylline levels were higher than in untreated control subjects, with glucose concentrations in the hyperglycemic range in two treated infants.[138] Neonates undergoing surgical procedures also are at increased risk for hyperglycemia, probably because of a combination of the large quantities of glucose-containing fluids and blood products that may be administered during the procedure and the effects of stress-related hormones. Infusions of catecholamines and glucocorticoids compound the effects of stress production of these hormones on inhibiting insulin secretion, promoting hepatic glucose production, and reducing peripheral insulin action and glucose intolerance.

Neonatal Diabetes

Neonatal diabetes is rare, and 40% to 50% of cases are due to *transient neonatal diabetes mellitus*

(TNDM). TNDM is associated with IUGR and may be difficult to distinguish from hyperglycemia due to increased levels of catecholamines and other stress hormones and related decreased insulin secretion and sensitivity. Genetic mutations or epigenetic anomalies in the chromosome region 6q24 have been identified in 70% of patients with TNDM.[132,151] In TNDM, unlike true diabetes mellitus, ketosis does not develop. Most cases self-resolve, but insulin therapy may be necessary. *Permanent neonatal diabetes mellitus* (PNDM) also occurs, although this is a rare disorder, with incidence estimated at 2 to 3 per 100,000 live births. Only about 25% of infants with PNDM have IUGR. Causes include mitochondrial diseases, pancreatic hypoplasia or aplasia, abnormal pancreatic glucokinase activity, and mutations of pancreatic K_{ATP} channel. Neonatal diabetes may be associated with other abnormalities including developmental delay, skeletal dysplasias, and intestinal atresia.

Prevention of Hyperglycemia

Recognition of those infants at risk for disturbances in glucose homeostasis is the most important step in preventing hyperglycemia. Hyperglycemia occurs most often in preterm infants receiving high rates of IV glucose. **In a VLBW infant, hyperglycemia may be avoided by starting IV glucose infusions at rates of 2 to 3 mg/kg/min and checking blood glucose concentrations frequently (as often as every 3 to 4 hours) while the infant continues to receive IV glucose.**[140] There is some evidence that **starting amino acid infusions shortly after birth in very preterm infants may limit the development of hyperglycemia,** perhaps by increasing insulin production and secretion and also by promoting protein turnover and its attendant glucose (energy) requirements.[17,22,156] As noted, introduction of **small-volume enteral feedings as soon as possible may also reduce the incidence or duration of hyperglycemia** in VLBW infants by stimulating incretin secretion and increasing glucose metabolism.[7,81]

Clinical Signs

Hyperglycemia usually is asymptomatic and most often is diagnosed on routine screening of the infant at risk. It should be suspected in any preterm infant, and is likely to be more exaggerated the more preterm the infant. It also should be suspected in infants who had hypoxic-ischemic conditions shortly before or during birth and in any sick or physiologically unstable infant.

If a problem with glucose homeostasis is suspected, documentation of the aforementioned data, history, physical examination, and clinical signs must reflect ongoing monitoring and measures taken.

LABORATORY DATA

Plasma (serum) glucose concentrations should be measured in any infant as soon as possible after starting IV dextrose (alone or as part of TPN). These measurements should be continued at reasonable frequencies depending on whether hyperglycemia is found and is very high or highly variable. During treatment, measurement continues until normal values are achieved and maintained for reasonable periods. Since hyperglycemia can persist in very preterm infants even after IV dextrose infusions have been discontinued, intermittent glucose concentrations should be measured for several days after stopping IV dextrose infusions or TPN. Persistent hyperglycemia has been associated with worse morbidities and even mortality and should not be allowed to continue. Enteral feeding is the best treatment, as it promotes secretion of incretins from the gut, which stimulate insulin secretion.

Treatment of Hyperglycemia

GLUCOSE

Most cases of hyperglycemia can be treated by reducing the neonate's IV glucose infusion rate. This approach, when combined with other measures such as early use of IV amino acids and early enteral feeding with reasonably rapid feeding advancement, commonly reduces glucose concentrations into more acceptable ranges within 24 hours. **Many LBW infants will tolerate glucose infusions at rates as low 4 mg/kg/min with normal glucose concentrations, although Zarif and colleagues[167] reported that more than 40% of infants weighing less than 1000 g had a blood glucose concentration higher than 125 mg/dL while receiving glucose at an average rate of 4.4 mg/kg/min.** VLBW infants with high fluid requirements resulting from large insensible

water losses through the skin may require a combination of water and glucose intake that could be administered only by using a hypotonic solution such as $D_{2.5}W$ to avoid hyperglycemia. **The use of a low glucose concentration in the IV infusate necessitates the addition of sodium** (e.g., $D_{2.5}W$ has approximately 130 mOsm/L, requiring the addition of sodium chloride to produce an isotonic solution with 280 mOsm/L), which may further complicate management of fluids and electrolytes. Another approach is to continue a lower fluid rate of IV dextrose infusion with D_5W but infuse sterile water through a gastric tube to meet fluid needs. A **VLBW infant needs adequate caloric intake (50–60 kcal/kg/day) to avoid a negative nitrogen balance and tissue catabolism. These needs often cannot be met without resultant hyperglycemia.** If the glucose is only mildly elevated (e.g., concentrations of 125–150 mg/dL) and the infant has no evidence of contributing adverse pathologic conditions, reducing the rate of IV glucose administration may not be necessary, as long as amino acid infusions and enteral feeding are increased, as they generally promote insulin secretion and incretin production and promote glucose utilization. There is little evidence, however, to determine whether this practice will lead to better or worse longer term neurodevelopmental outcomes. Regardless, such infants should have repeated glucose measurements made to ensure that the hyperglycemia resolves.

LIPID AND AMINO ACIDS

Intravenous lipid infusion rates can be decreased to help reduce hyperglycemia. This limits the contribution of FFAs produced by lipid metabolism that, on oxidation, generate energy to drive gluconeogenesis (acetyl CoA and reducing equivalents, NAD/NADH). Decreasing lipid supply also limits the competition of fatty acids with glucose for oxidation and the direct enhancement of gluconeogenic enzymes in the liver and thus the production of glucose. Limiting lipid supply also reduces the supply of glycerol, which is the primary support for gluconeogenesis in newborn infants. **As with reducing the glucose infusion rate, reducing lipid infusion rates also reduces energy supply.** The risks of reducing energy intake to lower glucose concentrations, versus those of the hyperglycemia itself, are uncertain.

Amino acid infusions should be started early to promote insulin secretion and enhance protein turnover with its obligatory energy (hence, glucose) requirements.[22,156] Amino acids do not contribute measurably to enhancing gluconeogenesis, even though they provide more substrate.[144]

INSULIN INFUSION

Because of the foregoing considerations, some authors have suggested the use of a **continuous insulin infusion in the infant who cannot tolerate infusion of glucose solutions with concentrations greater than 5 g/dL (e.g., D5W).**[18,46] **Infusion of insulin at rates of 0.2 to 0.8 mU/kg/min (0.01 to 0.05 U/kg/hr) for 12 to 24 hours may improve glucose tolerance.** However, insulin avidly binds to plastic IV tubing; thus the actual rate of insulin administration may be difficult to determine and may vary over time. Although various methods have been proposed, such as priming the tubing with insulin-containing solution or albumin, these have not been shown to be consistently effective.[149]

Hypoglycemia during administration of exogenous insulin can be avoided by starting with a low infusion rate (0.05 to 0.1 mU/kg/min) and increasing the rate by 10% to 20% every 60 to 90 minutes until the glucose concentration is less than 200 mg/dL. Blood glucose concentrations should be monitored every 15 to 20 minutes during initiation of the insulin infusion, and an IV glucose infusion should be maintained to avoid any abrupt changes in blood glucose concentration and to allow rapid correction of glucose concentration if it starts to fall below "normal" values. Use of **insulin infusion has been reported to improve tolerance to glucose infusions, resulting in increased carbohydrate intake and weight gain.**[4,15] **Most of the weight gain is fat,** however, and there is risk for fatty infiltration and secondary inflammation in the liver and heart when insulin and glucose infusions are maintained for long periods. Such insulin treatment inhibits glucose production, though not as readily as in adults.[27] The effect of insulin to promote glucose utilization is modest in very preterm infants, given the small amount of insulin-sensitive tissue (primarily skeletal muscle) per body weight. Acutely, **insulin infusion has been noted to increase lactate production, with lactate concentrations up to threefold greater than baseline, and may be associated with metabolic acidosis.** Administration of glucose and insulin at high rates also enhances CO_2 production, which might lead

to hypercarbia in infants with respiratory disease. Also, episodes of hypoglycemia can occur even with careful monitoring during insulin infusion. **The use of insulin to prevent hyperglycemia in neonates has been evaluated in a randomized prospective prophylactic study that showed no obvious benefit and considerable morbidity, particularly a significant increase in the incidence of hypoglycemic episodes.** The authors of this study and an editorial commentary concluded that **chronic insulin infusion cannot be recommended and must be used cautiously even in cases of acute hyperglycemia.**[15,78] This is especially true because there are no clinical studies that have demonstrated a cause-and-effect relationship between brief periods of neonatal hyperglycemia and adverse long-term outcomes, and long-term neurodevelopmental outcomes are not necessarily adversely affected by neonatal hyperglycemia in preterm infants.[158] **Theoretically, hyperglycemia can induce an osmotic diuresis, and close attention should be paid to fluid balance in the hyperglycemic infant.** However, this is rarely seen at blood glucose concentrations less than 400 mg/dL or when hyperglycemia occurs intermittently and for brief periods. Finally, as in hypoglycemia, efforts should be made to treat any underlying etiology, such as sepsis.

Two recent studies, one in neonatal lambs and one in **extremely preterm infants with chronic hyperglycemia, have shown reduced mortality when insulin was used to reduce plasma glucose concentrations.**[5,166] These studies did not include subjects who had their glucose concentrations lowered by other means. Thus, it remains unclear whether insulin itself has a specific beneficial effect on lowering mortality or whether it is just one approach to lowering glucose concentrations and avoiding their adverse effects. **A *Cochrane Review* of one study showed that insulin infusion versus reduced glucose infusion to treat hyperglycemia in ELBW preterm infants showed no difference between groups in all age/weight groups on death, sepsis, retinopathy of prematurity, necrotizing enterocolitis, intracranial hemorrhage, chronic lung disease, NICU days, or growth.**[104,134] **Insulin should be used with caution, therefore, and only when safer and more conventional approaches to lowering glucose concentrations have failed.**[69] Insulin actually makes the infant fatter and contributes to excess mitochondrial carbon load and production of reactive oxygen species. **Insulin does not increase glucose uptake by the brain or enhance neuronal growth or dendritic development**—in fact, it might do just the opposite (see later). **It does not increase linear growth or consistently increase lean mass growth when given in excess of normal physiologic doses;** positive effects are only found to a minimal extent when the insulin is accompanied by protein.

Complications of Hyperglycemia

Although there is no direct evidence, **hyperglycemia in the preterm infant has been postulated to increase the risk for IVH by causing rapid changes in osmolarity** with resultant rapid fluid shifts within the brain and germinal matrix. Increased mortality rate in hyperglycemic premature infants compared with their normoglycemic counterparts has been reported, although hyperglycemia may have been a marker for those infants with more severe illness rather than a direct cause of the increased mortality rate.[2] **Osmotic brain injury and death have occurred in infants accidentally infused IV with an erroneously high dextrose solutions, such as $D_{75}W$ rather than $D_{7.5}W$.** Increased morbidity may be seen in the form of greater difficulty with fluid and electrolyte management because use of dextrose-containing fluids must be limited and problems establishing adequate nutrition. Several studies also suggest **an association between hyperglycemia in ELBW infants and increased incidence of retinopathy of prematurity,**[29,55,111] perhaps due to increased production of reactive oxygen species and reduced angiogenesis and secondary neuronal necrosis, but no definitive cause-and-effect relationship has been demonstrated as of yet.

Complications of hyperglycemia are increasingly recognized in adults and children in ICUs, and many of the associated morbidities are seen in newborn infants even if not considered to be caused by hyperglycemia. Such morbidities include increased morbidity and mortality, impaired immunity and increased rates of infection, poor wound healing, suppressed autophagy, diminished cellular repair and organ recovery, and loss of skeletal and cardiac muscle. **Enteral feeding rather than continued IV feeding has been most successful in preventing or reversing these problems.** Similar evidence in

preterm infants is less clear. Other established effects of marked hyperglycemia are documented in preterm infants, including increased energy expenditure, increased O_2 consumption, increased CO_2 production with tachypnea, increased fat deposition in excess of lean mass, increased fatty infiltration with inflammation in the heart and liver, increased risk of deep venous thrombosis due to suppressed anticoagulant proteins and increased procoagulant proteins, risk of right ventricular dysfunction, interventricular septal hypertrophy, amplified sympathetic nervous and renin-angiotensin-aldosterone systems, increased health care–associated infections,[169] and accumulation of myocardial collagen and fibrosis from excessive production of free radicals.[24,114,118,147] There also is the **potential for increased bacterial sepsis with persistent hyperglycemia,** as bacteria thrive with excess glucose, leading to worse infections and death of the organism. **In the NICU, where bacterial infections are more common as causes of serious sepsis, normal to low-normal plasma glucose may be protective.**[165] **Hyperglycemia also worsens outcomes in infants with hypoxic ischemic encephalopathy, even more so than hypoglycemia.**[13] Perhaps more worrisome are animal studies that demonstrate marked adverse effects of chronic and marked **hyperglycemia in fetuses and neonates on neural development (reduced numbers of dendritic spines and synapse formation),**[74] and decreased neuronal density, increased oxidant status, and decreased antioxidant status in the brain along with increased mortality.[150] **Clinical studies in preterm infants also have shown that growth may or may not be affected (increased or decreased) with prolonged hyperglycemia in VLBW preterm infants, but linear growth is reduced,**[4] perhaps due to down regulation of the growth hormone axis, and such **poor growth is associated with reduced cognitive development.**[126] Most worrisome are continued reports of associations between severe hyperglycemia (two or more consecutive blood glucose concentrations greater than 216 mg/dL at least 3 hours apart) as part of **early enhanced TPN in ELBW preterm infants and increased mortality, as early as the first day of life and even after 7 days.**[140,161]

Infants with TNDM usually recover spontaneously within the first week; persistent insulin resistance is extremely rare. However, those infants with chromosomal mutations have an increased incidence of adult-onset diabetes later in life.[132] No neurologic sequelae have been directly attributed to the presence of transient hyperglycemia in these neonates.

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16 TOTAL PARENTERAL NUTRITION

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Total parenteral nutrition (TPN) support for critically ill newborns was first reported four decades ago.[44] However, in the modern era of neonatal care, TPN continues to be a critical aspect of intensive newborn care. Availability of **TPN has been one of the developments responsible for improved outcome of neonatal surgical patients.**[94,100,102] Increased survival of extremely preterm infants has provided new challenges for neonatal parenteral nutrition.[61] **Current evidence would suggest that early nutritional support is important to prevent postnatal growth restriction, which has been commonly recognized in these infants.**[40,45,61]

A neonatal service that uses TPN has the best results if it includes an experienced "nutrition team" comprising a neonatologist, surgeon, nutrition support nurse, pharmacist, dietitian, and social worker, with each member playing a vital role to make TPN a safe and effective therapy. This chapter discusses the nutritional needs of the high-risk newborn, specific indications for TPN, and guidelines for formulation and administration of intravenous (IV) nutritional solutions. An overview of mechanical, infectious, and metabolic complications is also presented with emphasis on prevention and early identification.

PHYSIOLOGY

Fuel Stores

During periods of fasting, tissue stores of energy provide the major source of fuel for the body. Carbohydrate is stored in the liver and muscle as glycogen. Stable blood sugar levels are maintained by hormonal regulation of glycogen production (glycogenesis) and breakdown to glucose (glycogenolysis). Newborns, particularly those who are growth restricted or preterm, have low glycogen stores and often have insufficient regulatory mechanisms.[118]

The body's greatest energy stores are in the form of fat, which provides a calorie yield of 9 kcal/g when metabolized. In addition to normal deposits of adipose tissue, newborns (and hibernating adult animals) have unique stores called brown fat. These stores, which are anatomically located between the scapulae, in the axillae and mediastinum, and around the adrenal glands, protect the body from hypothermia through nonshivering thermogenesis[91] (see Chapter 6).

Protein makes up lean body mass. Although protein generally is not used as an energy source postnatally, in fetal life, amino acids are oxidized apparently for energy.[122] This may be true for brief periods postnatally, but **extended periods of protein catabolism (breakdown of endogenous substrates), such as during times of starvation, may lead to body dysfunction**, as noted later.

The Effects of Insufficient Nutrition

The last trimester of gestation is a time of rapid fetal growth, with active transplacental transport of most nutritional substrates. **Preterm delivery interrupts the nutritional supply and abruptly results in a catabolic state, which, if prolonged, may alter growth potential.** It is unclear whether it is possible to achieve in utero growth rates for the postnatal preterm infant, but **reestablishment**

BLUE type highlights content that is particularly applicable to clinical settings.

of an anabolic state and maintenance of micronutrient sufficiency is necessary.[40,58,122] During this period of neonatal life, the rapidly growing brain is responsible for much of the nutritional requirements. Inadequate early nutrition may have irreversible effects on later neurodevelopmental outcomes.[79]

Postnatal growth restriction also is associated with neonatal medical complications, including apnea, ventilator dependence, and chronic lung disease.[36] Immune responses may be depressed with increased susceptibility to infection (see Chapter 22). Protein malnutrition is most frequently seen in extreme preterms and may contribute to poor growth potential and long-term morbidity in these infants.[36,122,123] Poor postnatal growth for most extremely low-birthweight (ELBW) infants has emphasized the need for additional strategies to improve nutrition for this population.[40,41,42]

One strategy is to initiate parenteral nutrition within the first hours after birth. Even though the exact benefits and harms are unknown, providing early, increased energy and protein support have been associated with improved short-term growth outcomes.[40] Longer-term outcomes, such as reductions in the incidence of common neonatal morbidities, increased brain growth, and improved neurodevelopmental outcomes, are more difficult to link directly to early parenteral nutrition. There is no evidence that early parenteral nutrition increases morbidity or mortality risks, but also unclear is the influence of early nutritional support on the incidence of childhood obesity and the risk for cardiovascular disease and metabolic syndrome in adults.[88]

Nutritional Requirements of the Neonate

CALORIC

Caloric requirements for preterm infants, including very-low-birth-weight (VLBW) and small-for-gestational-age (SGA) infants, are approximately 110 to 130 kcal/kg/day.[141] Caloric requirements for near-term and term infants are 90 to 120 kcal/kg/day. These estimates are based on enteral intake (see Chapter 17). Parenteral requirements are about 20% less, or approximately 80 to 100 kcal/kg/day. Factors affecting caloric requirements include the infant's gestational age, chronologic age, weight, activity level, body temperature, ambient temperature, underlying disease, and degree of stress. Infections, including nosocomial, may also contribute to additional caloric needs.[125] Resting energy expenditure is an estimate of the approximate range of basic energy needs and is approximately 45 kcal/kg/day in infants less than 900 g and 50 kcal/kg/day for infants larger than 1000 g.[141] Physical activity, which usually is infrequent in preterm infants, contributes less than 10% to the energy needs.[78]

However, in pathologic states, such as with repetitious seizures or neonatal abstinence syndrome, increased activity may increase caloric needs. An elevation of body temperature increases caloric expenditure by approximately 12% for each degree Celsius above 37.8° C (100° F). Metabolic demands of surgery and postoperative healing, or severe cardiac or pulmonary distress, may increase caloric requirements by as much as 30% and chronic failure to thrive by 50% to 100%. In addition, postnatal dexamethasone therapy may slow weight and linear growth rates and potentially may negatively affect brain growth.[31,36,90,140]

WATER

Water requirements vary with gestational and postnatal age (postconceptual age) and environmental conditions (e.g., care in an incubator versus radiant heat warmer, use of phototherapy) (see Chapter 14).

ELECTROLYTE AND MINERAL

Sodium requirements are minimal for the first days of life. After 1 week, the average requirement is 3 to 4 mEq/kg/day. Large renal losses (greater than 5 mEq/kg/day) may occur in very immature infants (less than 28 weeks of gestation) in the first weeks of life. Potassium and chloride requirements are approximately 2 mEq/kg/day and 3 to 4 mEq/kg/day, respectively. Glucosuria with resulting osmotic diuresis may increase sodium and potassium urinary losses.[49]

Calcium is an important cofactor in hemostasis, enzyme function, muscle contraction, and cell membrane stability. In the newborn, 98% of calcium is stored in the bone. The initial calcium requirement is 1 mEq/kg/day to maintain calcium homeostasis and to avoid irritability and tetany associated with low serum ionized calcium levels.

In utero, the accretion rate is 4 to 5 mEq/kg/day, which the growing preterm infant should receive in addition to adequate phosphorus and vitamin D to avoid osteopenia, rickets, and bone fractures.[134] Excess calcium intake may cause central nervous system (CNS) depression or signs of renal toxicity.

The phosphorus requirement for the growing preterm infant is 40 to 60 mg/kg/day (31 mg = 1 mmol). Bone contains 80% of the body's phosphorus. Low phosphorus intake causes increased renal calcium excretion and a depletion of bone calcium phosphate. **A calcium-to-phosphate ratio of 1.7:1 (mg:mg) or 1.3:1 (mmol:mmol) is recommended in short-term parenteral nutrition for preterm neonates.**[24] Low phosphorus intake or chronic furosemide diuretic therapy also may lead to hypercalciuria and nephrolithiasis.[29] Because phosphorus is a major constituent of cellular energy function (adenosine triphosphate, 2,3-diphosphoglycerate, creatinine phosphate), severe depletion may result in muscle paralysis, respiratory failure, and interruption of important cellular functions, such as the hemoglobin-oxygen dissociation curve and leukocyte activity.

Magnesium is essential for intracellular enzyme systems. The requirement is 0.25 to 0.5 mEq/kg/day.[7] Magnesium deficiency states mimic hypocalcemia, manifesting as irritability, tremulousness, tetany, and cardiac dysrhythmias. Magnesium excess may manifest as lethargy, hypotonia, and delayed stooling.

CARBOHYDRATE

During fetal life, glucose is the primary source of energy.[122] At birth, the preterm infant has only a small supply of glycogen, the storage form of glucose (equivalent to about 200 kcal of energy). **Glucose is particularly important for the CNS, because other substrates are not available.** Initially, a glucose infusion rate (GIR) of 6 mg/kg/min is sufficient to meet metabolic needs of the newborn infant. Requirements are greater for infants who are stressed (e.g., from sepsis or hypothermia) or hyperinsulinemic (e.g., infants of diabetic mothers or infants with Beckwith-Wiedemann syndrome).

With long-term parenteral nutrition, at least 50% of total caloric requirement should be provided as carbohydrate (GIR 8 to 10 mg/kg/min), generally as dextrose (calculated as 3.4 kcal/gm of hydrated carbohydrate). Preterm infants, especially ELBW patients, who receive early and higher amino acids in their parenteral nutrition, have been shown to have a decreased incidence of hyperglycemia requiring insulin treatment.[2] **To avoid metabolic consequences of excessive glucose loads, a GIR of more than 13 mg/kg/min (19 g/kg/day of glucose) should be avoided.**

PROTEIN

The quantity of daily nitrogen required by a term newborn infant, based on estimates from breast milk intake, is approximately 325 mg/kg/day (approximately 2 g/kg/day of protein).[8] Requirements for preterm infants are much higher, as indicated by in utero accretion rates during the latter half of pregnancy. At 28 weeks' gestation, the fetus requires 350 mg/kg/day of nitrogen. This figure declines to 150 mg/kg/day by term gestation. **When the estimated accretion rate is added to the obligatory postnatal nitrogen excretion, the requirement for a 28-week gestation preterm infant may be calculated to be approximately 495 mg/kg/day (3.1 g/kg/day of protein). If one assumes parenterally administered amino acids are converted to body proteins at 75% efficiency, the estimated parenteral amino acid requirement would be as high as 3.7 g/kg/day.**[47,125]

In fetal life, protein is actively transported from the mother's circulation across the placenta in quantities greater than needed for accretion, with the excess being oxidized by the fetus or placenta for energy.[121] Clinicians have found that increasing protein intake postnatally at all energy intake levels above 40 kcal/kg/day results in increased protein accretion. **Current evidence indicates that protein intake up to 4 g/kg/day is safe with no clinically significant increase in azotemia, acidemia, or hyperaminoacidemia.**[95] Although more studies are looking at higher amino acid administration, further investigations are needed to determine safe upper limits for maximum protein administration beyond that level.[27]

Studies have shown that administration of amino acids shortly after birth decreases protein catabolism, which is extremely important, particularly for VLBW infants.[47,71,121] Early amino acid administration is also associated with reductions in hyperkalemia and hyperglycemia.[21,27,92] **Based on the current evidence, providing VLBW**

infants with 3 g/kg/day of protein on the first day of life is safe.[41] Many NICUs have created a "stock" or "starter TPN (protein-containing) solution" to achieve the goal of providing 2 to 3 g/kg/day of protein to promote anabolism immediately after admission. Although current studies support the early use of parenteral protein nutrition, further investigation is needed to document the effect of this supplementation on post-NICU long-term growth and development.[88]

The quality of the infused amino acid mixture is important for efficacy and safety.[1] Although there is no formulation specifically for preterm infants, **pediatric solutions provide greater quantities of essential amino acids and result in plasma amino acid levels similar to those of postprandial breastfed infants.** An essential amino acid is one that cannot be synthesized in adequate quantity to meet the requirements for normal growth and development. The differentiation between essential and nonessential amino acids is not clear in newborn infants, because the ability to synthesize some amino acids may vary with the clinical situation or stage of maturity. Lysine and threonine are essential in their entirety. There is a high requirement for branched-chain amino acids (e.g., leucine, isoleucine, valine) in the growing newborn. These are metabolized primarily in skeletal muscle.[87,123]

Methionine is an essential sulfur-containing amino acid that is metabolized to cysteine and taurine. **For preterm infants of less than 32 weeks' gestation, cystathionase activity is insufficient for cysteine synthesis. Some investigators have found that cysteine supplementation results in greater nitrogen retention, and for this reason it is recommended for short-term supplementation for high-risk preterm infants, although the effects of prolonged use have not been fully investigated.[114]** Cysteine is not stable in amino acid solutions, so cysteine hydrochloride supplements must be added separately to the parenteral nutrition. Taurine is a nonprotein amino sulfonic acid that is converted from cysteine by cysteine sulfonic acid decarboxylase. Taurine concentrations are low in infants who have received nonsupplemented TPN infusions. **Taurine deficiency may have a detrimental effect on the developing nervous system.** Taurine is present in commonly used pediatric amino acids and **may prevent cholestasis in some newborns by more effectively conjugating bile salts and creating soluble end products.[116,130]**

Tyrosine is another amino acid that appears to be essential in the newborn period. It is present in small amounts in most amino acid solutions, although one manufacturer uses a soluble form, *N*-acetyl-L-tyrosine, which infants slowly metabolize to tyrosine.[101] Tyrosine is a byproduct of phenylalanine metabolism, so supplementation has an effect on the phenylalanine requirement. Histidine is considered to be an essential amino acid for newborns, with the lowest levels evident in preterm infants. Arginine may be essential only for the newborn with reduced arginine synthetase activity. This amino acid is thought to facilitate clearance of nitrogenous waste products by "priming the urea cycle." Use of amino acid infusate with insufficient arginine has been associated with hyperammonemia.[60] Glutamine also has been considered a conditionally essential amino acid, but no benefit was shown in randomized trials for parenteral glutamine in relation to mortality, incidence of necrotizing enterocolitis (NEC), or infection rates.[86]

Nonessential amino acids make up the largest percentage of the amino acid pool in the fetal body. The desired quantities of these amino acids for parenteral solutions are not known. It is thought that they should be provided in a balanced formulation. Pediatric solutions differ from adult solutions by providing glutamic acid and aspartic acid with lower glycine concentrations.[1,9]

FAT

Long-chain fatty acids are essential in the newborn for brain development and appear to be important for gene expression and other molecular mechanisms.[73] **Essential fatty acids (EFAs) include linoleic and linolenic and, in the newborn, arachidonic acid.[7]** Biochemical evidence of EFA deficiency may be seen in less than 1 week in VLBW infants receiving a deficient diet, and the administration of parenteral glucose and amino acids may accelerate these abnormalities.[119] EFA deficiency results in an imbalance in fatty acid production with an overproduction of nonessential fatty acids. **Clinical manifestations appearing at variable times after biochemical changes of EFA deficiency include scaly dermatitis, poor hair growth, thrombocytopenia, failure to thrive, poor wound healing, and increased susceptibility to bacterial infection. Clinical manifestations of EFA deficiency can be avoided if 3% to 4% of caloric intake is supplied as linoleic acid (approximately 0.5 g/kg/day of soybean-based IV lipid).[62]**

In addition to preventing EFA deficiency, lipid emulsion is a concentrated source of nonprotein calories, which promotes nitrogen retention. Preterm infants appear to have limited capability to oxidize fatty acids. This limitation may be related to deficiency of carnitine, which, in the form of acylcarnitine, promotes transfer of fatty acids into mitochondria, where oxidative metabolism occurs. However, a systematic review of randomized studies found no benefit for carnitine supplementation on weight gain, lipid utilization, or ketogenesis, so routine supplementation is not recommended.[28]

VITAMINS

The biologic role of vitamins, signs and symptoms of deficiency states, and recommended oral requirements are available in Chapter 17. Although there is not a multivitamin formulation specifically for preterm infants, the American Society for Clinical Nutrition (ASCN) has suggested that **preterm infants receive 40% to 65% of the daily recommended vitamin doses for term infants and children.**[110] These guidelines may result in excessive intakes of some water-soluble vitamins, particularly pyridoxine and riboflavin. Although preterm infants have limited stores of lipid-soluble vitamins because of low body fat, potential toxicity from excess administration is a concern. **Vitamin A is a lipid-soluble vitamin that is important for tissue growth, protein synthesis, and epithelial differentiation.** Vitamin A may be administered more effectively in lipid emulsion rather than dextrose amino acid solutions.[7,38] However, **vitamin A supplementation has been proven to be effective in lowering chronic lung disease rates only when given by intramuscular injections three times per week.**[39,128]

Vitamin E is a lipid-soluble biologic antioxidant that is deficient in preterm infants. However, **daily parenteral intake of 2 to 3 mg/kg has been associated with serum levels generally in the recommended range of 1 to 2 mg/dL.** Pharmacologic doses have been tried unsuccessfully for prevention of bronchopulmonary dysplasia and retinopathy of prematurity, and IV high-dose vitamin E may increase risk for sepsis.[25] Therefore, aiming for tocopherol levels greater than 3.5 mg/dL is not recommended. **Vitamin K production by intestinal flora is impaired by insufficient enteral feedings and use of broad-spectrum antibiotics in infants on long-term TPN.** Vitamin K is provided at the recommended dosage through parenteral pediatric multivitamin solutions.[7]

TRACE MINERALS

Although trace minerals are relatively scarce (less than 0.01% of the weight of the human body by definition), they play an important role in normal growth and development.[50] Early supplementation of selenium has shown a reduction in sepsis events.[3] Deficiencies of both zinc and copper have been identified in infants on long-term TPN not supplemented with trace minerals. Postsurgical infants with ongoing gastrointestinal losses may have negative zinc balance even if given usual zinc replacement in TPN.[109]

Manifestations of deficiency and recommendations for intake are provided in Chapter 17. Parenteral recommendations are lower than enteral, which are based on physiologic requirements. **Preterm infants receiving breast milk and not receiving frequent blood transfusions should receive 2 mg/kg/day of enteral iron supplementation starting by 1 month of age. For term, breastfed infants not receiving frequent blood transfusions, enteral iron supplementation at 1 mg/kg/day may be necessary by 4 months of age.**[12] **Infants receiving erythropoietin therapy need additional iron supplementation, given either enterally or parenterally.**[84,98]

INDICATIONS

Parenteral nutrition, including protein supplementation and carbohydrate at basal levels, should begin on the first day of life for preterm infants not being fed, as well as for other newborns who are not likely to tolerate enteral feedings within a few days. A preterm infant has limited nutritional stores and quickly develops negative protein balance without early supplementation. TPN continues to be a critical aspect of long-term management for neonatal surgical patients.[102] **When parenteral nutrition solutions are administered through a peripheral vein, caloric intake is limited because the fluid osmolarity should not exceed 900 mOsm/L, which results in relatively limited concentrations of carbohydrate (less than 12.5% dextrose) and amino acids (less than 3%).**[24] **Some recommend even more conservative limits on osmolarity**

for peripheral lines (500 mOsm/L).[53] When used with lipid emulsions, peripheral parenteral nutrition (PPN) allows caloric intake of about 70 to 80 kcal/kg/day and protein intake of 2.5 to 3.0 g/kg/day. This level of nutritional intake prevents catabolism and, in some cases, results in moderate growth. PPN usually is adequate for term newborns with transient bowel disease (such as may be seen after the repair of a small omphalocele) or for larger preterm infants whose enteral feedings are delayed for a few days. PPN is commonly used to supplement nutrition in newborns who are receiving partial enteral feedings. When caloric needs can be met by PPN, this route is preferred to the central route, because the catheter insertion risks of central catheters are avoided and generally, the risk for infection is less.

If parenteral nutritional duration is longer than 1 week, administration of TPN solution through a central line is recommended. The placement of a central line for parenteral nutrition allows a higher carbohydrate load to be used, giving more calories with less fluid. In preterm infants at risk for a patent ductus arteriosus and pulmonary edema, diminishing fluid intake and improving nutritional status may be important aspects of management.

Specific indications for TPN by a central catheter include the following:

- ELBW infants (less than 1000 g birth weight) and others who do not tolerate a significant volume of enteral feeding within the first week of age or who cannot receive adequate caloric intake by PPN
- Infants who have had gastrointestinal surgery and will have a significant delay in enteral nutrition, such as those with a gastroschisis, bowel resection after NEC, or meconium peritonitis
- Infants with chronic gastrointestinal dysfunction, such as intractable diarrhea

DATA COLLECTION

Monitoring Growth

Weight loss or insufficient weight gain is the initial effect of inadequate caloric intake. Linear growth, although less affected, is diminished after long periods of poor nutrition. Because of "brain sparing," head circumference growth is the least affected. Measurements should be obtained in a standardized fashion and recorded weekly.

Fetal weight gain in utero at each week of gestation is currently used as the standard to assess adequacy of postnatal growth. In the midtrimester (24 to 27 weeks' gestation), expected weight gain is 1.5% of body weight.[122] Charts are available to monitor postnatal growth rates based on data from a large preterm population, although for long-term monitoring, use of growth curves from normal populations, which are available from the World Health Organization (WHO), may be more appropriate.[133]

Minimum monitoring of growth should consist of the following:

- Weigh daily, or more frequently in ELBW infants with rapidly changing extracellular fluid status. Maintenance of a thermostable environment with minimal handling of ELBW infants can be achieved through the use of in-bed scales. Strict attention to consistency of technique during the weighing process is essential to obtain accurate, reliable measurements.[127] Monitoring weight gain on a weekly basis in grams per kilogram of weight gained daily (g/kg/day) may help in reducing postnatal growth restriction and positively affect long-term neurodevelopmental outcome. An ideal rate of weight gain for ELBW infants appears to be 18 to 21 g/kg/day.[46]
- Measure length weekly.
- Measure head circumference weekly.

Biochemical Monitoring

In addition to anthropometric measurements, biochemical parameters may be monitored to assess nutritional adequacy. Periodic assessment of calcium, phosphorus, and alkaline phosphatase levels is important to detect metabolic disturbances associated with osteopenia.[134] Tests for protein malnutrition include serum total protein, albumin, transferrin, retinol-binding protein, and transthyretin (prealbumin); the latter two are suggested primarily for preterm infants.[8,51] Routine clinical use of these measurements awaits greater definition of normal variation and independent effects of systemic illness and medications.

Biochemical monitoring of the infant's physiologic status is necessary to avoid complications

TABLE 16.1 METABOLIC MONITORING FOR INFANTS RECEIVING PARENTERAL NUTRITION

	FREQUENCY	
VARIABLE	ACUTE	STABLE
Electrolytes, BUN	Daily	2×/wk
Calcium, phosphorus	Weekly	Biweekly
Alkaline phosphatase	—	Biweekly
Serum glucose screen	q8hr	Daily
Urine glucose	q8hr	Daily
Hemoglobin/hematocrit	Daily	Weekly
Liver function:		
Bilirubin	2×/wk	PRN
Transaminase	Weekly	Biweekly
Triglyceride*	—	Weekly

*When on lipid emulsion.
BUN, Blood urea nitrogen; *PRN,* as needed.

of TPN. Usefulness of the laboratory data should be balanced with the economic costs and risks from iatrogenic blood losses for the infant (Table 16.1).

When serum electrolyte levels are abnormal, urinary electrolyte levels may be useful to clarify sodium and potassium requirements (e.g., if body sodium is depleted, low urine concentration would be expected).

TREATMENT

Vascular Access

UMBILICAL ARTERY CATHETERS AND UMBILICAL VEIN CATHETERS

Umbilical artery catheters (UACs) and umbilical vein catheters (UVCs) are commonly placed in sick newborns to provide vascular access for IV fluids, blood samplings, and blood pressure monitoring. Because of the risks for thromboembolic and infection complications, these lines generally are removed as soon as possible when no longer needed. **Optimally UACs should not be left in place longer than 5 days, although UVCs can be used up to 14 days if managed aseptically.**[15,37,51]

PERIPHERAL AND MIDLINE CATHETERS

If continued venous access is necessary after this time, a peripheral, midline, or peripherally inserted central catheter (PICC) can be placed. The type of line used is determined by the anticipated length of time needed and the osmolarity of the substances to be infused.[53]

Peripheral IV lines are indicated for short-term IV access. A midline catheter, which is threaded to the proximal portion of an extremity or neck, can provide longer IV access than a peripheral IV line when prolonged peripheral strength TPN is indicated. Midline catheters appear to be associated with lower rates of phlebitis than short peripheral catheters and with lower rates of infection and cost than central lines.[77]

PERIPHERALLY INSERTED CENTRAL CATHETERS

A PICC line can provide maximal nutritional intake when long-term parenteral access is necessary.[4] Percutaneous placement of a 1.9-Fr to 3.0-Fr Silastic (silicone) or polyurethane catheter can be performed routinely in even the smallest of neonatal patients by trained nurses and physicians.[137] The catheter usually is placed in the antecubital or axillary veins in the arms, but leg, scalp, or external jugular veins may be used to achieve central access. Veins that may be needed for percutaneous central line placement should not be sites for routine venipuncture (see Chapter 7).

Percutaneous line placement involves stabilization of the vein, maximum barrier precautions (sterile gloves, gown, large drape, masks), and antiseptic preparation of the skin with 2% chlorhexidine or povidone-iodine and alcohol product.[15,72,137] Infrared vein detectors or ultrasound may be used as adjuncts to identify appropriate veins for PICC cannulation.[26,93] Fully equipped prepackaged kits are available for this procedure from a number of manufacturers. Most kits include an insertion needle that is used to puncture and tunnel through the subcutaneous tissue before entering the vein. Once the needle is within the vein, the catheter, which has been flushed with heparinized saline solution, is passed through the needle into the vein and advanced to a premeasured distance, which is the estimated location of the superior vena cava.54 The catheter tip position should be documented radiographically. The addition of heparin to IV fluids is commonly used by practitioners to prevent occlusion of vascular catheters. However, there is no indisputable evidence for this practice.[106,107]

BROVIAC CATHETER

Large-bore Silastic catheters (Broviac) are placed surgically in infants in whom the percutaneous method is not successful and long-term access is anticipated. Generally, the catheters are placed in the internal or external jugular veins or common facial vein by cutdown and threaded to a central venous site but can also be placed via the femoral vein. The distal end is tunneled subcutaneously and exited through the anterior chest wall or thigh if placed in the leg.[89] The catheter must be secured and dressed under sterile conditions.

OTHER VASCULAR ACCESS OPTIONS

Other sites that may be used for TPN infusion on a short-term basis include subclavian, jugular, and femoral veins. Some centers use a UVC for short-term parenteral nutrition when another site is not feasible.

Composition of Infusate

CARBOHYDRATE

The prime source of calories for the neonate usually is dextrose. Peripherally, dextrose fluids up to 12.5% solution can be used. When central access is obtained, more concentrated dextrose (up to 30%) can be utilized. The glucose load is increased if either the infusion rate or glucose concentration of the infusate is increased. **Too rapid an increase in glucose load may exceed an infant's carbohydrate tolerance and result in hyperglycemia. A rapid decrease in the infusion rate or the glucose concentration of the infusate may result in hypoglycemia.**

When calculating caloric intake, use the following:

$$1\,\text{g dextrose} = 3.4\,\text{kcal}$$

or

$$100\,\text{mL/kg of } D_{10}W = 34\,\text{kcal/kg}$$

or

$$100\,\text{mL/kg of } D_{30}W = 102\,\text{kcal/kg}$$

The glucose infusion rate (GIR) can be calculated as follows:

$$\text{GIR}\ (\text{mg/kg/min}) = \frac{[\text{g glucose/day} \times 1000}{1440(\text{min/day})]} \Big/ \text{weight}(\text{kg})$$

Endogenous glucose production is approximately 4 mg/kg/min. Parenteral nutrition infusions should start with a GIR between 5 and 6 mg/kg/min for VLBW and ELBW infants.[126] Daily increases in dextrose concentration or fluid volume to increase carbohydrate administration by 2 mg/kg/min usually are tolerated. **ELBW infants may be carbohydrate intolerant, and initial GIR should be lower (4 or 5 mg/kg/min) for these infants.** An insulin infusion may be considered for ELBW infants experiencing persistent hyperglycemia with physiologic glucose infusion rates.[138] **Glucose infusion rates should not exceed 13 mg/kg/min unless severe hypoglycemia is ensuing. Blood glucose determinations and screening for glucosuria should be performed several times each day when glucose delivery is initiated or altered.**

LIPIDS

Traditionally lipid emulsion products have been derived from soybean oil. Newer lipid emulsion products contain a mix of soybean oil, fish oil, medium chain triglycerides, and olive oil. Soybean oil lipid emulsion at a rate of 0.5 to 1 g/kg/day is sufficient to prevent EFA deficiency, but additional lipids should be provided to supplement nonprotein caloric intake and support growth.[122] **When mixed oil lipid emulsions are used, a minimum of 2 gm/kg/day may be necessary to prevent EFA deficiency. Lipids should never make up more than 50% of total caloric intake. Fat emulsions should be given cautiously, beginning with 0.5 to 1 g/kg/day and advanced 0.5 g/kg every 1 to 2 days as tolerated to 3 g/kg/day maximum.** Fat emulsions are available as either 10% or 20%, but the 20% concentration is universally used for VLBW infants, because its lower phospholipid concentration results in lower plasma levels of triglyceride and cholesterol and less fluid administration (Table 16.2).[96]

Emulsified fat particles are similar in size and metabolic rate to naturally occurring chylomicrons. Most are cleared through passage in the adipose and muscle tissue. The capillary endothelial lipoprotein lipase hydrolyzes triglycerides and phospholipids, generating free fatty acids (FFAs), glycerol, and other glycerides. Most of the FFAs diffuse into the adipose tissue for reesterification and storage. A small portion circulates to be used by other tissues for fuel or for conversion by the liver into

TABLE 16.2 COMPOSITION OF FAT EMULSIONS

COMPOSITION	INTRALIPID (BAXTER) 20%	LIPOSYN II (HOSPIRA) 20%	SMOF (FRESENIUS KABI) 20%
Fatty Acid Distribution (%)			
Linoleic acid	53	54.5	19.5
Oleic acid	24.5	22.4	29
Palmitic acid	10.5	10.5	9.5
Linolenic acid	7.5	8.3	2.5
Stearic acid	3.4	4.2	2.8
Components (grams/100 mL)			
Soybean oil	20	20	6
Egg phospholipids	1.2	1.2	1.2
Glycerin	2.25	2.5	2.5
Caloric contents (kcal/dl)	200	200	200
Osmolarity (mOsm/L)	260	292	270

very-low-density lipoprotein. **Extremely preterm and SGA infants with decreased adipose tissue have prolonged clearance of fat emulsions. In general, because complications of lipids are related to delay in clearance, lipids should be infused over a 24-hour period to provide the lowest hourly rate.**[94] Infusion rates faster than 0.2 g/kg/hr for lipid infusions have been associated with hyperlipidemia.[126] The rate-limiting step for lipid clearance is the metabolism by lipoprotein lipase. The use of heparin stimulates the release of this enzyme and may enhance clearance of IV lipids. Carbohydrate also must be administered with fat to facilitate fatty acid oxidation and to promote FFA clearance.

AMINO ACID SOLUTION

Multiple amino acid solutions are available for neonatal and infant parenteral use. Each solution is sterile, is hypertonic, and contains crystalline amino acids. Each solution provides a mixture of essential and nonessential amino acids and may or may not contain taurine and a soluble form of tyrosine. The amino acid formulation provides a well-tolerated nitrogen source for nutritional support. The essential amino acids typically found in formulations are leucine, isoleucine, lysine, valine, histidine, phenylalanine, threonine, methionine, tryptophan, and cystine. The nonessential amino acids that are typically included are alanine, arginine, proline, glutamic acid, serine, glycine, and aspartic acid. The composition of amino acid varies by manufacturer.

A minimum quantity of energy substrates must be provided for effective utilization of parenteral protein. For ELBW infants, approximately 40 kcal/kg/day of carbohydrates or fat and 1.5 g/kg/day of protein are necessary for resting metabolic needs to prevent catabolism. However, urinary protein losses are greatest for preterm infants, so additional supplementation is needed to prevent protein deficits. **For each gram of protein provided above the basal amount, approximately 10 kcal of nonprotein energy is needed.**[41,47,122]

Contraindications to amino acid administration include untreated anuria, hypersensitivity to the solution, or inborn errors of metabolism, including those involving branched-chain amino acid metabolism, such as maple syrup urine disease and isovaleric acidemia.

ELECTROLYTES

Sodium and potassium may be supplied with chloride, acetate, or phosphate anions. The daily chloride requirement is approximately 3 mEq/kg/day and should be balanced with

acetate to avoid alkalosis or acidosis (acetate is converted to bicarbonate). Amino acid preparations also supply anions that must be recognized to calculate a balanced anion solution. For example, TrophAmine and Premasol supplies approximately 1 mEq of acetate per gram of protein. On the other hand, cysteine addition to the TPN solution reduces the pH, necessitating buffering with acetate.

MINERALS

Phosphorus may be provided as sodium or potassium phosphate. Calcium may be provided as 10% calcium gluconate (9.7 mg of elemental calcium/100 mg of salt). Both calcium gluconate and potassium phosphate have relatively high levels of aluminum and should be used judiciously for chronic TPN in infants with renal dysfunction (see discussion of aluminum toxicity under Trace Elements later in this chapter). When preparing a solution with both calcium and phosphate, care must be taken to avoid calcium phosphate precipitation, which may limit the intake of these important minerals. Magnesium is supplied as magnesium sulfate.

If one is using a potassium phosphate solution at pH 7.4, 4.4 mEq of potassium supplies 93 mg of elemental phosphorus (3 mM). When a solution of sodium phosphate is used at pH 7.4, 4.0 mEq of sodium is given with each 93 mg of elemental phosphorus.

CALCIUM

- **Because of increased risk for precipitation, calcium chloride generally should not be used (but may be considered for an infant at risk for aluminum toxicity).**
- **An elevation in ambient temperature, increased storage time, rise in pH, and decrease in protein or glucose concentration may increase the likelihood of precipitation. The addition of cysteine, which lowers solution pH, may enhance calcium and phosphate solubility.**[9]
- **When one is preparing the solution, calcium and phosphate salts should be added separately, but not in sequence, during the last stages of solution mixing. The solubility of the added calcium should be calculated from the volume at the time the calcium is added, not the final volume.**
- **The use of a physiologic ratio of calcium to phosphorus (1.8:1) in the TPN solution allows increased concentration of these minerals.**[97,114]

VITAMINS

A preparation approximating the American Medical Association's recommended formulation of IV vitamins is available (MVI-Ped). **The daily recommended dose is 1.5 mL/day for infants weighing less than 1 kg, 3.25 mL/day for those infants who weigh 1 to 3 kg, and 5 mL/day for infants weighing greater than 3 kg.**[85]

TRACE ELEMENTS

Zinc is supplied as zinc sulfate. Serum zinc levels usually approximate the maternal levels at birth and decline over the first week of life. **Zinc supplementation should be considered from the time parenteral nutrition is initiated.**[139] It may be important to initiate zinc intake earlier in neonates with intestinal loss, such as after gastrointestinal surgery.

Copper is supplied as cupric sulfate. Approximately two thirds of stored copper is accumulated during the last trimester. Therefore, a preterm infant may need early supplementation, but a term infant has adequate hepatic stores for at least several weeks. Because copper is excreted through the biliary system, this mineral should be decreased by 50% or removed from parenteral fluids for infants with cholestasis.[85]

Selenium, manganese, and *chromium* salts are commonly provided in long-term parenteral nutrition. **Supplementing very preterm infants with selenium is associated with reduction in sepsis.**[3] Manganese supplementation should not be provided to infants with cholestasis. The chromium dose may be reduced or discontinued in an infant with impaired renal function. Some studies have suggested that manganese and chromium should not be provided in parenteral nutrition due to the degree of cross contamination of these two trace elements in other parenteral nutrition products.[57,139]

Traces of aluminum are incorporated into parenteral solutions during processing.[70] Although aluminum is not known to have a physiologic role in the body, high aluminum levels have been associated with bone disease, encephalopathy, anemia, and hepatic cholestasis and may contribute to neurodevelopmental damage in preterm infants on chronic parenteral nutrition.[18] **Infants with disturbance of renal clearance are at greatest risk for aluminum loading.** Although the U.S. Food and Drug Administration (FDA) requires manufacturers to report the aluminum content of parenteral products, a recent Canadian study found that TPN remains

a significant source of aluminum toxicity.[56] Thirty samples of TPN in the same hospital showed that although the FDA advises the maximum exposure to aluminum be under 5 mcg/kg/day, aluminum contamination in TPN for infants younger than 30 days of age was three times higher than the FDA advisory.[56] **Clinicians should attempt to reduce aluminum intake and should monitor levels for infants at highest risk.**[6]

Table 16.3 outlines a suggested composition for a TPN solution (guideline only). Even in the most knowledgeable hands, accurate calculation and ordering of parenteral nutrition for preterm or ill infants is a complex task. **Online TPN ordering programs are available in many units to assist the clinician with this task. Use of such programs has been shown to decrease order entry errors** and are cost effective.[76,80] The Case Study illustrates considerations in writing orders for TPN solutions.

Preparing the Solution

Solutions should be prepared in the hospital pharmacy under a laminar flow hood in a work area isolated from traffic and contaminated supplies. There should be quality control checks to monitor for sterility breaks in equipment, personnel, environment, and solutions.

Because many additives potentially can be insoluble in combination, a mixing sequence should be established that separates the most incompatible ingredients. Storage increases the risk for microbial contamination; therefore **TPN solutions should be prepared on the day they are needed.**[82] **However, to be able to provide an amino acid infusion to preterm infants immediately after admission, some units maintain a "stock" amino acid solution (10% dextrose with 2 to 3 g of amino acids per 100 mL).**[119]

Administering the Total Parenteral Nutrition Solution

Proper administration of the TPN solution is as important as its preparation in preventing complications. The label on the solution always should be checked to correctly identify the patient, using at least two identifiers, and to verify current formulation order.

TABLE 16.3 SUGGESTED COMPOSITION FOR DAILY INTRAVENOUS NUTRITION REGIMEN

COMPONENT	DAILY AMOUNT
Calories	
Dextrose 3.4 kcal/g	10–15 g/kg
Lipids 2.0 kcal/mL (20%) solution	1–3 g/kg
Protein (6.25 g protein = 1 g N_2)	3.5–4 g/kg
Electrolytes	
Sodium	3 mEq/kg
Potassium	2–3 mEq/kg
Chloride	3–4 mEq/kg
Acetate	3 mEq/kg
Phosphate	2 mM/kg
Calcium	3 mEq/kg
Magnesium	0.3 mEq (range 0.25–0.5 mEq/kg) or 20 mg/kg (range 10–40 mg/kg) of elemental magnesium
Vitamins	
MVI-Ped	
<1 kg	1.5 mL/day
1–3 kg	3.25 mL/day
>3 kg	5 mL/day
Trace Elements	
Zinc (zinc sulfate)	
<3 kg	400 mcg/kg/day
≥3 kg	250 mcg/kg/day (Max of 4 mg/day)
Copper (cupric sulfate)	20 mcg/kg
Manganese sulfate	5 mcg/kg
Chromium chloride	0.2 mcg/kg
Selenium	2 mcg/kg

Standardized procedures must be established to avoid infectious complications from solution contamination. **Solutions on the nursing units may be returned to the pharmacy for additives before hanging, but no additives should be placed in the solution once it is hanging. The bag or bottle**

CASE STUDY

The following case example illustrates considerations in writing orders for total parenteral nutrition (TPN).

History

A male infant born at 26 weeks of gestation at 900 g is now 10 days old and unable to be fed because he has developed necrotizing enterocolitis (NEC). Because there will be a prolonged delay in enteral alimentation, a central vein catheter is placed for TPN. He is currently receiving $D_{10}W$ at 140 mL/kg with maintenance electrolytes. His current weight is 850 g. Serum electrolytes and blood glucose are normal. He is receiving continuous infusion pain medications and vasopressors that are equal to 21 mL/kg/day of fluid. The approach to calculating TPN requirements is as follows.

Caloric Requirement

Because the patient has already had a significant postpartum period without adequate nutrition, achieving caloric intake necessary for growth is a very important part of his care. The infant will probably require 100 kcal/kg or more for tissue repair and growth. We will begin with approximately 60 to 70 kcal/kg **(the birth weight is used until weight gain is established)** and advance the intake daily to reach this level.

Carbohydrate

Initially, a dextrose load just above what has been previously tolerated should be used. Thus the patient may receive $D_{12.5}W$ at approximately 140 mL/kg/day; the volume could vary depending on the infant's fluid requirements. When TPN is ordered, carbohydrate amount should be ordered as glucose infusion rate (GIR) rather than percent dextrose to minimize errors.[85] This represents:

$$12.5\text{g/dl} \times 140\text{ml/kg} = 17.5\text{g glucose/kg}$$

$$17.5\text{g glucose/kg} \times 3.4\text{kcal/g glucose} = 60\text{kcal/kg}$$

Fat

Lipid emulsion should be added to increase the caloric intake, starting with 1 g/kg/day.

$$5\text{mL/kg 20\% lipid emulsion (1.0g)} \times 2\text{kcal/mL} = 10\text{kcal/kg/day}$$

Thus the total nonnitrogen calories on the first day of TPN is 70 (60 + 10).

Protein

Provision of protein nutrition is critical to this preterm infant for growth and to repair damaged tissues. The initial amino acid replacement is 2.5 to 3 g/kg/day.

Electrolytes

The patient should receive maintenance sodium ion (approximately 3 mEq/kg) and potassium ion (2 to 3 mEq/kg) unless there are excessive renal or gastrointestinal losses.

Anions

Balancing anions is the next consideration. The 3 g/kg of amino acids, if given as TrophAmine, adds approximately 3 mEq/kg of acetate to the solution (1 mEq acetate/1 g amino acids). If 3 mEq/kg of potassium is provided as potassium chloride, the solution has balanced anions. Giving 3 mEq/kg of sodium as sodium phosphate provides approximately 2.2 mM/kg of elemental phosphorus:

$$(3\text{ mM } PO_4/4\text{mEq}Na^+) = (3\text{ mEq } Na^+/\text{kg}) = 2.25\text{ mM } PO_4$$

Minerals, Vitamins, and Trace Elements

Calcium, magnesium, phosphorus, vitamins, and trace elements should be ordered at this point. Calcium initially should be started at 2 to 3 mEq/kg/day but may be increased as tolerated with growth to 4 to 5 mEq/kg/day.

Use of an online TPN ordering program may assist the clinician by automating many of these calculations.[76]

TPN Orders

Thus the TPN orders would be written for this patient as follows:

Total Fluids = 140 mL/kg/day
Nutritional Volume = 140 mL/kg/day
Fat Emulsion Order: 1 g/kg/day to run at 0.19 mL/hr for 24 hours
TPN Order: 135 mL/kg/day = 5.1 mL/hr

TPN Order	Ordered Components
Glucose infusion rate (GIR)	4 mg/kg/min
Amino acids	3 gm/kg/day
Cysteine	40 mg/gram of amino acids
Potassium chloride	2.8 mEq/kg/day (2.8 mEq/kg/day K^+; 2.8 mEq/kg/day Cl^-)
Sodium phosphate	2.8 mmol/kg/day (3.7 mEq/kg/day Na^+; 2.8 mmol/kg/day phosphate)
Calcium gluconate	2.8 mEq/kg/day
Magnesium sulfate	0.3 mEq/kg/day
Multivitamin	1.5 mL/day
Zinc	400 mcg/kg/day
Copper	20 mcg/kg/day
Manganese	5 mcg/kg/day (some would not add manganese due to cross contamination of other TPN products)

CASE STUDY

TPN Order	Ordered Components
Chromium	0.2 mcg/kg/day (some would not add manganese due to cross contamination of other TPN products)
Selenium	2 mcg/kg/day

Progression

On subsequent days, the dextrose concentration and lipids would be advanced slowly to increase the caloric intake to requirement as tolerated. The quantity of protein would also be increased to about 4 g/kg/day.

of TPN solution should be changed every 24 hours, and the tubing administration sets should be changed no more frequently than every 72 to 96 hours. Lipid emulsions and tubing should be changed every 12 to 24 hours.[13,15,53,72,81,85] **Tubing for lipid administration should include a 1.2 micron filter. Polyvinyl chloride tubing and IV bags containing phthalates should be avoided to reduce potential toxicity from plasticizers.**[48,120]

Exposure of TPN to light generates peroxides, which induce vasoconstriction and oxidant stress associated with bronchopulmonary dysplasia. Photoprotection of bags, syringes, and tubing used to deliver TPN and lipids may reduce the oxidant effect on the lungs and mesenteric blood flow. Light shielding also appears to diminish oxidative stress and alterations of lipid metabolism, resulting in lower levels of triglyceride and better substrate delivery. Amber-colored tubing may be used for this purpose.[32,52,66,67]

Changes in TPN infusion rates result in changes in glucose delivery to the newborn and may lead to hypoglycemia or hyperglycemia if the glucose homeostatic mechanisms do not adjust fast enough. **Reactive hypoglycemia may occur if the glucose load is abruptly reduced or discontinued,** such as from loss of vascular access or rapid decrease in dextrose concentration or infusion rate.[10] **Parenteral nutrition solutions must infuse at a constant rate via an infusion pump. Infusion rates should not be rapidly increased or decreased. If the parenteral nutrition infusion is suddenly discontinued because of a clotted catheter or accidental removal, an appropriate solution with dextrose should be infused via a peripheral vein and blood glucose should be monitored closely.**

Use of parenteral nutrition may increase an infant's risk for hyperglycemia during surgery. Because rapid fluid infusions may be necessary during operative procedures, the TPN solution should be discontinued and replaced with a physiologic infusate during the perioperative period. After surgery, TPN should be as when the patient is euglycemic, with recent evidence of early postoperative protein tolerance and improved protein balance.[100]

Tapering of the TPN solution occurs as the infant begins to tolerate enteral feedings. When the patient is taking approximately two thirds of the necessary calories enterally, the central line may be removed.

Administering Fat Solution

Rapid infusion of the fat emulsion may exceed its clearance rate from the body and accentuate complications; therefore fat emulsions should not be infused faster than 0.2 g/kg/hr.[7,96] Lipids generally are given through a Y-site connection to bypass the filter in the TPN line or may be given through a separate venous site. However, some hospitals use a combined dextrose, amino acid, and lipid solution known as three-in-one or total nutrient admixture (TNA).[19,110] **A 1.2 micron filter is used with this solution to remove certain drug precipitates (Ca/PO_4), air, and Candida species but is not effective in removing bacteria.** The decision to use TNA should be approached with caution in infants. Lipid emulsions increase the pH of the TPN solution, limiting the amount of calcium and phosphorus that can be delivered because of the risk for precipitation. Precipitates are particularly difficult to detect in TNA, which is a milky solution. High concentration of calcium and low pH of the solution also can disrupt TNA, causing it to "crack" and leading to

separation of oil from the rest of the solution. One must store the admixture emulsion at an ambient temperature below 28° C to prevent coalescence.[74] **When administering lipids to ill infants receiving other infusions, care must be taken to ensure that medications are compatible with lipids or medications must be provided by a separate IV route to prevent precipitation. It should also be noted that IV compatibility is different between lipid products, with mixed oil based lipid emulsions having limited data regarding compatibility with other medications or fluids.**

COMPLICATIONS

Metabolic Complications

GLUCOSE METABOLISM

Hyperglycemia may occur with increased carbohydrate load, especially in ELBW[138] infants who may have inadequate endogenous insulin production or decreased sensitivity to insulin. ***Hyperglycemia*** **is arbitrarily defined as a blood glucose concentration greater than 125 mg/dL (6.9 mmol/L) or a plasma or serum blood glucose concentration greater than 150 mg/dL (8.3 mmol/L).**[59,103] Elevated blood sugar may lead to hyperosmolality and osmotic diuresis, resulting in dehydration. Manifestations include polyuria, glucosuria, and excessive weight loss. Serum sodium is not a reliable measure of serum osmolality if there is hyperglycemia. Direct measurement or estimate by use of the following formula is necessary:

$$\text{Serum osmolality} = (1.86)\ Na^{+} + (\text{BUN}/2.8) + (\text{Glucose}/18)$$

Transient glucose intolerance may be seen with stress. If hyperglycemia occurs without apparent change in glucose infusion, the possibility of sepsis, pain, hypoxemia, intraventricular hemorrhage (especially if the infant is less than 34 weeks' gestation), glucocorticoid administration, or inadvertent increase in carbohydrate administration (mistake in preparation or rate of infusion) should be considered. **Glucose intolerance also may be accentuated during infusions of lipid emulsion, especially in an ELBW infant.** Discontinuation of the lipid infusion without alteration of the carbohydrate load will often eliminate hyperglycemia in this situation. Some ELBW infants remain hyperglycemic even on reduced carbohydrate intakes. Controversy still remains over the use of a continuous insulin infusion to attain adequate caloric intake. A recent *Cochrane* review of neonatal hyperglycemia and insulin treatment showed no improvement in outcomes with continuous insulin infusion compared with reduced glucose infusion rates.[23] **Treatment with insulin varies, but the usual infant dose is 0.05 to 0.1 unit/kg/hour and should be reserved for severe hyperglycemia,** with clinical symptoms and resistance to other medical management changes.[6] **Routine use of insulin to promote growth in the preterm infant is not advised because of side effects.**[14]

Hypoglycemia may result from an abrupt interruption of glucose infusion or excessive exogenous insulin administration. Manifestations of hypoglycemia include apnea, lethargy, jitteriness, and seizures. If these signs occur immediately after an interruption of the TPN infusion, an IV glucose infusion must be initiated at once, followed by close monitoring of the blood glucose to allow appropriate glucose administration. The glucose concentration of the infusate may usually be safely decreased by a glucose infusion rate (GIR) of 2 mg/kg/min every 12 hours. Blood glucose values should be monitored hourly until stable after each change.

AMINO ACID METABOLISM

Hyperammonemia may be seen in preterm infants given excessive protein loads. Hyperammonemia will occur also in an infant with a congenital metabolic disturbance, such as a urea cycle defect, when challenged with an amino acid load. **Hyperammonemia may manifest as somnolence, lethargy, seizures, and coma.** Biochemical screening is necessary to identify this complication before symptoms appear.

Azotemia may occur before hyperammonemia, but blood urea nitrogen (BUN) elevation in the first week of life of a preterm infant is usually associated with dehydration and has not been a reliable marker of protein excess.[41] Therefore, **although daily monitoring is common in the first week, rising BUN is not an indication by itself to decrease the protein load.**

CHOLESTASIS

Infants receiving TPN for more than 2 weeks frequently develop cholestatic jaundice (direct

bilirubin greater than 2 mg/dL).[34,99,117] The risk appears to be greatest for the least mature infants and those receiving the longest period of TPN without enteral feeding. The cause appears to be multifactorial, including lack of bile flow stimulation, delayed enteral feedings, malnutrition, or inflammation after localized or generalized infection.[135] More recently, IV fat emulsions, particularly polyunsaturated fatty acid, are thought to contribute to cholestasis.[124] Serum amino transferases often are normal early in the clinical course. Serum albumin and prealbumin levels usually remain normal. An abnormality in hepatic synthetic function or early rise in isoenzyme levels should lead the clinician to investigate other forms of liver disease.

The differential diagnosis of cholestatic jaundice includes the following:

- **Bacterial sepsis**
- **Congenital viral infection**
- **Postpartum acquisition of cytomegalovirus**
- **Neonatal hepatitis**
- **Bile duct obstruction, such as biliary atresia or choledochal cyst**
- **Galactosemia**
- **Cystic fibrosis**
- Alpha$_1$-antitrypsin deficiency

Management of cholestatic jaundice should include the following (when possible):

- **Increase enteral feedings** as tolerated and decrease proportionately the parenteral nutrition
- **Dose reduction** of soybean-based IV fat emulsion[129,132]
- **Reducing copper** by 50% or eliminating copper
- **Eliminating manganese** from trace minerals in TPN
- **Protecting solutions from light** by covering the bag and IV tubing to reduce levels of light-induced toxic peroxides[33,66]
- **Trial of an agent that induces bile flow**[30,111]
- For infants with short bowel syndrome, controlling intestinal bacterial overgrowth[64]
- Considering an alternative type of fat emulsion[55,75]

LIPID METABOLISM

High-risk infants, including preterm and SGA low-birth-weight infants, may demonstrate intolerance to fat emulsion infusions. Hyperlipidemia may result, causing elevation of triglyceride, FFA, and lipoprotein levels. In extreme cases, lactescence may be visible in serum on a spun blood specimen (increased plasma turbidity). **For screening, a triglyceride level should be checked after initiation of therapy and then weekly and doses adjusted based on results.** Steroid therapy may elevate the triglyceride level.[104] Transient hyperglycemia may result from lipid infusion. This complication is usually dose related and rarely requires treatment.[43]

Competitive displacement of bilirubin by FFA theoretically may increase the risk for kernicterus in preterm infants with hyperbilirubinemia. However, studies of preterm infants have indicated that lipid infusions may be used in jaundiced infants, but attention to the infusion rate and monitoring of FFAs are necessary.[96]

Mechanical Complications

Pneumothorax, hemothorax, hydrothorax, air embolism, thromboembolism, catheter misplacement, cardiac perforation, and tamponade are all recognized complications of Broviac, subclavian, or jugular catheter insertions. Potential mechanical complications of percutaneous central lines include catheter occlusion, accidental dislodgement, erythematous tracking, phlebitis, thrombosis, superior vena cava syndrome, catheter migration, perforation, and catheter entrapment or breakage.[5,20,105,136] (See Box 7.1.) A pleural or pericardial effusion may be blood or chyle or may be a signal that the catheter has eroded into the pleural or pericardial space. The effusion may be the infusate. **Therefore chest x-ray examination is necessary to document correct catheter placement before a hypertonic solution is instilled,** with the superior vena cava the preferred catheter tip location.

The preceding complications may occur at any time while the catheter is present. Documentation of catheter position should be repeated if there is any history of pulling or tension on the catheter or any apparent change in its external position or change in the clinical condition associated with the preceding complications.

Any signs of catheter malfunction require troubleshooting and assessment for potential interventions to salvage the line. Some clinicians will flush a partially occluded line with a thrombolytic agent, such as recombinant tissue plasminogen activator (rt-PA).[65,115] The risk of this practice must be weighed against the benefits of maintaining the central line.

In most cases, if the catheter is a temporary line, it may be better to remove it and place a new line in another site.

Infectious Complications

Infections associated with the central line may occur from contamination of the solution, tubing connections, or hubs. Although organisms may contaminate the solution during preparation, usually **colonization occurs with entry into the line or bag. Intermittent administration of medications, removal of blood samples through the line, or multiple tubing changes provide opportunity for organisms to contaminate the solution.**

Rigid criteria for sterile preparation of the solutions are mandatory (see Preparing the Solution earlier in this chapter).

An in-line 0.22 mcm membrane filter, which is incorporated into the IV tubing for TPN administration, is capable of trapping bacteria and fungi (although not endotoxin) and should help minimize the risk for septicemia from a contaminated IV bag. In addition, filters lessen the risk for an air embolism. An in-line filter setup is available that decreases the number of connections.

Nothing should be added to the TPN solution after it leaves the pharmacy.

AVOIDING LINE COLONIZATION

Use of a dedicated central line team for placement, monitoring, maintenance, and troubleshooting has been found to improve line outcomes and reduce the incidence of neonatal catheter-related bloodstream infections. Line insertion and maintenance bundles, which include hand hygiene, skin antisepsis, maximal barrier precautions, strict adherence to proper hub care, and daily review of line necessity, are also important for avoiding line complications.

In addition, pay attention to the following to avoid line colonization[15,53]:

- When changing IV fluids, one should **avoid bleed-back into the catheter.**
- Line setups should be designed to **minimize number of ports and connections.**[69]
- **Generally, medications should not be given into injection ports in the IV tubing but should be given into a dedicated heparin-locked Y-site entry port instead.** Stopcocks are not recommended.
- **The source of an infection is usually contamination with an organism that has colonized the hub or surrounding skin.** Scrupulous attention to hand hygiene and disinfection of catheter tubing, hubs, ports, and connections by vigorous rubbing with 70% alcohol before tubing changes or entry are critical infection-prevention strategies.[15,68,69]

Dressings are not routinely changed on PICC lines. If the dressing becomes nonocclusive or moistened, the site should be cleaned according to hospital protocol and redressed with a sterile transparent dressing.[53] This should be performed using sterile gloves. The exposed catheter should be remeasured to ensure that it was not inadvertently moved during this process. **Dressings are changed routinely on Broviac, subclavian, jugular, and femoral catheters.** Dressing changes are recommended at least weekly or more frequently if drainage is noted or the dressing is no longer occlusive.

EVALUATING INFANTS FOR INFECTIOUS DISEASE COMPLICATIONS

Central line–associated bacteremia represents an important source of nosocomial infections in the intensive care nursery. The prevalence of this complication varies by unit based on patient demographics including birth weight, gestational age, diagnoses (proportion of surgery and medicine), and care practices.

Bacteremia must be considered in a newborn with a central line in place who exhibits signs of sepsis (e.g., temperature instability, lethargy, poor skin perfusion, increased cardiopulmonary distress, apnea). Some neonatal infections may be treated successfully with the line in place. **However, if the infant remains systemically ill, even if the blood culture result is negative, the central line should be removed.**[22]

Altered immune function by lipid deposition in macrophages and the reticuloendothelial system must be considered in infants with sepsis. ***Malassezia furfur* is a lipophilic, opportunistic fungal organism that may cause sepsis in infants receiving long-term lipid infusions.**[112] Although this organism is infrequently seen, it may contaminate the line and appear as a white film. This organism often will not grow in routine blood culture media. Specific culture techniques are necessary when *Malassezia* is suspected.[35]

Guidelines for management of an infant with a central line in place with suspected sepsis are as follows:

- **The infant should be evaluated for potential sources of infection,** including a general physical examination looking for non–TPN-related sources and inspection of peripheral and central venous sites for erythema.
- **Laboratory assessment** should include (1) complete blood cell count with platelet count and (2) aerobic blood cultures. Other cultures, including urine, tracheal aspirate, and cerebrospinal fluid, may be indicated, based on clinical findings. A blood fungal culture should be considered if the infant has had preceding antibiotic treatment or signs of fungal infection.[16,17,63]
- **A chest x-ray evaluation** should be performed if the infant demonstrates signs of respiratory distress or there is a need to reassess catheter position.
- **Consider decreasing or discontinuing lipid infusion** until the infection has been treated for 24 to 48 hours.[11,108]
- **If the infant is critically ill, the central line should be removed immediately. If the infant is stable, treatment may be considered through the line.**
- **A positive blood culture generally is considered to indicate bacteremia or sepsis in a newborn with a central line in place.** However, the coagulase-negative *Staphylococcus,* an opportunistic organism that is a common cause of catheter-related sepsis, also is normal skin flora and frequently contaminates blood cultures. Use of ancillary diagnostic tools, such as the C-reactive protein levels and complete blood counts, are helpful to distinguish false-positive results from true infections. Some clinicians also recommend obtaining two cultures (two peripheral, or one peripheral and one from the line) before starting antibiotics. If both yield positive results, catheter-related sepsis is confirmed.[83]
- **If bacteremia is documented but the signs of sepsis are improved, the catheter may remain in place while being used for antibiotic treatment.** One should be sure that the antibiotics are compatible with the TPN solution (to avoid stopping the TPN during the antibiotic infusion). A follow-up blood culture and close clinical monitoring are necessary to document that the infection has been treated adequately.

If a central line is pulled because of sepsis, a new central line should not be placed for 48 to 72 hours.

PARENT TEACHING

In-Hospital Total Parenteral Nutrition

Clinicians caring for an ill newborn must be attentive to the involvement and emotional state of the parents. There remain a number of concerns for child abuse, foster placement, and relinquishment among infants who have been cared for in the NICU compared with healthy term newborns, especially when care has been prolonged and complex.

Clinical conditions or policies that promote separation of parents from their infant increase the risk for bonding problems. When a newborn infant cannot be fed orally, an important, normal part of the infant's care is no longer available for the parents. The placement of a central line may be frightening to parents and result in less handling and caregiving. **Infants requiring continuous care, including TPN, should have primary nursing (one regularly scheduled nurse), and the parents should have regular and consistent communication with a primary physician. Care providers should attempt to keep the parents involved in other parts of the infant's care because the parents are unable to feed the infant. Parents should be fully informed about the purpose and appropriate care of the infant's central line so they will feel comfortable handling their infant with the line in place.**[53]

Home Total Parenteral Nutrition

Home parenteral nutrition has been used in infants with congenital intestinal anomalies or after massive bowel resection for NEC. TPN is initiated in the hospital. If growing and otherwise well, the infant may be a candidate for TPN at home. Issues to be addressed include ability and willingness of parents to care for the infant at home, available financial support, adequate home setting, pharmacy support services, and additional skilled nursing care needed. The infant should have a more permanent central line placed as early in the discharge process as possible. Parent teaching should begin early, including verbal and written instruction and hands-on practice and return demonstrations (Box 16.1).

Administration of TPN at home is different from hospital administration of TPN and is typically

BOX 16.1 PARENT/CAREGIVER TEACHING HOME ADMINISTRATION OF PARENTERAL NUTRITION

- Strict handwashing and aseptic handling of tubing connections and hubs
- Use of infusion pump
- Monitoring of site for signs of infection, phlebitis, or leaking
- Troubleshooting for occlusion, leaking, extravasation
- Evaluation for signs of systemic infection
- Emergency response to broken or dislodged catheter, loss of electrical power
- Developmental care: oral stimulation, holding, appropriate play activities
- Dressing care and changes
- Monitoring for signs and symptoms of hypoglycemia
- Securing or taping of line to avoid dislodgement with positioning and handling

managed by a pediatric gastroenterology service in conjunction with a home infusion therapy or pharmacy service. Infants often go home on a cyclic TPN regimen (12 hours/day). An ambulatory pump improves the mobility and flexibility of the parent and infant and allows a more normal life.

Compliance and success with home TPN are greatly increased when the parents understand the need for and the appropriate way to administer TPN and how to troubleshoot and care for the catheter.[54]

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17 ENTERAL NUTRITION

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Providing optimal nutrition to support term and preterm infants in the neonatal intensive care unit (NICU) continues to be challenging, but it is fundamental for improving infant health. **Recent research has provided new evidence-based guidelines for clinicians that have led to adoption of human milk as the primary enteral feeding for all term and preterm infants. For very preterm infants, it is important to start enteral feeding as soon after birth as possible, advance feedings briskly, and fortify "mature" mother's milk or donor milk.** Other research has emphasized the importance of early enteral feeding for the best support of gastrointestinal (GI) development, somatic growth, metabolic homeostasis, prevention of infection, neurodevelopment, and future health. **Taken together, starting enteral feeding as soon after birth as possible complements parenteral nutrition and allows for expeditious weaning from parenteral nutrition, thereby reducing its potential complications. Early enteral feedings are now accepted as fundamental and not optional in neonatal management.**

This chapter provides an overview of the physiology of fetal and neonatal nutrition and growth, anatomic and functional development of the GI tract, and the fundamentals of neonatal enteral nutritional requirements. Specific details about the assessment and monitoring of growth, feeding strategies and techniques, and the possible complications of enteral feeding of at-risk infants are included. The ongoing nutritional needs of infants recovering from complications of preterm birth and other disorders also are presented, as well as the elements of providing for these needs after hospital discharge.

PHYSIOLOGY

Fetal Growth

Fetal growth is regulated by complex genetic, nutritional, endocrine, environmental, and epigenetic factors.[49,102,271] Maternal factors such as prepregnancy weight, body composition, weight gain during pregnancy, and a diet rich in simple sugars and high in fat directly correlate with placental[274] and fetal size and fetal fat mass.[1,45,140] **Maternal nutrition and the quality of the maternal diet (protein, energy, vitamins, and minerals) are critically important in the regulation of placental-fetal development and therefore directly affect fetal growth.** For example, a growing body of evidence shows that maternal obesity, and even modestly increased maternal body mass index (BMI), increase the risk of perinatal complications, including fetal and neonatal death,[19] increased birth weight,[205,266] and lifelong risk of obesity in the offspring.[210] **Conversely, suboptimal nutrition during pregnancy can result in low birth weight and also increases the risk of metabolic complications for offspring later in life.**[29,242] The growth and function of the placenta strongly determine fetal growth by providing oxygen and essential nutrients.[62,131] Critical fetal anabolic hormones, such as the insulin-like growth factors (IGF-1 and IGF-2) and insulin, are regulated by circulating concentrations of nutrients and are themselves regulators of fetal nutrient uptake and metabolism. Infants with intrauterine growth restriction (IUGR), who have very little glucose supply from the placenta and very little circulating insulin, are among the smallest of infants; infants of gestational diabetic mothers, who respond

BLUE type highlights content that is particularly applicable to clinical settings.

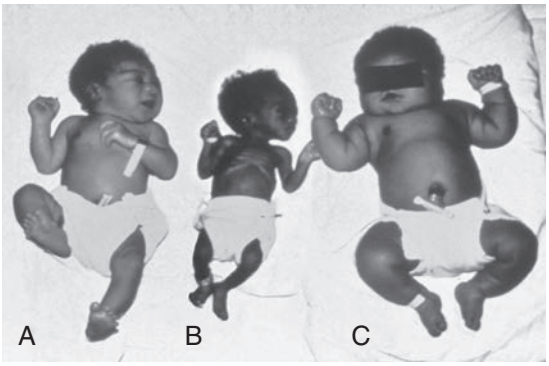

FIGURE 17.1 Fetal nutrition and patterns of fetal growth. **A**, 3200-g birth weight term appropriate-for-gestational age (AGA) infant. **B**, 1500-g term small-for-gestational age (SGA) infant who had intrauterine growth restriction (IUGR). **C**, 5200-g large-for-gestational age (LGA) macrosomic infant of a gestational diabetic mother (IDM). (Courtesy Newborn Service, University of Colorado Hospital, Denver, Colorado [WW Hay Jr].)

to increased maternal glucose concentrations and maternal-fetal glucose delivery with increased insulin secretion, are among the largest (Fig. 17.1). Thyroid hormone also contributes to fetal growth by regulation of oxidative metabolism. Infants with other endocrine deficiencies, such as those resulting from anencephaly, panhypopituitarism, or hypothyroidism, are near normal in age-specific size at birth, indicating a complex interplay between the fundamentally required supply of nutrients to the fetus and the supporting roles of the fetal endocrine milieu that regulate intrauterine growth.

Gastrointestinal Development

Enteral feeding supports GI development in the preterm infant that normally would occur during fetal life. The fetal GI tract is anatomically complete by 20 to 22 weeks after conception. Functional development of the GI tract begins in utero and continues into infancy (Table 17.1). In utero, the fetal intestine is exposed to nutrients and growth factors from the mother, placenta, amniotic fluid, and fetal tissues. The fetal GI tract elongates 1000-fold from 5 to 40 weeks, but strikingly the length doubles during the last 15 weeks of gestation, or from about 25 to 40 weeks, the period of neonatal intensive care of extremely preterm infants. The mean length of the GI tract at 40 weeks is 275 cm. **The fetal GI tract is in communication with the external amniotic fluid environment by 7 weeks postconception.** Growth factors, enzymes, immunoglobulins, and hormones present in amniotic fluid and swallowed by the fetus support early development and functional priming of the GI tract.[183] Fetal swallowing can be observed as early as 11 weeks of gestation.[83]

TABLE 17.1 DEVELOPMENT OF THE HUMAN GASTROINTESTINAL TRACT: FIRST APPEARANCE OF DEVELOPMENTAL MARKERS

DEVELOPMENTAL MARKER	WEEKS OF GESTATION
Gastrulation	3
Gut tube formed, early differentiation of foregut, midgut, and hindgut	4
Gut lumen in continuity with amniotic cavity	7
Growth of intestines into umbilical cord	7
Intestinal villus formation	9
Intestines into abdominal cavity	10
Δ glucosidase, dipeptidase, lactase enzymes	10
Glucose transporters	10
Liver lobules, bile metabolism	11
Swallowing	11
Parietal cells, pancreatic islets, bile secretion	12
Stomach fundus, body, pylorus, greater and lesser curvature	14
Gastric glands	14
Intestinal crypts, elongation of intestinal villi	14
Intestinal lymph nodes	14
Differentiation of pancreatic endocrine and exocrine tissue	14
Active transport of amino acids	14
Sucking movements	19
Superficial esophageal glands	20
Gastric motility and secretion	20
Fatty acid absorption	24
Coordination of suck and swallow	33–36

Data from Lebenthal E. The impact of development of the gut on infant nutrition. *Pediatric Ann.* 1987;16:215–216; Montgomery RK, Mulberg AE, Grand RJ. Development of the human gastrointestinal tract: twenty years of progress. *Gastroenterology.* 1999;116:702–731.

The components of the amniotic fluid, including carbohydrates and amino acids, change during development, as does the volume of amniotic fluid swallowed, varying from a few milliliters per day to more than 450 mL/day, or 20% of fetal weight, late in gestation.[104,112] Amniotic fluid contains growth factors that promote intestinal mucosal cell differentiation. Such growth factors and nutrients in the amniotic fluid stimulate production of enteric hormones that act locally to promote further gut development. The timing of the appearance of GI hormones, polypeptides, gut-stimulated neurotransmitters that link central nervous systems conditions of hunger or satiety to GI motor and secretive functions, and digestive enzymes in the fetus is variable, but most are present in the GI tract by the end of the first trimester of pregnancy. Nutrient transport systems are in place by 14 weeks for amino acids, 18 weeks for glucose, and 24 weeks for fatty acids.

After birth, the GI tract must further adapt for mucosal growth and differentiation, peristalsis, digestion of food, and absorption of nutrients. **Some GI functions are "switched on" at birth** (e.g., decrease in intestinal permeability, increase in mucosal lactase activity), regardless of the length of gestation. **Others, however, are intrinsically "programmed" to occur at a certain postconceptual age** (e.g., the onset of peristalsis at 28 to 30 weeks and the coordination of suck, swallow, and breathing at 33 to 36 weeks). Environmental influences, including colonization of the GI tract by bacteria and the introduction of nutrients into the GI tract, also affect postnatal GI and immunologic development.[10,54,167] The microbial population within the GI tract, termed the *gut microbiome,* **is acquired at birth and may even begin to develop in utero with influences from the maternal microbiome via ascending migration from the maternal genital tract.**[260] Many factors influence the development of the gut microbiome, including mode of delivery (vaginal vs. cesarean delivery), early exposure to antibiotics, maternal health conditions (e.g., diabetes or obesity), and composition of the diet (breast milk vs. formula, high- vs. low-protein formulas, cow vs. human milk supplements, degree of protein hydrolysis, and inclusion of long-chain polyunsaturated fatty acids [LC-PUFAs], particularly docosahexaenoic acid [DHA]).[52,172] **Importantly, evidence shows that establishment of the gut microbiome during infancy may influence the development of obesity later in life, among other noncommunicable diseases.**[232,253]

Infants born before term have both anatomic and functional limits to the digestion and tolerance of enteral feedings. Neurologic maturation is important not only for coordination of sucking, swallowing, and breathing during feeding but also for GI motility. **Peristalsis in the esophagus is immature and bidirectional in the preterm infant, with forward movement of food to the stomach developing only near term.**[128] **Abnormal esophageal peristalsis and transient relaxations of the lower esophageal sphincter muscle likely contribute to the common problem of *gastroesophageal reflux (GER)* seen in preterm infants. Enteral feeding, however, promotes the ongoing maturation and development of the GI tract in both term and preterm infants.**[51]

Intestinal motor activity in the preterm infant is immature and disorganized compared with term infants. Term infants have distinct fasting phases of GI quiescence and nonmigrating motor activity followed by migrating motor complexes. Very preterm infants have absence of migrating motor complexes and prominence of nonmigrating clusters rather than mature coordinated peristalsis. Additional suck-swallow incoordination necessitates tube feedings in very preterm infants. After feeding, term infants show a dramatic increase in the intensity of motor activity that is not observed in preterm infants. **A measure of GI motility is provided by the passage of stool within 24 hours of birth in more than 95% of full-term infants; however, the more preterm the infant, the greater the delay in passing the first stool. Initial gastro-anal transit time is 2 to 5 days in extremely low-birth-weight (ELBW) infants, but only 12 to 24 hours in term infants.**[38] **Passage of meconium is delayed in about 20% of infants less than 1500 g birth weight, and is delayed up to 10 days in infants less than 1250 g birth weight.**[133,177,270] **Once enteral feedings are established, however, gastric emptying rate and gastro-anal transit time are similar in term and preterm infants.**[194,265] Coordinated, mature GI motility and peristalsis with feeding develop in the preterm infant between 33 weeks and term.

Digestion occurs in the lumen of the intestine. Nutrient absorption occurs at the enterocyte interface (microvillus membrane [MVM]). **Protein digestion and absorption are remarkably efficient in the preterm infant at 26 to 30 weeks of gestation** despite the fact that *enterokinase,* a rate-limiting enzyme in the activation of pancreatic proteases via activation of *trypsinogen,* has only 6% of the activity found in the term newborn and 10% of adult activity. Reduced enzymatic activity and low gastric acidity may delay protein digestion, but usually only temporarily. Nevertheless, this potential delay has led to some use of partially hydrolyzed protein formulas in very preterm infants. **Such formulas may slightly reduce gastro-anal transit time (e.g., 10 vs. 12 hours), but these formulas do not have the total protein or mineral content needed for rapidly growing very preterm infants and should be used only with caution.**[38,180] After luminal hydrolysis, peptides are further hydrolyzed at the MVM. Some amino acids and oligopeptides are absorbed via transporters. Some peptides that are absorbed intact are hydrolyzed by intracellular peptidases that further aid in protein digestion. MVM and intracellular peptidases mature early in gestation.

Carbohydrate absorption is limited initially by a relative deficiency of lactase, which splits lactose into glucose and galactose. **Lactase in the infant of less than 34 weeks' gestational age is present at only about 30% of the activity found in the normal term infant, although lactose intolerance is rare in these infants, particularly when they are fed human milk.**[248] **Lactase functional activity increases with feeding and approaches term levels by 10 days after birth in most preterm infants.**[249] Human milk feedings increase lactase activity more than formulas. Twenty percent of dietary lactose may reach the colon in neonates. Lactose lowers fecal pH, a beneficial effect in that it promotes *Bifidobacterium* and *Lactobacillus* proliferation.[119] Lactose in mother's milk also promotes butyrate formation in the colon. Butyrate increases colonocyte proliferation and differentiation and tightens interepithelial junctions.

Preterm infants malabsorb 10% to 30% of dietary fat because of a small bile acid pool size and relative lack of pancreatic lipase.[170] Bile acid synthesis and reabsorption are lower in preterm infants than in term infants. Duodenal bile acid concentrations are usually low for a few weeks after very early preterm birth. Some compensation is provided by lingual and gastric lipases, as well as the lipase present in human milk. Combined with gastric lipase, milk bile salt–stimulated lipases (BSSLs) facilitate lipid hydrolysis and prepare intraluminal lipid for further cleavage by pancreatic enzymes. BSSLs are higher in milk of mothers delivering preterm than in those delivering at term.[111] Bile salts are not necessary for digestion or absorption of medium- and short-chain fatty acids. **Despite relative deficiencies in many enzymes important in nutrient processing, the preterm infant usually can digest and absorb complex nutrient mixtures such as human milk quite effectively.**

Postnatal Growth of Preterm Infants

After birth, usual nutritional regimens, even when provided more aggressively, fail to produce growth rates in preterm infants that mimic normal rates of intrauterine growth, the accepted goal of nutrition for the preterm infant.[82] **A variety of complications contribute to this growth failure, but the primary problem is that most preterm infants are fed less protein and calories immediately after birth than are needed to support normal fetal rates of protein accretion and body growth.** In addition, the preterm infant is exposed to environmental factors that increase energy expenditure, including low relative humidity and radiant and convective heat losses, as well as energy-consuming demands of breathing, resistance to gravity, and the processes of digestion, absorption, and synthesis of nutrients into body structure. Stress-induced hormones that are catabolic in sick infants, particularly corticosteroids and catecholamines, limit the production and action of anabolic growth factors, particularly insulin and IGFs, further preventing normal rates of growth and weight gain at rates comparable to those of healthier infants of the same gestational age.[225] Overall, however, **even in sick or physiologically unstable infants, the principal factor causing postnatal growth failure and unfavorable neurodevelopmental outcome is delayed and inadequate intake of protein and energy.**[82,88,90]

After birth, all infants lose excess extracellular salt and water. Term infants usually lose 5% to 8% of birth weight by the third day of life. In ELBW preterm infants (<1000 g birth weight), normal diuresis and common fluid management strategies to limit fluid overload over the first 10 to 14 days of life usually produce a net loss of body weight. Such infants may lose 8% to 15% of birth weight, though fluid management among institutions varies considerably. **Currently, mild fluid restriction that does not lead to dehydration appears safe and might decrease the incidence and/or severity of a patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), and bronchopulmonary dysplasia (BPD), and even reduce the risk of death.**[30,200] Relative fluid restriction during the later stages of enteral feeding can be accomplished in milk-fed infants by concentrating nutrients in milk with human milk fortifiers or preterm or postdischarge formula powder. Deficits accumulated daily during early neonatal life may take weeks to months to replenish. **Serial measurements of body length and head circumference are particularly useful in the newborn period because linear growth and head circumference represent lean mass growth and have the potential to help predict neurodevelopmental outcome.**[216] Employing validated methods, such as recumbent length boards, and training staff on correct technique will improve the validity of these measurements (Box 17.1).[72] More recent methods to assess body composition in the neonate include dual x-ray absorptiometry (DEXA), air displacement plethysmography, magnetic resonance imaging (MRI), anthropometric prediction equations, and isotope dilution, all of which partition new tissue accrual into water, fat, and lean body mass components.[79] More sophisticated assessment of body composition would define needs for additional specific nutrients (protein, lipids, carbohydrates) for body growth (even during the early postnatal period of fluctuating water weight). However, these methods are not usually available for routine clinical use and are used primarily as research tools.[229] **Thus assessment of postnatal growth is limited to following the trajectories of height, weight, and head circumference and calculating BMI or Ponderal index (weight in grams × 100/length in centimeters^3)** (Fig. 17.2). Recent studies demonstrate that BMI correlates with body fat composition, though with limited accuracy.[95,139,254] Improving the capacity to accurately assess body composition is fundamental for determining optimal nutrition, because with current feeding practices and nutritional regimens, preterm infants develop less lean tissue than the normally growing fetus in utero. Body fat content varies among studies, from similar fat mass compared with infants born at term to excess body fat, with the excess distributed more to the intra-abdominal region.[134]

Assessment of Growth and Nutritional Status

The generally accepted goal of postnatal nutrition for preterm infants is to achieve and maintain the normal rate of intrauterine growth (Fig. 17.3). Many growth curves have been developed from anthropometric measurements taken at birth in populations of infants born at different gestational ages.[93,201] The most recent reference growth charts are based on cross-sectional data from nearly 400,000 births in the United States[201] and from nearly 4 million births worldwide.[92] **Expected weight gain trajectories are remarkably consistent among many standard growth charts, and, on average, the expected weight gain in the appropriately growing preterm infant is approximately 15 to 20 g/kg/day.** Because preterm birth is not a normal outcome, cross-sectional anthropometric measurements obtained at birth may underestimate expected fetal growth rates.[50,142,206] The Intergrowth 21st study group and the World Health Organization have produced standard growth charts based on prospective serial ultrasound measurements of fetuses who were born to healthy women with low-risk pregnancies from across the world.[142,206] (Fig. 17.4). A subpopulation of infants from the Intergrowth 21st study who were born preterm was used to generate postnatal growth standards for preterm infants.[206,267] **Regardless of the growth chart used, slow growth rates and large losses in the change in both weight and length z-scores from birth to NICU discharge should be avoided as they are predictive of poor neurodevelopment.**[88,99,237,244,283]

Good methods are lacking to assess nutritional adequacy over time in very small infants. **Rates**

BOX 17.1 GROWTH MONITORING

1. *Weight* is subject to large variations based on fluctuations in fluid balance (e.g., presence or absence of edema, congestive heart failure, renal failure) and attached equipment (e.g., intravenous lines and boards, endotracheal tubes). Infant weight should be measured daily as follows:
   a. Use the same scale and weigh infant naked or using supportive weighing method as possible. Supportive weighing, or swaddled weights, help ensure an infant's physiologic and behavioral stability during the weighing procedure. Remove "attached" equipment if possible, or weigh similar items separately and subtract from total weight. Swaddled weights are equal to the naked weight after the weight of the diaper and blanket are subtracted. Unswaddled weights still can be used to improve accuracy for very small infants or if swaddling puts the infant at risk or interferes with the infant's care needs. In-bed scales are useful for ELBW infants or infants who become unstable with handling. An electronic scale that averages several measurements reduces movement artifact and may be useful for active infants.
   b. Reference standards for the weights of nursery equipment (e.g., diapers, intravenous boards, tubing, endotracheal tubes) should be available for nursery use.
   c. Weigh the infant at the same time daily, preferably before a feeding.
   d. Record the infant's weight, the time of weight measurement, and the scale used on the chart. Record energy (calories) and fluid intake on the same chart. This information combined with biochemical parameters (e.g., serum electrolytes, hemoglobin, albumin) and the physical examination provides the best overview of the infant's nutritional status. Once weekly, a daily weight should be plotted on the appropriate preterm or term growth chart. Weekly review of the infant's weight change provides useful information on trends in overall growth or weight loss that may be overlooked in the daily charting.
2. *Crown-heel length and head circumference* are measured and recorded on admission and at least weekly thereafter. Accurate length measurements are difficult to obtain without special equipment, such as a length board, but accuracy can be improved by repeated measurements and use of the tonic-neck reflex to straighten the hip and knee. Length and head circumference monitoring are just as important as, if not more important than, weight measurements. Increase in length reflects lean mass growth, and head circumference is used as an indicator of brain growth. Both measurements are predictors of neurodevelopmental outcome.[216,228]
   a. To measure the crown-heel length, two people are required for measuring patients using the statiometer: one registered nurse (RN) and one assistant. The assistant may be another RN, another NICU care team member, or a parent. Position the infant supine on the board with his or her head at the stationary head piece and the feet facing the movable foot piece. The assistant positions infant's head against the head piece by securing the head and shoulders between his or her hands. The top of the patient's head should touch the stationary head piece. The eyes should be facing straight up. Avoid hyperextension of the patient's neck. The RN straightens the infant's body along the center of the board. Apply gentle pressure to patient's knees, and hold the legs in place. Using a free hand, slide the foot piece until it is positioned firmly against the infant's heels. The toes should point directly up. Measurements with one lower limb extended may result in less patient discomfort than when both lower limbs are extended.[214] Repeat three times.
   b. Head circumference is obtained using a paper or soft tape measure. Record the largest measurement obtained with the tape placed over the frontal, parietal, and occipital prominences.
3. *The Ponderal index* (or weight-length index; see Fig. 17.2) is used to assess "quality" of growth. The Ponderal index is calculated as the weight in grams multiplied by 100, divided by the cube of the length in centimeters. True organ growth and tissue accretion are accompanied by increases in both weight and length and can be evaluated partly using the Ponderal index.
4. *Biochemical monitoring* of the growing infant may include periodic measurement of serum electrolytes, calcium, phosphorus, alkaline phosphatase, total protein, albumin, and hemoglobin. These data can be used to help prevent specific deficiencies in the diet, such as hyponatremia in preterm infants with excessive renal solute losses or hypophosphatemia with increased alkaline phosphatase as seen in rickets and osteopenia.

of change in anthropometric measurements provide some retrospective information, but they do not specify what an infant needs to maintain a normal growth rate (see Box 17.1). Too often, growth charts simply document continuing and, all too often, worsening growth, highlighting the failure to provide adequate nutrition during the previous days to weeks. Indirect calorimetry offers some advantage for determining at least the energy requirements for growth, but instruments that are clinically practical and sufficiently accurate to quantify nutrient

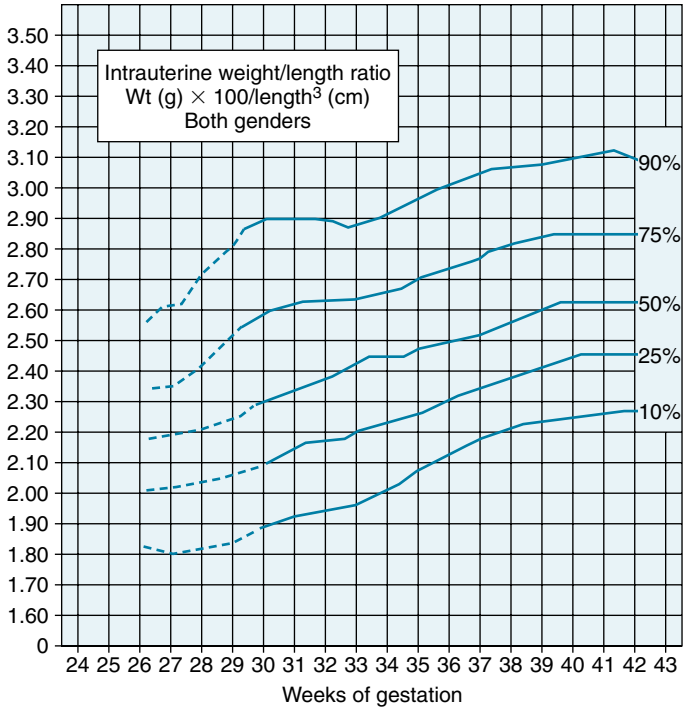

FIGURE 17.2 Ponderal index. (From Lubchenco L, Hansman C, Boyd E. Intrauterine growth in length and head circumference as estimated from live birth at gestational ages from 26 to 42 weeks. Reproduced with permission from *Pediatrics* 1966;37:403–408. © American Academy of Pediatrics.)

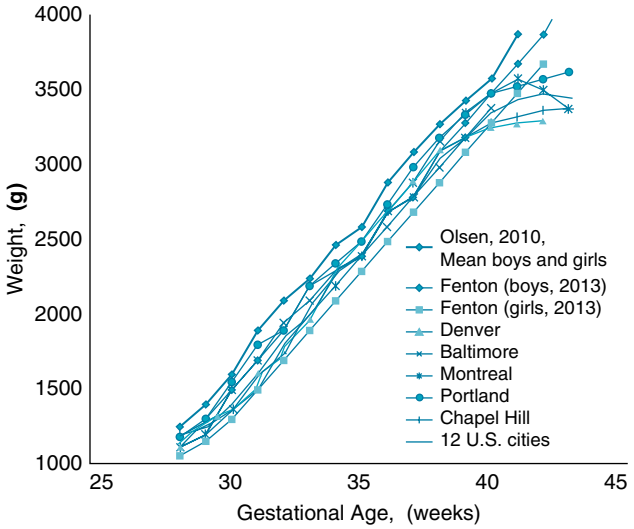

FIGURE 17.3 Fetal growth by selected references.

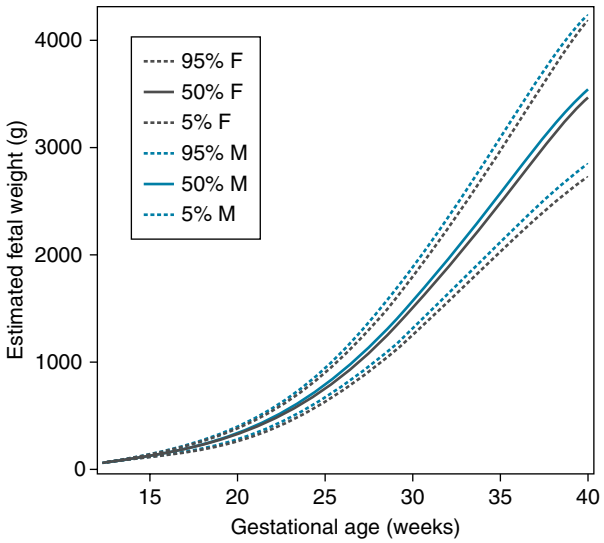

FIGURE 17.4 Female and male growth of estimated fetal weight during gestational weeks 14 to 40 based on serial ultrasound biometric measurements. (From Kiserud T, Piaggio G, Carroli G, et al. The World Health Organization fetal growth charts: a multinational longitudinal study of ultrasound biometric measurements and estimated fetal weight. *PLoS Med.* 2017;14(1):e1002220. Erratum in: *PLoS Med.* 2017;14(3):e1002284.)

metabolism in tiny infants are not yet available. Similarly, application of stable isotope methodology to measure utilization and oxidation rates of individual nutrients remains confined to research studies in large medical centers with sophisticated mass spectrometry facilities. Evaluation of an individual infant's immediate nutrient requirements and responses to the administration of different mixtures and amounts of nutrients remains an elusive but still necessary goal.

NUTRITIONAL REQUIREMENTS FOR ENTERAL NUTRITION

Nutritional requirements should be considered in general categories: energy (or calories), protein, carbohydrate, fats, minerals, and vitamins. Water requirements and limits must also be considered when designing nutrition support strategies. The source, complexity, and constituents of these nutrients are important, as well as the route of administration. **Box 17.2 lists commonly used nutritional conversion factors and formulas.** See Chapter 16 for parenteral nutrition and Chapter 18 for breastfeeding.

Energy

Energy is necessary for all vital functions of the body at the molecular, cellular, organ, and systemic levels. **Preterm infants have minimum energy requirements for basal metabolism and growth, but also have requirements for unique physiology and metabolism that influence energy expenditure.** These include their smaller body size with increased surface area, postnatal age, physical activity, dietary intake, variable environmental temperatures, energy losses in the stool and urine, and clinical conditions and diseases, as well as changes in body composition. **Both energy and protein are necessary to produce normal rates of growth.** Carbohydrates (primarily glucose) are principle sources of energy for the brain and heart until lipid oxidation develops over several days to weeks after birth.[113] **Many preterm infants are energy deficient early in their postnatal life. This is largely a result of insufficient amounts of glucose and lipid with early intravenous (IV) nutrition and, later, energy deficits as IV nutrition is weaned before enteral nutrition has been increased sufficiently to meet energy requirements.** Thus cumulative energy deficiencies (and protein) are common and may contribute to slower postnatal growth rates.[82,115]

BOX 17.2 COMMONLY USED CONVERSION FACTORS AND FORMULAS

Energy
- 1 kcal = 4.184 kJ

Gross energy (kcal/g)
- Protein = 5.65
- Carbohydrate = 3.95
- Fat = 9.25

Metabolizable energy (kcal/g)
- Protein = 4
- Carbohydrate = 4
- Fat = 9

Protein
- Total protein (g/dL) = total nitrogen (g/dL) × 6.25

Vitamins
- 1 International unit vitamin A = 0.3 retinol equivalent = 0.3 mcg retinol = 1.8 mcg beta-carotene
- 400 International units vitamin D = 10 mcg vitamin D
- 1 International unit vitamin E = 1 mg DL-α-tocopherol

Minerals
- 1 mEq Na = 1 mmol Na = 23 mg Na
- 1 mEq K = 1 mmol K = 39 mg K
- 1 mEq Cl = 1 mmol Cl = 35 mg Cl
- 2 mEq Ca = 1 mmol Ca = 40 mg Ca
- 1 mmol P = 31 mg P
- Osmolarity (mOsm/L) = Osmolality (mOsm/kg H_2O) × kg H_2O/L solution
- Renal solute load (mOsm/dL) = [Protein (g/dL)] × 4 + [Na + K + Cl (mEq/dL)]
- Potential renal solute load (mOsm/dL) = [Protein (g/dL)] × 5.7 + [Na + K + Cl (mEq/dL)] + [P (mg/dL)/31]

Energy requirements are determined by an infant's total energy expenditure, energy excretion, and energy stored in new tissue as growth. Total energy expenditure can be subdivided into contributions of basal metabolic rate, activity, thermoregulation, and the energy costs of digestion and metabolism. Energy excretion is composed of fecal and urinary losses, as well as heat lost by radiation and evaporation. **Caring for and feeding infants under thermoneutral temperature conditions in humidified incubators, starting at admission to the NICU, substantially decreases energy expenditure in preterm infants. Reducing unnecessary care episodes to keep the incubator temperature and humidity constant and exposing the infant's skin when under radiant warmers helps ensure maintenance of thermoneutral conditions.** Estimates of energy requirements for growing preterm infants are shown in Table 17.2. The large range of these estimates reflects the variability of infant activity and environmental conditions. In general, the infant's muscle activity does not contribute much to total energy expenditure.[261] Most preterm infants also are tightly swaddled and do not move much.[120]

Caloric requirements for the healthy term breastfed infant average 90 to 100 kcal/kg/day.[116] Formula-fed term infants often receive more, up 100 to 110 kcal/kg/day, because of the greater caloric content of term formula, especially in comparison with breast milk, and particularly as the energy content of milk declines over longer periods of lactation. Concern that formulas had less efficient nutrient absorption from the GI tract contributed to formula manufacturers ensuring higher energy contents. **The higher energy content of formula, paired with volume intakes that are often higher with bottle feeding, can lead to greater fat mass gain over the first few months of life in formula-fed term infants.** More recently, energy content in some term formulas has been reduced to 19 kcal/oz to prevent excess fat mass accumulation and to match the energy intake (both fat and carbohydrate) of breastfed infants.

Caloric requirements are 110 to 130 kcal/kg/day for enterally fed very-low-birth-weight (VLBW) preterm infants and 85 to 95 kcal/kg/day for parenterally fed VLBW preterm infants because of better efficiency.[113] **Increased energy requirements can be anticipated during sepsis, acute and chronic respiratory illness, and recovery from surgery (Fig. 17.5). Daily caloric intake should be calculated for each infant in the NICU. A useful approach for calculating caloric intake is shown in Box 17.3.**

Protein

Protein accretion (net protein balance) is fundamental for normal growth. The amounts and types of protein necessary for optimal growth in preterm infants have been difficult to establish. Metabolic balance studies, fetal animal protein and amino acid metabolism, and human fetal body composition growth studies support a **need for higher protein intakes in the growing preterm infant**

than in the term infant. Throughout the normal period of breastfeeding, the concentration of protein in human milk decreases; however, the preterm infant's need for protein continues to be higher than in the term infant.[17] Human milk is highly variable in its protein and lipid concentrations.[78] Unfortified human milk is not adequate to meet the recommended goals of 3.5 to 4 g/kg/day for preterm infants because of their higher fractional protein accretion rates.[7,14,55]

TABLE 17.2 ESTIMATED DAILY ENERGY REQUIREMENT (kcal/kg) FOR ENTERALLY FED PRETERM INFANTS

FACTOR	AMERICAN ACADEMY OF PEDIATRICS	EUROPEAN SOCIETY OF GASTROENTEROLOGY AND NUTRITION	RANGE
	ENERGY EXPENDITURE		
Resting metabolic rate	40–50		45–50
Activity	0–5		15–20
Thermoregulation	0–5		
Synthesis	15		
Energy stored	20–30		
Energy excreted	15		29–41
Total requirements	**105–120**	**110–135**	**105–131**

Data from American Academy of Pediatrics Committee on Nutrition. Nutritional needs of the preterm infant. In: Kleinman RE, ed. *Pediatric Nutrition Handbook*. 6th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009:79–112; European Society of Paediatric Gastroenterology, Hepatology and Nutrition. Committee on Nutrition of the Preterm Infant (Agostoni C, Buonocore G, Carnielli VP, et al.). Enteral nutrient supply for preterm infants. Commentary from the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition. *J Pediatr Gastroenterol Nutr*. 2010;50:85; Zeigler EE. Meeting the nutritional needs of the low-birth-weight infant. *Ann Nutr Metab*. 2011;58:8.

	Normal Requirements		Likely Changes in Requirements with Illness						
	Well Term	Well Preterm	RDS	CLD	CHD		Sepsis	NEC/SBS	IUGR
					Cyanotic	CHF			
Free water (mL/kg)	100 to 120	120 to 140	↓	↓	Ø	↓	↑	↑	↑
Energy (kcal/kg)	100	120	↑	↑↑	↑	↑↑	↑↑	↑↑	↑
Carbohydrate (g/kg)	10	12 to 14	↑	↓	↑	↑	↑	↑	↑
Protein (g/kg)	1.5 to 2.2	3.0 to 4.0	Ø	↑	↑	↑	↑↑	↑	↑
Fat (g/kg)	3.3 to 6	4 to 7	Ø	↑	↑	↑	Ø	↑↑*	↑
Calcium (mg/kg)	45 to 60	120 to 230	Ø	↑↑•♦	↑◊	↑•◊	Ø	↑*	↑
Iron (mg/kg)	1	2 to 4	Ø	↑♦	↑	Ø	Ø	↑	↑
Vitamin A (IU/kg)	333	700 to 1500	↑◊	↑◊	Ø	Ø	Ø	Ø	Ø

Ø No change.
* Particularly with loss of the terminal ileum.
• Particularly with calciuric diuretics such as furosemide.
◊ Particularly if postoperative.
♦ In <1500-g preterm infants.

FIGURE 17.5 Daily nutritional requirements and changes with illness. *CHD,* Congenital heart disease; *CHF,* congestive heart failure; *CLD,* chronic lung disease; *IUGR,* intrauterine growth restriction; *NEC,* necrotizing enterocolitis; *RDS,* respiratory distress syndrome; *SBS,* short bowel syndrome. (Modified from Thureen PJ, Hay WW Jr. Conditions in preterm infants requiring special nutritional management. In: Tsang R, Lucas A, Uauy R, Zlotkin S, eds. *Nutritional Needs of the Preterm Infant: Scientific Basis and Practical Guidelines*. Baltimore, MD: Williams & Wilkins; 1993.)

In one study, preterm infants receiving protein and energy supplementation during enteral feedings had increased gains in length and head circumference in relation to increased protein intake. In the same study, extra energy (149 kcal/kg/day) increased primarily weight and triceps skinfold thickness, demonstrating the need for protein to grow bone, brain, and lean body mass, whereas excess energy leads primarily to increased fat deposition (Fig. 17.6).[136,137] These benefits unique to protein and energy have since been supported by Cochrane reviews of the literature.[94,149,150]

Preterm infants, especially those who develop growth failure in the NICU, are at risk for abnormal neurodevelopment.[98] Insufficient nutrition in the preterm infant, principally of protein, results in growth restriction of the brain (neuronal number, axonal length, dendrite growth, and synapse formation) **and deficits in later behavioral** (interactive behavior) **and cognitive outcomes** (learning and memory).[41,100] When protein and energy intake is inadequate, long-term benefits to developmental outcome with particular feeding strategies are not observed.[250,251] **Preterm infants maintained on diets fortified with protein and energy, however, have shown improved brain growth** (larger brain regions shown by MRI studies) across a broad range of gestation, **and improved neurodevelopmental test scores in early life.[35,240] Increased provision of protein and calories during the first week of life uniquely increases fat-free mass gains, but not fat mass gains (which happen more commonly**

BOX 17.3 CALCULATING DAILY CALORIC INTAKE (kcal/kg/day)

Conversion Factors

20 kcal/oz = 0.67 kcal/mL
24 kcal/oz = 0.80 kcal/mL
1 kcal = 1 calorie
1 oz = 30 mL

Calculation

1. Add total daily feeding intake (in mL).
2. Divide total intake (mL) by the infant's weight (kg). This equals enteral intake in mL/kg/day.
3. Multiply mL/kg/day intake by kcal per ounce of feeding.
4. Divide by 30 mL.
   This equals enteral intake in kcal/kg/day.

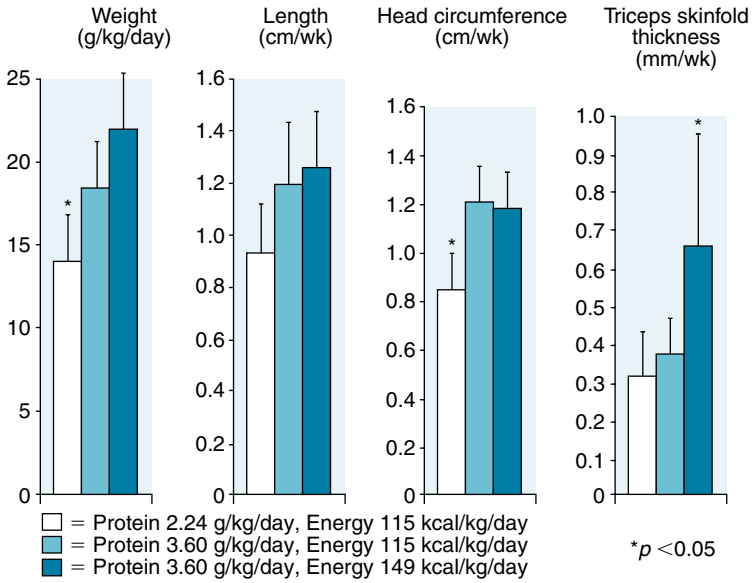

FIGURE 17.6 Growth rates with varying protein and energy intakes. (From Kashyap S, Schulze KF, Forsyth M, et al. Growth nutrient retention and metabolic response in low-birth-weight infants fed varying intakes of protein and energy. *J Pediatr.* 1988;113:713–721; Kennaugh JM, Hay WW Jr. Nutrition of the fetus and newborn. *West J Med.* 1987;147:435–448.)

with later periods of high energy intakes along with the protein).[227] Some evidence also indicates that longer periods of maintaining higher protein intakes will increase brain growth.[219] Larger total brain tissue, white matter, and cerebellar volumes at term-equivalent age are associated with better neurodevelopment in infants born moderately and late preterm. Brain volumes may be an important marker for neurodevelopmental deficits described in moderate and late preterm children.[59]

Neurodevelopmental outcome in preterm infants is unequivocally improved when they are fed human milk.[165] **Most studies indicate that such development is supported better when mature milk or donor milk is supplemented with protein and energy.** Improvements in neurodevelopmental outcome extend into adolescence. This was demonstrated in 17-year old former preterm infants whose brain size, caudate nucleus volume, and intelligence quotient (IQ) were directly associated with protein and energy intake during the postnatal period.[121,124,125] The slower weight gain of preterm infants fed exclusively with breast milk appears to be caused by a deficit in lean mass, likely reflecting lower protein intake. Whether this pattern persists into childhood, is altered by breast milk fortification or later diet, or relates to functional outcomes are important research questions.[162] **Higher protein intakes have been shown to lead to greater length gain. Linear growth is associated with improved neurodevelopment,** including increased cognitive, language, and motor scores, higher IQs, and less cerebral palsy.[28,155,226] **Gains in fat-free mass also are associated with improved neurodevelopment,** including higher motor and cognitive scores, faster speed of brain processing and improved working memory, and faster speed of processing and IQ in preschool.[215,227,239] A current challenge in nourishing the preterm infant is that higher energy intakes required to achieve linear growth also resulted in increased fat mass, a risk for later obesity.[27,47]

Human milk from an infant's own mother is unique and the preferred source of protein for that newborn. There are times when mother's own milk is not available. In such situations, **donor human milk (DHM) is a valid alternative.** DHM is a viable substitute when obtained from established milk banks that follow protocols established by the Human Milk Banking Association of North America (www.hmbana.org).[34,115] Human milk contains whey-predominant protein (whey:casein ratio of 70-80:30-20), whereas cow's milk has a whey:casein ratio of 18:82. Whey protein is particularly rich in essential and conditionally essential amino acids. **Milk and colostrum expressed from mothers of preterm infants is higher in protein than milk from mothers of term infants, but both have higher protein concentrations at the onset of lactation than later during full or mature lactation.**[222] **Nonetheless, fortification of preterm maternal milk with protein (and calcium, phosphorus, sodium, potassium, and lipid) is necessary to promote growth rates approximating those of normal human fetuses, particularly in ELBW and VLBW preterm infants (Table 17.3).**[4,233] Products to fortify human milk commonly used in US NICUs include Enfamil Human Milk Fortifier (Mead Johnson Nutritionals, Evansville, IN) and Similac Human Milk Fortifier (Abbott Nutrition, Columbus, OH), which provide an additional 1.4 g/dL of protein. Current human milk fortifiers contain partially hydrolyzed protein formulations to improve digestion, improve absorption, and reduce the risk of bovine protein-induced inflammation in the intestine. A human milk–based fortifier, Prolact+ H^2MF (Prolacta Bioscience, Monrovia, CA), also is available. Recent studies indicate that an exclusive human milk–based diet for preterm infants reduces the risk of NEC.[168,211]

A liquid protein supplement may be required to meet protein requirements in preterm infants.[166,181] **Enteral protein intakes of 3.2 to 4.2 g/kg/day are recommended for preterm infants born at 29 to 34 weeks of gestation. However, enteral protein requirements are 4.0 to 4.5 g/kg/day for less than 29-week ELBW infants** to meet the higher protein synthesis and growth requirements at this stage of gestation and to compensate for accumulated protein deficits and stool losses. From a practical perspective, a rough estimate for human milk protein content is ~1.4 g/dL at postnatal week 2 to 3 and ~1.1 g/dL at postnatal week 4 and beyond. Thus, a milk intake of 150 to 160 mL/kg/day of 24 kcal/oz feedings would provide 4.2 to 4.5 g protein/kg/day at week 2 to 3, but only 3.8 to 4.0 g protein/kg/day at week 4 and beyond, which would not support optimal protein balance and lean body growth. A reasonable approach, therefore, would be to supplement ELBW infants with liquid protein, which would add 0.45 g protein/kg/day. **Liquid protein supplementation**

TABLE 17.3 COMPOSITION OF PRETERM HUMAN MILK AND HUMAN MILK FORTIFIERS

		COW'S MILK–DERIVED HUMAN MILK FORTIFIERS (PER 4 PACKETS OR VIALS)					HUMAN MILK–DERIVED HUMAN MILK FORTIFIER (PER 20 mL)
	MATURE PRETERM HUMAN MILK (28 DAYS, APPROXIMATE PER 100 mL*)	ENFAMIL HUMAN MILK FORTIFIER POWDER†	ENFAMIL HUMAN MILK FORTIFIER ACIDIFIED LIQUID†	SIMILAC HUMAN MILK FORTIFIER POWDER‡	SIMILAC HUMAN MILK FORTIFIER CONCENTRATED LIQUID‡	SIMILAC HUMAN MILK FORTIFIER EXTENSIVELY HYDROLYZED PROTEIN CONCENTRATED LIQUID‡	PROLACT+4 H²MF
Energy (kcal)	67–75	14	30	14	27	28	28
Protein							
Amount (g)	1.3–1.8	1.1	2.2	1	1.4	2	1.2
Source	Human milk	Milk protein isolate and whey protein isolate hydrolysate	Whey protein isolate hydrolysate	Nonfat milk and whey protein concentrate	Nonfat milk and whey protein concentrate	Casein hydrolysate	Human milk
Fat							
Amount (g)	3–3.9	1	2.3	0.36	1.06	0.84	1.8
Source	Triglycerides	MCT oil (70%) Soy oil (30%)	MCT oil Soy oil High oleic sunflower oil	MCT oil	MCT oil, *M. alpina* oil, *C. cohnii* oil	MCT oil, soy oil, coconut oil, *M. alpina* oil, *C. cohnii* oil	Triglycerides
Carbohydrate							
Amount (g)	6–11	<0.4	<1.2	1.8	3.23	3	1.8
Source	Lactose and glucose	Mineral salts and corn syrup solids	Mineral salts	Corn syrup solids	Corn syrup solids	Maltodextrin, modified corn starch	Lactose and glucose
Minerals							
Calcium (mg)	25	90	116	117	140	120	103
Phosphorus (mg)	13	50	63	67	80	68	53.8

Sodium (mEq)	0.9 ± 0.2		0.7	1.2	0.65	0.9	0.8	37
Potassium (mEq)	1.2 ± 0.3		0.7	1.15	1.61	2.12	2	50
Chloride (mEq)	1.5 ± 0.2		0.4	0.8	1.07	1.51	1.6	29
Iron (mg)	0.2		1.44	1.76	0.35	0.43	0.44	0.1
Zinc (mg)	0.3		0.72	0.96	1	1.21	1.24	0.7
Magnesium (mg)	3		1	1.84	7	8.6	8.4	4.7
Other Characteristics								
Potential renal solute load (mOsm/100 mL)	12.6	24	25.8		23.1	23.1	25.6	N/A
Osmolality (mOsm/kg water)	290	+35 (above human milk when mixed)	+36 (above human milk when mixed)		+95 (above human milk when mixed)	+95 (above human milk when mixed)	+160 (above human milk when mixed)	+ <70 (above human milk when mixed)[§]
pH			~4.3 product alone ~4.7 at normal dilution					
Emulsifier							Gellan gum	

This table lists the major constituents; refer to product inserts for a complete listing of vitamins, minerals, and trace elements. *MCT,* Medium-chain triglyceride.

*Data from Klein CJ. Nutrient requirements for preterm infant formulas. *J Nutr.* 2002;132:1395S.

†Mead Johnson Nutritionals, Evansville, Indiana.

‡Ross Products Division, Abbott Nutrition, Columbus, Ohio.

§Sullivan S, Schanler RJ, Kim JH, et al. An exclusive human milk based diet is associated with a lower rate of necrotizing enterocolitis than a diet of human milk and bovine milk-based products. *J Pediatr.* 2010;156:562.

BOX 17.4 INDICATIONS FOR USING HIGH-PROTEIN PRETERM FORMULAS

- Weight <1500 g
- Fluid-/volume-restricted infants
- Promotion of wound healing
- Cumulative deficit of protein intake
- Inadequate growth in length and/or head circumference
- Unfortified human milk feeds (e.g., direct breastfeeding or use of donor milk)

should be considered in infants less than 1000 to 1250 g after they reach approximately 24 weeks and day of life 21 to increase enteral protein delivery to the higher end of the protein goals. It may be added sooner with DHM because of the even lower donor maternal milk protein, or if there are concerns for poor linear growth. **Liquid protein supplementation should be stopped at 34 to 35 weeks when protein requirements decline. When human milk is not available, "high-protein" preterm formulas are available that contain higher protein contents than standard preterm formulas (3.3 to 3.6 g/100 kcal) and are recommended to increase protein delivery for ELBW infants[48] (see Table 17.3) (Box 17.4). Higher BUN values are often found in such infants, but this should not indicate excess protein intake, as it is an appropriate metabolic response of increased protein oxidation producing ammonia and hepatic detoxification of ammonia to urea.**[7,146]

The amino acid profile in the newborn diet is as important as the amount of protein provided. **Growth rate of lean body mass is determined directly by the intake of the essential amino acids.** Conditionally, or developmentally, essential amino acids (those that are uniquely required in larger amounts at certain developmental stages and cannot be synthesized at sufficient rates for requirements) also are important to the infant, especially if preterm. Normal growth, energy metabolism, and immune function depend on appropriate availability of these amino acids. Particularly in the rapidly growing infant, growth requirements may not be met by the relatively limited intake of essential amino acids common with most current nutritional regimens or by the limited biosynthesis of conditionally essential amino acids.

Fat

Human neonates are unique among neonatal mammals in having a relatively high white fat content of 12% to 18% of body weight at term. The term infant also has stores of brown fat, which are necessary for neonatal thermogenesis. **In utero fat deposition occurs predominantly during the last 12 to 14 weeks of gestation,** and fat accretion in adipose tissue adds increasingly large caloric requirements to the lean tissue growth. **Infants born preterm before fat deposition has occurred have insufficient fat stores for use as energy and for thermogenesis.** Dietary fats also are important to sustain growth. Once protein intake is sufficient to promote net lean body accretion, however, additional energy primarily produces more body fat, which increases almost linearly at energy intakes greater than 80 to 90 kcal/kg/day in normal, healthy preterm infants. **Rapid gains in adiposity have the potential to produce later-life obesity, an increasingly recognized risk of excessive energy intake.**[113]

Dietary fats also provide essential fatty acids (EFAs) and promote the absorption of fat-soluble vitamins. Newborn infants absorb fat less efficiently than older children. Preterm infants demonstrate even greater deficiencies in fat digestion and metabolism. Pancreatic lipase and bile acids are less available for fat digestion and absorption. Lingual and gastric lipases, present in greater amounts in term newborn oral-pharyngeal secretions than in the preterm infant, compensate for deficient pancreatic lipase, as does mammary gland lipase if the infant is receiving breast milk, but even these are reduced in the preterm infant. **Current recommended intakes for dietary fat consist of 40% to 52% of total calories (4.4 to 5.7 g/100 kcal).**

LC-PUFAs are essential for normal growth and development, particularly of the retina and brain (especially affecting cognition). LC-PUFA supplementation, therefore, has been a topic of much discussion and research in recent years. Of particular interest are the n-3 and n-6 EFAs, alpha-linolenic acid (ALA) and linoleic acid (LA), and their metabolites, docosahexaenoic acid (DHA) and arachidonic acid (ARA), respectively.[171] **Both term and preterm human milk contain considerable quantities of ALA. The term infant can synthesize DHA from its precursor ALA, but whether the synthesized amount is sufficient**

for growth and development in preterm infants remains uncertain. Human milk also contains preformed LC-PUFAs, but the DHA content of human milk is highly variable, ranging from ~0.08% to ~0.2% in the US, to ~0.3% in other parts of the world and in formulas.[20] Nevertheless, **current diets for very preterm infants do not provide enough EFA to match normal fetal development.** For example, fetal white adipose tissue accumulation of n-3 fatty acids during the last trimester is about 45 to 65 mg/day, mostly as 22:6n-3 or DHA. Human milk has on average 3.7 g fat/dL with 0.2% to 0.4% of fatty acids as 22:6n-3, so a 1-kg preterm infant fed at full enteral feeds of 180 mL/day would get only 13 to 25 mg 22:6n-3/day, clearly below normal in utero accretion rates. As a result, **the current diet for preterm infants is deficient in DHA, but the long-term significance of this deficiency is not known, or how these infants would develop if fed to sufficiency.**[152]

In an effort to make formula more like human milk, manufacturers in the United States have added DHA and ARA to both term and preterm infant formulas. This also has made clinical cases of EFA deficiency relatively rare. When severe and prolonged enough, EFA deficiency can lead to a clinical syndrome consisting of dermatitis (especially in the perianal region), thrombocytopenia, infection, and failure to thrive. The metabolic profile is characterized by an increased triene/tetraene ratio (increased nonessential trienoic:ETA 20:3ω9 to decreased essential tetraenoic:AA 20:4ω6).[109]

LC-PUFA supplementation is thought to be safe for both term and preterm infants.[91,96,122,147] **The evidence for long-term benefit, however, particularly for term infants, has been mixed.**[117] A recent Cochrane review concluded that the majority of randomized controlled trials have not shown benefit nor harm of LC-PUFA supplementation on the neurodevelopmental outcomes of term infants.[132] **For preterm infants, in whom PUFAs are particularly important for growth, brain, and visual development and who have not had the opportunity for late gestation accumulation of fats, there may be benefit and little risk with supplementation.**[96,97,145,235] A recent systematic analysis of the literature found a trend for LC-PUFAs to reduce the risk of BPD and NEC.[281] However, similar to LC-PUFA in term infants, the most recent Cochrane review concluded that no clear long-term benefits or harms were demonstrated for preterm infants receiving LC-PUFA–supplemented formula.[184]

Some fats (e.g., EFAs) are essential for normal infant growth.[145] **The amount of medium-chain triglycerides (MCTs) is also important for fat nutrition because of their greater absorptive capacity, especially in the underdeveloped GI tract of preterm infants.** MCTs do not require bile salts for absorption and can be directly absorbed into the portal venous circulation. This offers theoretical advantages for the preterm infant, although there is little evidence that inclusion of MCTs improves energy or protein/nitrogen absorption or retention, or growth of the healthy preterm infant.[273] The content of MCTs varies considerably among current feedings for preterm and term infants: expressed human milk, 2%; fortified human milk, 2% to 18%; preterm formula, 40%; and term formula, 8%. The considerable variability in milk MCT content parallels that of fat content of human milk and occurs because of interindividual variation and changes in milk fat content during the day, throughout lactation, and within one feeding (foremilk to hind milk). MCTs do improve fat absorption and energy intake in infants with hepatic dysfunction or short bowel syndromes. Excess MCTs can lead to diarrhea and dicarboxylic acid excretion.

Carbohydrates

Carbohydrate reserves begin to accumulate as glycogen in the developing fetus as early as the start of the second trimester. Most of this glycogen (as much as 90% of total body glycogen in term infants) serves local cellular needs in different organs, whereas hepatic glycogen specifically provides glucose for other glucose-dependent tissues, primarily the brain. Immediately after birth, with cessation of glucose supply from the placenta, the neonate must use stored glycogen for energy. **The newborn can exhaust the supply of stored glucose from the liver within 12 hours of birth under severely stressful conditions** (e.g., hypoxia, hypotension, increased catecholamine and glucagon release) **if milk/formula or IV glucose is not provided. The normal glucose utilization rate in the term newborn is 3 to 5 mg/kg/min, but slightly higher (5 to 7 mg/kg/min) in preterm infants. The brain accounts for most of the glucose used in the whole body, especially in preterm and asymmetrically growth-restricted infants, who have a larger-than-normal brain:body-weight ratio.**

The predominant carbohydrate in human milk is lactose, a disaccharide composed of glucose and galactose. **Glucose has a central role in energy metabolism.** Galactose provides 50% of the calories derived from lactose; its major metabolic role is in energy storage, because the newborn liver readily incorporates galactose from the portal circulation into hepatic glycogen.

Provision of 40% to 50% of total caloric intake as carbohydrate (10 to 12 g/kg/day) prevents breakdown of fat and oxidation of lipids that produce ketone bodies. Ketones can substitute for glucose for energy production, particularly in the brain, when glucose is limited and hypoglycemia develops. **Carbohydrate generally is supplied as lactose in human milk or commercial formulas. Preterm formulas have reduced lactose content, 40% to 50% of the total carbohydrate, and human milk fortifiers provide little to no lactose.** If there are signs of lactose intolerance, such as frequent loose stools, abdominal distention, apparent cramping, or positive stool reducing substances (Clinitest), a lactose-free infant formula may be considered (Table 17.4). **Use of such lactose-free products should be reserved for those rare infants with clinically proven lactose intolerance.**

Vitamins

Vitamins are organic substances that are present in trace amounts in natural food sources and are essential for normal metabolism. **Lack of vitamins in the diet produces well-recognized deficiency states in children and adults, but the biological roles of many vitamins are not completely understood in preterm infants, and recognition of clinical deficiency states is difficult.** Certain vitamins have received close attention in neonatology, in particular vitamin C for its role in enhancing iron absorption from the GI tract, vitamin K for prevention of hemorrhagic disease of the newborn,[13] vitamin D for the prevention of rickets,[2] and vitamins A and E as antioxidants.[118] Vitamin E protects lipid-containing red blood cell membranes against oxidative injury, thus reducing hemolysis, and may prevent neonatal oxygen toxicity, including retinopathy of prematurity (ROP) and intraventricular hemorrhage (IVH). Vitamin A is essential for cell growth and differentiation of epithelial tissues, including those in the lung. **Preterm infants have low stores of vitamin A at birth, and preterm infants with lung disease have lower plasma vitamin A levels than those without lung disease. Supplementation has been shown in some studies to decrease chronic lung disease in ELBW infants.**[76] Vitamin A supplementation has not become standard practice, in part because of the need for repeated intramuscular injections, as absorption from the GI tract does not appear to be sufficient. **Infants with short bowel syndrome who have lost function of the terminal ileum should receive supplementation of the fat-soluble vitamins to avoid deficiency.**[110]

Because **vitamins have a central role in many metabolic processes, signs of vitamin deficiency can be nonspecific, such as lethargy, irritability, and poor growth.** Table 17.5 is a summary of the recommended vitamin intake for enterally fed infants. For comparison, the average vitamin content of term human milk and commercial infant formulas is included in Table 17.4. **Vitamins are generally given on a weight-specific basis, not a gestational age basis.** Routine supplementation of vitamins above the recommended doses is not advised because of possible toxicity and lack of clearly demonstrated benefits. For example, the recommended dose of vitamin D for preterm infants, once they have reached full enteral feeds and weigh more than 1500 g, is 400 IU/day, up to a maximum of 1000 IU/day.[2] **Higher doses (800 to 1000 IU per day) have been recommended for infants born extremely preterm or infants with short bowel syndrome, cholestasis, and long-term exposure to diuretics or corticosteroids. In ELBW very preterm infants, serum vitamin D concentrations should be measured once they are on full enteral feedings and starting to grow, and then repeated every 2 to 4 weeks to ensure that with or without vitamin D treatment, serum concentrations remain above a reasonable level** (>50 nmol/L). Excessive dosing, particularly noted in former ELBW extremely preterm infants and especially after discharge from the NICU and at home, can produce hypercalcemia, constipation, muscle weakness, and vomiting. In more severe cases, it damages the bones and kidneys. Infants on high-dose vitamin D should have their serum vitamin D concentration checked on discharge from the NICU and soon after in clinic to ensure that serum concentrations do not increase to dangerous levels when growth is slowing and milk or formula feedings are increased.

TABLE 17.4 COMPARATIVE NUTRITIONAL COMPOSITION OF TERM INFANT FEEDINGS PER 100 kcal

			COW'S MILK–BASED WITH INTACT PROTEIN			LACTOSE FREE	SOY PROTEIN–BASED	
	MATURE HUMAN MILK (28 DAYS)	ENFAMIL NEWBORN	ENFAMIL INFANT†	SIMILAC ADVANCE STAGE 1‡	SIMILAC ADVANCE STAGE 2‡	SIMILAC SENSITIVE	ENFAMIL PROSOBEE LIPIL†	SIMILAC ISOMIL ADVANCE‡
Nutrient density (kcal/oz)	20	20	20	20	19	19	20	19
Energy (kcal)	98–110	100	100	100	100	100	100	100
Protein								
Amount (g)	1.8	2.1	2	2.07	2.07	2.14	2.5	2.45
% Total calories	7	8	8	8	8	8.5	10	10
Source	Human milk	Nonfat milk and whey protein concentrate	Nonfat milk and whey protein concentrate	Nonfat milk and whey protein concentrate	Nonfat milk and whey protein concentrate	Milk protein isolate	Soy protein isolate and L-methionine	Soy protein isolate and L-methionine
Fat								
Amount (g)	4.3–4.9	5.3	5.3	5.4	5.6	5.4	5.3	5.46
% Total calories	50	48	48	49	50	49	48	49
Source	Triglycerides	Palm olein Soy oil Coconut oil High oleic sunflower oil Single-cell oil products (DHA and ARA)	Palm olein Soy oil Coconut oil High oleic sunflower oil Single-cell oil products (DHA and ARA)	High oleic safflower oil Soy oil Coconut oil Single-cell oil products (DHA and ARA)	High oleic safflower oil Soy oil Coconut oil Single-cell oil products (DHA and ARA)	High oleic safflower oil Soy oil Coconut oil Single-cell oil products (DHA and ARA)	Palm olein Soy oil Coconut oil High oleic sunflower oil Single-cell oil products (DHA and ARA)	High oleic safflower oil Soy oil Coconut oil Single-cell oil products (DHA and ARA)
Linoleic acid (mg)	440–1500	860	800	1000	1000	1000	860	1000

Continued

TABLE 17.4 COMPARATIVE NUTRITIONAL COMPOSITION OF TERM INFANT FEEDINGS PER 100 kcal—cont'd

Carbohydrate								
Amount (g)	10–11	11.2	11.3	10.8	10.7	10.7	10.6	10.4
% Total calories	40–44	45	45	43	43	43	42	42
Source	Lactose and glucose	Lactose	Lactose	Lactose	Lactose	Maltodextrin and sugar	Corn syrup solids	Corn syrup and sucrose
Minerals								
Calcium (mg)	39–45	73	78	78	82	88	105 (5.2)	110 (5.5)
Phosphorus (mg)	18–24	43	43	42	44	59	69	79
Ca:P ratio	1.9–2.1	1.8	1.8	1.8	1.8	1.5	1.5	1.4
Sodium (mg [mEq])	18–26 [0.8–1.1]	27 [1.2]	27 [1.2]	24 [1]	25 [1.1]	32 [1.4]	36 [1.6]	44 [1.9]
Potassium (mg [mEq])	60–80 [1.5–2]	108 [2.8]	108 [2.8]	105 [2.7]	110 [2.8]	110 [2.8]	120 [3.1]	110 [2.8]
Chloride (mg [mEq])	55–63 [1.6–1.8]	63 [1.8]	63 [1.8]	65 [1.8]	68 [1.9]	68 [1.9]	80 [2.3]	65 [1.8]
Iron (mg)	0.05–0.75	1.8	1.8	1.8	1.9	1.9	1.8	1.9
Zinc (mg)	0.2–0.3	1	1	0.75	0.79	0.79	1.2	0.79
Magnesium (mg)	4.5–5	8	8	6	6	6	8–11	7.9
Vitamins								
Vitamin A (international units)	110–320	300	300	300	300	300	300	300
Vitamin D (international units)	3–3.2	75	60	60	75	60	60	60
Vitamin E (international units)	0.3–0.6	2	2	1.5	1.5	1.5	2	1.5
Vitamin K (mcg)	0.3	9	9	8	8	8	8–9	11
Vitamin C—ascorbic acid (mg)	5.6–6	12	12	9	9	9	12	9
Vitamin B_1—thiamine (mcg)	29–31	80	80	100	100	100	80	63

TABLE 17.4 COMPARATIVE NUTRITIONAL COMPOSITION OF TERM INFANT FEEDINGS PER 100 kcal—cont'd

Vitamins								
Vitamin B_2—riboflavin (mcg)	49–51	140	140	150	160	160	90	95
Vitamin B_6 (mcg)	10–46	60	60	60	63	63	60	63
Folic acid (mcg)	2.5–18	16	16	15	16	16	16	16
Other Characteristics								
Potential renal solute load (mOsm)	14	19.1	18.6	18.7	20.5	20.3	23	23.2
Osmolality (mOsm/kg water)	290–305	300	300	310	310	200	200	200

This table lists the major constituents; refer to product inserts for a complete listing of vitamins, minerals, and trace elements.
†Mead Johnson Nutritionals, Evansville, Indiana.
‡Abbott Nutrition, Columbus, Ohio.
ARA, Arachidonic acid; *DHA,* docosahexaenoic acid
Data from Klein CJ, ed. Nutrient requirements for preterm infant formulas. *J Nutr* 2002;132:1395S; Koletzko B, Poindexter B, Uauy R, eds. Nutritional care of preterm infants: scientific basis and practical guidelines. *World Rev Nutr Diet.* vol. 110. Basel: Karger; 2014:1–3.

Minerals and Trace Elements

The content of minerals in human milk is the gold standard for mineral requirements in term infants. Mineral requirements for the preterm infant have been estimated from in utero accretion rates. **Preterm infants are relatively lacking in some important minerals (e.g., iron, calcium, zinc) because their accumulation occurs mostly in the third trimester.** Published recommendations for selected daily intakes in healthy, enterally fed preterm infants are shown in Tables 17.5 and 17.6.[143]

Trace mineral supplementation of human milk or use of an enriched preterm formula usually is necessary to achieve the recommended trace element requirements. Iron intake should be 2 to 4 mg/kg/day for both term and preterm infants who are enterally fed, but increased to 6 mg/kg/day for preterm infants with anemia of prematurity who are receiving recombinant erythropoietin. Risks of iron overload and toxicity (e.g., possible increased risk of ROP) increase with red cell transfusions. Iron supplementation often is delayed for 2 weeks after a transfusion, but timing is variable. **Formula-fed infants should receive only iron-fortified formula, beginning with the first formula feedings.**

Enteral absorption rates for both calcium and phosphorus are limited in preterm infants, but are relatively greater with milk feeding and calcium- and phosphorus-enriched preterm formulas. **Adequate enteral intake for term infants in the first 6 months of life is about 70 mg/kg/day of calcium and about 100 mg/day of phosphorus. The requirements for preterm infants are much higher because of more active bone formation and remodeling: 150 to 220 mg/kg/day for calcium and 60 to 140 mg/kg/day for phosphorus.** The ideal Ca:Phos ratio is 1.8:1–2:1 mg weight basis. **Fortification of human milk is necessary to ensure adequate intakes of calcium and phosphorus to preterm infants who are fed human milk, particularly with mature mother's milk**

TABLE 17.5 RECOMMENDED ENTERAL MINERAL AND VITAMIN INTAKE FOR INFANTS

	TERM (PER 100 kcal)	PRETERM (PER 100 kcal)
Minerals		
Calcium (mg)	50–140	123–185
Phosphorus (mg)	20–70	82–109
Ca:P ratio by weight	1.1–2:1	1.7–2:1
Sodium		
mg	25–50	39–63
mEq	1.1–2.2	1.7–2.7
Potassium		
mg	60–160	60–160
mEq	1.5–4.1	1.5–4.1
Chloride		
mg	50–160	60–160
mEq	1.4–4.6	1.7–4.6
Magnesium (mg)	4–17	6.8–17
Iron (mg)	0.2–1.65	1.7–3
Zinc (mg)	0.4–1	1.1–1.5
Manganese (mcg)	1–100	6.3–25
Copper (mcg)	60–160	100–250
Iodine (mcg)	8–35	6–35
Selenium (mcg)	1.5–5	1.8–5
Fluoride (mcg)	0–60	Maximum 25
Chromium (mcg)	—	—
Molybdenum (mcg)	—	—
Vitamins		
Vitamin A (mcg RE)	60–150	204–380
(international units)	203–506	679–1265
Vitamin D (international units)	40–100	75–270
Vitamin E (mg α-TE/100 kcal)	0.5-(5 mg α-TE/g PUFA)	2–8
Vitamin K (mcg RE)	1–25	4–25
Vitamin C—ascorbic acid (mg)	6–15	8.3–37
Pantothenic acid (mcg)	300–1200	300–1900
Biotin (mcg)	1–15	1–37
Vitamin B_1—thiamine (mcg)	30–200	30–250
Vitamin B_2—riboflavin (mcg)	80–300	80–620
Vitamin B_3—niacin (mcg)	550–2000	550–5000
Vitamin B_6—pyridoxine (mcg)	30–130	30–250
Vitamin B_{12}—cobalamin (mcg)	0.08–0.7	0.08–0.7
Folate (mcg)	11–40	30–45

RE, Retinol equivalents.

Data from Klein CJ, ed. Nutrient requirements for preterm infant formulas. *J Nutr.* 2002;132:1395S; Greer FR. Vitamins. In Thureen PJ, Hay WW Jr, ed. *Neonatal Nutrition and Metabolism.* 2nd ed. Cambridge, MA: Cambridge University Press; 2006.

TABLE 17.6 COMPARATIVE NUTRITIONAL COMPOSITION OF HYDROLYZED INFANT FEEDINGS PER 100 kcal

	PARTIALLY HYDROLYZED		EXTENSIVELY HYDROLYZED			COMPLETELY HYDROLYZED		
	ENFAML GENTLEASE	SIMILAC TOTAL COMFORT	ENFAMIL NUTRAMIGEN	SIMILAC EXPERT CAREALIMENTUM	ENFAMIL PREGESTIMIL	ENFAMIL PURAMINO	ELECARE (FOR INFANTS)	NUTRICIA NEOCATE INFANT DHA/ARA
Nutrient density (kcal/oz)	20	19	20	20	20	20	20	20
Energy (kcal)	100	100	100	100	100	100	100	100
Protein								
Amount (g)	2.3	2.32	2.8	2.75	2.8	2.8	3.1	2.8
% Total calories	9	9	11	11	11	11	15	11
Source	Partially hydrolyzed nonfat milk and whey protein concentrate solids (soy)	Whey protein hydrolysate	Casein hydrolysate, L-cystine, L-tyrosine, L-tryptophan	Casein hydrolysate, L-cystine, L-tyrosine, L-tryptophan	Casein hydrolysate, L-cystine, L-tyrosine, L-tryptophan	Free L-amino acids	Free L-amino acids	Free L-amino acids
Fat								
Amount (g)	5.3	5.4	5.3	5.54	5.6	5.3	4.8	5.1
% Total calories	48	49	48	48	48	48	43	46
Source	Palm olein, soy, coconut, and high oleic sunflower oils Single-cell oil products (DHA and ARA)	High oleic safflower oil, soy and coconut oil Single-cell oil products (DHA and ARA)	Palm olein, soy, coconut and high oleic sunflower oils Single-cell oil products (DHA and ARA)	Safflower oil, MCT oil, soy oil Single-cell oil products (DHA and ARA)	MCT oil, soy oil, corn oil, and high oleic safflower oil or sunflower oil Single-cell oil products (DHA and ARA)	Palm olein, coconut, soy and high oleic sunflower oils Single-cell oil products (DHA and ARA)	Safflower oil, MCT, soy oil Single-cell oil products (DHA and ARA)	MCT, high oleic sunflower oil, sunflower oil, canola oil Single-cell oil products (DHA and ARA)
Oil ratio (approximate)	44:19.5: 19.5:14.5	40:30 :29	44:19.5: 19.5:14.5	38:33:28	55:25: 10:7.5	44:19.5: 14.5	39:33: 28	N/A
Linoleic acid (mg)	800–860	1000	860	1900	940	860	840	738

Continued

TABLE 17.6 COMPARATIVE NUTRITIONAL COMPOSITION OF HYDROLYZED INFANT FEEDINGS PER 100 kcal—cont'd

	PARTIALLY HYDROLYZED		EXTENSIVELY HYDROLYZED			COMPLETELY HYDROLYZED		
	ENFAML GENTLEASE	SIMILAC TOTAL COMFORT	ENFAMIL NUTRAMIGEN	SIMILAC EXPERT CAREALIMENTUM	ENFAMIL PREGESTIMIL	ENFAMIL PURAMINO	ELECARE (FOR INFANTS)	NUTRICIA NEOCATE INFANT DHA/ARA
Carbohydrate								
Amount (g)	10.8	11	10.3	10.2	10.2	10.3	10.7	10.8
% Total calories	43.5	42	41	41	41	41	42	43
Source	Corn syrup solids	Corn syrup solids, sugar, galacto-oligo-saccharides	Corn syrup solids	Sugar, modified tapioca starch	Corn syrup solids	Corn syrup solids, modified tapioca starch	Corn syrup solids	Corn syrup solids
Minerals								
Calcium (mg)	82	105	94	105	94	94	116	116
Phosphorus (mg)	46	70	52	75	52	52	84.2	82.2
Ca:P ratio	1.8:1	1.5:1	1.8:1	1.4:1	1.8:1	1.8:1	1.4:1	1.4:1
Sodium mg (mEq)	36 (1.6)	46 (2)	47 (2)	44 (1.9)	47 (2)	47 (2)	45 (2)	39.1 (1.7)
Potassium mg (mEq)	108 (3.1)	121 (3.1)	110 (2.8)	118 (3)	110 (2.8)	110 (2.8)	150 (3.9)	109 (2.8)
Chloride mg (mEq)	63 (1.8)	68 (1.9)	86 (2.4)	80 (2.3)	86 (2.4)	88 (2.5)	60 (1.7)	79.9 (2.2)
Iron (mg)	1.8	1.9	1.8	1.8	1.8	1.8	1.8	1.5
Zinc (mg)	1	0.79	1	0.75	1	1	1.15	1.1

Minerals								
Magnesium (mg)	8	6	8–11	7.5	8	11	84	10.3
Vitamins								
Vitamin A (international units)	300	300	300	300	350	300	273	280
Vitamin D (international units)	60	60	50	45	50	50	60	72.9
Vitamin E (international units)	2	1.5	2	3	4	2	2.1	1.4
Vitamin K (mcg)	9	8	8–9	15	12	8	13	8.8
Vitamin C—ascorbic acid (mg)	12	9	12	9	12	12	9	10.7
Vitamin B_1—thiamine (mcg)	80	100	80	60	80	80	210	140
Vitamin B_2—riboflavin (mcg)	140	160	90	90	90	90	105	110
Vitamin B_6 (mcg)	60	63	60	60	60	60	84.2	112
Folic acid (mcg)	16	16	16	15	16	16	29.5	13.3
Other Characteristics								
Potential renal solute load (mOsm)	21	22.5	25	25.3	25	25	18.7	16.8
Osmolality (mOsm/kg water)	220–230	200	260–320	370	260–280	350	350	340

This table lists the major constituents; refer to product inserts for a complete listing of vitamins, minerals, and trace elements.
†Mead Johnson Nutritionals, Evansville, Indiana
‡Abbott Nutrition, Columbus, Ohio.
ARA, Arachidonic acid; *DHA,* docosahexaenoic acid; *MCT,* medium-chain triglycerides.

and donor milk. Risk factors in preterm infants for calcium and phosphorus deficiency and subsequent rickets are: gestational age less than 27 weeks or birth weight less than 1000 g; long-term parenteral nutrition (>4 to 5 weeks); severe BPD requiring diuretics and fluid restriction; long-term steroid treatment; history of NEC; and intolerance to enteral formula or human milk. **Supplementation with calcium and phosphorus has been shown to decrease the incidence of metabolic bone disease (osteopenia) in preterm infants.**[2] Mineral supplementation of human milk or use of an enriched preterm formula (Table 17.7) usually is necessary to achieve the recommended mineral requirements.

COMPOSITION OF ENTERAL FEEDINGS

Human Milk

The ideal enteral diet for almost all term newborn infants is human milk,[16,247] **which provides sufficient energy, protein, fat, carbohydrate, micronutrients, and water for normal growth.** Contraindications to the use of human milk, which are rare, are found in Box 17.5. **The development of a beneficial intestinal flora, characterized by a large prevalence of bifidobacteria and lactobacilli, is strongly supported by human milk feedings.**[52,163,173,174] In addition, human milk, unlike formulas, provides a variety of antimicrobial factors that protect against infections, such as secretory immunoglobulins (IgA), leukocytes, complement, lactoferrin, and lysozyme.[193] **The provision of human milk is particularly important for the preterm infant to reduce the rate of NEC**[53,66,168] **and to promote immune development.**[160,257] Human milk also contains hormones and growth factors such as epidermal and nerve growth factors, IGF-1 and IGF-2, erythropoietin, prolactin, calcitonin, steroids, thyrotropin-releasing hormone, and thyroxine.[238] **These milk hormones and trophic factors play active roles in organ maturation, growth, and health.** Several essential and conditionally essential amino acids are present in high concentrations in human milk.[280]

The protein and fat components of human milk are readily digestible, and human milk contains large numbers of enzymes that aid in nutrient digestion and processing (e.g., lipase). Exclusive human milk feeding of infants at high risk for atopy or milk protein allergy may reduce the development of disease in infancy.[106,126,224] Furthermore, human milk is protective against the development of obesity in childhood and beyond.[276] **Preterm infants breastfed at discharge have less subnormal neurodevelopment at 2 to 5 years of age.**[236] These effects last into infancy,[269] childhood,[165] and even into adolescence.[123] Thus, as clearly stated by the American Academy of Pediatrics, **human milk is the recommended basis of nutrition for the preterm infant**[16]**: (1) all preterm infants *should* receive human milk; (2) human milk should be fortified with protein, minerals, and vitamins to ensure optimal nutrient intake for infants weighing less than 1500 g at birth**[282]**; and (3) pasteurized DHM, appropriately fortified, *should* be used if mother's own milk is unavailable or its use is contraindicated.**

The preterm infant will not grow at the normal rate of fetal growth on human milk alone, because of the special nutritional requirements addressed previously. In fact, the larger the fraction of total feeding provided by just human milk without supplementation, the greater the reduction in final weight at term gestational age.[65] **Recommended daily requirements for energy, protein, calcium, sodium, phosphorus, magnesium, iron, zinc, and several vitamins necessary to meet the normal rate of in utero growth usually will not be achieved in the growing "healthy" preterm infant who is fed with unsupplemented human milk.** The preterm infant with respiratory distress, infection, excessive heat losses, GI disorders, or surgical stress has even greater nutritional needs. Nonetheless, **milk from mothers of preterm infants has more protein and sodium than milk obtained at term and occasionally provides for adequate growth in larger and healthier preterm infants who have the capacity to take in large volumes, at times over 200 mL/kg/day. The lowest rates of NEC and possibly related sepsis have been found in preliminary studies with an exclusive breast milk diet** consisting of mother's milk and/or donor milk supplemented with human-milk–based fortifier (Prolacta Human Milk Fortifier, Prolacta, Monrovia, CA),[150,257] particularly compared with formula-fed infants.[74]

***Donor human milk* is a pasteurized product from accredited milk banks that is used when**

TABLE 17.7 MINERALS AND TRACE ELEMENTS IN NEONATAL NUTRITION

MINERAL OR ELEMENT	BIOLOGIC ROLE	DEFICIENCY STATE	RECOMMENDED INTAKE FOR GROWING PRETERM INFANTS
Sodium	Growth and tissue accretion, body fluid equilibrium, cellular energy, electrical charge balance	Poor growth, fluid imbalance, hypotension, neurologic dysfunction, lethargy, seizures	3–5 mEq/kg/day
Potassium	Growth and tissue accretion, acid-base balance, cellular energy, electrical charge balance	Myocardial damage, dysrhythmia, hypotonia, muscle weakness	2–3 mEq/kg/day
Chloride	Growth and tissue accretion, cellular energy, electrical charge balance	Failure to thrive, muscle weakness, alkalosis, vomiting	3–5 mEq/kg/day
Calcium	Bone and tooth formation, fat absorption, nerve conduction, muscle contraction	Osteomalacia, tetany, dysrhythmias, seizures	200 mg/kg/day
Phosphorus	Bone and tooth formation, energy transfer compounds	Rickets, neuropathy, weakness	100–140 mg/kg/day
Magnesium	Metalloenzymes, cellular electrical charge balance	Hypocalcemia, hypokalemia, diarrhea, tremor, arrhythmia	5–10 mg/kg/day
Iron	Hemoglobin formation, metalloenzymes	Anemia, apathy	2 mg/kg/day after 1 month of age
Zinc	Metalloenzymes, DNA-RNA synthesis, wound healing, host defenses	Growth restriction, dermatitis, alopecia, diarrhea, delayed wound healing, hypogonadism	1.2–1.5 mg/kg/day
Copper	Metalloenzymes, protein metabolism	Neuropathy, anemia, neutropenia, osteoporosis, depigmentation of hair and skin	100–200 mcg/kg/day
Manganese	Metalloenzymes, carbohydrate metabolism, antioxidants, hemostasis	Neurologic dysfunction, defects in lipid metabolism, reduced coagulants, growth restriction in animals	10–20 mcg/kg/day
Chromium	Carbohydrate metabolism, component of nucleic acids	Impaired glucose tolerance, impaired growth	2–4 mcg/kg/day
Selenium	Metalloenzymes, antioxidants	Cardiomyopathy, anemia, myositis	1.5–3 mcg/kg/day
Iodine	Thyroid hormone synthesis	Hypothyroidism, goiter, cretinism	1 mcg/kg/day
Molybdenum	Metalloenzymes	Neurologic and visual dysfunction, growth restriction in animals	2–3 mcg/kg/day

DNA, Deoxyribonucleic acid; *RNA,* ribonucleic acid.
From Kleinman RE, ed. *Pediatric Nutrition Handbook.* 6th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009.

maternal milk is insufficient or unavailable, because of the multitude of benefits associated with the use of human milk in preterm infants.[15] Donor milk is pasteurized to prevent infection, but this removes most of the anti-infective properties of milk. Nevertheless, infection rates and NEC rates are much lower with donor milk than with formulas.[191] There may be differences in milk composition as well, especially in protein content, but also energy, lactose, and fat content. Differences are particularly marked between human milk donated by women later in lactation after having delivered term infants compared with milk expressed by mothers delivering preterm infants[275]

BOX 17.5 CONTRAINDICATIONS TO BREASTFEEDING AND USE OF MATERNAL EXPRESSED BREAST MILK

- Mothers who have untreated brucellosis
- Mothers who have human immunodeficiency virus (HIV) infection
- Mothers who are positive for human T-cell lymphotrophic virus type I or II
- Mothers who have untreated miliary tuberculosis, active herpes virus lesions on the breast, acute H1N1 influenza, or acute varicella (*Note:* Expressed milk can be used because there is no concern about these infectious organisms passing through the milk and breastfeeding can be resumed when a mother with tuberculosis is treated for a minimum of 2 weeks and is documented that she is no longer infectious.)
- Maternal drug abuse (e.g., narcotics, phencyclidine, cocaine, cannabis) (*Note:* This contraindication is relative; mothers who test positive for such drugs should be enrolled in drug reduction programs rather than stopping breastfeeding, particularly among mothers with preterm infants, in whom the advantages of mother's milk generally outweigh the risks of addiction and neurodevelopmental defects in the infant.)
- Infants who have galactosemia

From American Academy of Pediatrics. Section on Breastfeeding. Breastfeeding and the use of human milk. *Pediatrics* 2012;129:e827.

(see Chapter 18). Donor milk in the United States also is low in DHA, containing only 50% to 75% the amount of milk from women in other parts of the world whose natural diets include more fish and vegetable oils that contain ALA and DHA.[20] **Donor milk is an appropriate choice for VLBW preterm infants whose maternal milk is unavailable[64] with greater than 75% improvement in feeding tolerance,[42] lower risk of NEC, and comparable neurodevelopmental outcomes when compared with supplementation with preterm formula.[221,198]**

There also is a growing interest in the use of *probiotics,* principally *Lactobacillus* species and *Bifidobacterium,* to assist in colonization of the preterm infant's gut with bacteria that might promote a more normal gut flora, replenish such flora after antibiotic use, and reduce the risk of GI disorders associated with abnormal gut flora, principally NEC. Several international trials support the use of probiotics to reduce the risk of NEC. **Use of probiotics in individual institutions might be considered if the NEC rate, particularly of surgical NEC and/or death from NEC, is relatively high (greater than 2%) despite efforts to reduce the risk of NEC. Such efforts to reduce NEC include the use of exclusive breast milk feeding (mother's own or donor), restricted use of antibiotics (in both mother and infant), and promotion of early trophic or gut-priming feedings with colostrum or mother's milk or donor milk.** A recent multicenter collaborative United Kingdom (UK) trial[23] and an updated *Cochrane* meta-analysis[9] that included 24 trials from around the world showed that **there is a significant decrease in NEC and all-cause mortality rate with the use of probiotics.**[11] Probiotic preparations containing either lactobacilli alone or in combination with bifidobacteria were found to be effective. Length of stay was 3 to 4 days shorter. Although there remains a risk for probiotic-related sepsis, especially in the most vulnerable ELBW infants, this has only rarely been reported and only in case reports outside of the UK trials and those reported in the Cochrane review. Recommendations for developing local institutional protocols to use probiotics have been published.[258] However, one of the primary reasons routine use of probiotics in preterm infants is not more widespread is the lack of available preparations that are regulated by the U.S. Food and Drug Administration (FDA).

The nutritional composition of term human milk is compared with commercial term infant formulas in Table 17.4. The nutrient content of "mature" preterm human milk is compared with fortified preterm human milk and preterm formulas in Table 17.8. Use of commercially available supplements to human milk that provide additional energy, protein, vitamins, and minerals is recommended.[136] Nutrient composition of these fortifiers is shown in Table 17.3. Most of the new formulations of the commercially available fortifiers now use hydrolyzed cow's milk protein, which might lead to less GI intolerance and possibly less NEC.

Formulas

Cow's milk–derived formulas have been modeled after the composition of human milk to provide biologically available protein mixtures with appropriate protein:energy ratios for normal growth. In general, **formulas designed for term infants contain 19 to 20 kcal/oz and are adequate to meet the needs of term infants with an intact GI tract and "normal" fluid requirements.** A whey and casein mixture approximating that of human milk is preferred.

TABLE 17.8 COMPARATIVE NUTRITIONAL COMPOSITION OF PRETERM FEEDINGS PER 100 kcal

		PREMATURE INFANT FORMULAS					
	MATURE PRETERM HUMAN MILK (UNFORTIFIED)*	ENFAMIL PREMATURE†	ENFAMIL PREMATURE 24 cal HIGH PROTEIN†	SIMILAC SPECIAL CARE WITH IRON‡	SIMILAC SPECIAL CARE 24 HIGH PROTEIN‡	POSTDISCHARGE FORMULAS	
						ENFAMIL ENFACARE†	SIMILAC EXPERT CARE NEOSURE‡
Nutrient density (kcal/oz)	19–21	20 or 24	24	20 or 24	24	22	22
Energy (kcal)	100	100	100	100	100	100	100
Protein							
Amount (g)	2.2 ± 0.2	3	3.5	3	3.3	2.8	2.8
% Total calories	8	12	14	12	13	11	11
Source	Human milk	Whey protein concentrate and nonfat milk	Whey protein concentrate, nonfat milk	Nonfat milk, whey protein concentrate	Nonfat milk, whey protein concentrate	Nonfat milk, whey protein concentrate	Nonfat milk, whey protein concentrate
Fat							
Amount (g)	5.4 ± 0.9	5.1	5.1	5.43	5.43	5.3	5.5
% Total calories	44–52	44	44	47	47	47	49
Source	Triglycerides	MCT oil Soy oil High oleic vegetable oil Single cell oil products (DHA and ARA)	MCT oil Soy oil High oleic vegetable oil Single cell oil products (DHA and ARA)	MCT oil Soy oil Coconut oil Single cell oil products (DHA and ARA)	MCT oil Soy oil Coconut oil Single cell oil products (DHA and ARA)	High oleic oil Soy oil MCT oil Coconut oil Single cell oil products (DHA and ARA)	Soy oil Coconut oil MCT oil Single cell oil products (DHA and ARA)
Oil ratio (approximate)	99	40:30: 27:2:1	40:30: 27:2:1	50:30: 18.3: 0.25:0.4	50:30: 18.3:0.25: 0.4	34:29:20: 14:2.2:0.8	44.7:29: 24.9:0.25: 0.4
Linoleic acid (mg)	440–1500	810	810	700	700	950	750

Continued

TABLE 17.8 COMPARATIVE NUTRITIONAL COMPOSITION OF PRETERM FEEDINGS PER 100 kcal—cont'd

		PREMATURE INFANT FORMULAS					
	MATURE PRETERM HUMAN MILK (UNFORTIFIED)*	ENFAMIL PREMATURE†	ENFAMIL PREMATURE 24 cal HIGH PROTEIN†	SIMILAC SPECIAL CARE WITH IRON‡	SIMILAC SPECIAL CARE 24 HIGH PROTEIN‡	POSTDISCHARGE FORMULAS	
						ENFAMIL ENFACARE†	SIMILAC EXPERT CARE NEOSURE‡
Carbohydrate							
Amount (g)	10 ± 0.6	11	10.5	10.3	10	10.4	10.1
% Total calories	40–44	44	42	41	40	42	40
Source	Lactose, glucose	Corn syrup solids, lactose	Corn syrup solids, lactose	Corn syrup solids, lactose	Corn syrup solids, lactose	Corn syrup solids, lactose	Corn syrup solids, lactose
Minerals							
Calcium (mg)	37–44	165	165	180	180	120	105
Phosphorus (mg)	19–21	83	83	100	100	66	62
Ca:P ratio	1.9–2.2:1	2:1	2:1	1.8:1	1.8:1	1.8:1	1.7:1
Sodium mg (mEq)	30–37 (1.3–1.6)	58 (2.5)	58 (2.5)	43 (1.9)	43 (1.9)	35 (1.5)	33 (1.4)
Potassium mg (mEq)	78–85 (2–2.2)	98 (2.5)	98 (2.5)	129 (3.3)	129 (3.3)	105 (2.7)	142 (3.6)
Chloride mg (mEq)	63–82 (1.8–2.3)	90 (2.5)	90 (2.5)	81 (2.3)	81 (2.3)	78 (2.2)	75 (2.1)
Iron (mg)	0.2	1.8	1.8	1.8	1.8	1.8	1.8
Zinc (mg)	0.5	1.5	1.5	1.5	1.5	1.25	1.2
Magnesium (mg)	4.4–4.9	9	9	12	12	8	9

Vitamins							
Vitamin A							
(mcg RE)	104–125	375	375	375	375	135	105
(international units)	(345–416)	(1250)	(1250)	(1250)	(1250)	(450)	(350)
Vitamin D (international units)	3–3.2	240	240	150	150	80	70
Vitamin E (international units)	1.9	6.3	6.3	4	4	4	3.6
Vitamin K (mcg)	0.3	8	9	12	12	8	11
Vitamin C—ascorbic acid (mg)	5–6.25	20	20	37	37	16	15
Vitamin B_1—thiamine (mcg)	200	200	200	250	250	200	175
Vitamin B_2—riboflavin (mcg)	270–310	300	300	620	620	200	150
Vitamin B_6 (mcg)	18–20	150	150	250	250	100	100
Folic acid (mcg)	12	40	40	37	37	26	25
Other Characteristics							
Potential renal solute load (mOsm)	18.7	27	30	27.8	27.8	24.5	25.2
Osmolality (mOsm/kg water)	290	275–300	300	258–280	280	250	250

This table lists the major constituents; refer to product inserts for a complete listing of vitamins, minerals, and trace elements.

*Klein CJ, editor: Nutrient requirements for preterm infant formulas, *J Nutr* 132:1395S, 2002; Koletzko B, Poindexter B, Uauy R, eds. *Nutritional Care of Preterm Infants: Scientific Basis and Practical Guidelines. World Rev Nutr Diet.* vol. 110. Basel: Kargerl; 2014:1–3.

†Mead Johnson Nutritionals, Evansville, Indiana.

‡Abbott Nutrition, Columbus, Ohio.

ARA, Arachidonic acid; *DHA,* docosahexaenoic acid; *MCT,* medium-chain triglycerides.

Preterm formulas contain whey:casein ratios of 60:40 and have higher protein contents than those of term formulas (2.4 g/100 mL in preterm formula versus 2 g/100 mL in term formula or human milk). Preterm formulas also contain less lactose as a carbohydrate source and substitute corn syrup solids for lactose to provide approximately 42% to 44% of the calories derived from this carbohydrate (largely sucrose). Preterm formulas provide some of the fat in the form of MCTs because of the ease with which they are absorbed. **Calcium (Ca) and phosphorus (P) content is increased, with a Ca:P ratio of 1.8 to 2:1, which provides for improved bone mineralization.** Other minerals and vitamins also are present in higher concentrations in preterm formulas to reflect the special nutritional needs of the VLBW infant. **Preterm formulas are available in 20, 24, and 30 kcal/oz preparations, with similar osmolalities and renal solute loads.** Newer generations of **high-protein preterm formulas containing approximately 2.8 g/100 mL may be indicated for VLBW preterm infants who are not growing well, have experienced a cumulative deficit of protein intake, have inadequate growth in length and/or head circumference, or are fluid/volume restricted.**[48]

Soy protein formulas should be reserved for term infants with galactosemia, severe lactose intolerance, hereditary lactase deficiency, vegan families, or those who have IgE-mediated cow's milk protein allergy. Soy-derived formulas should not be used for preterm infants because of the poorer quality of protein, lower digestibility and bioavailability, and lower calcium and zinc accretion rates seen with these formulas.[37] In addition, there are concerns for all infants about the concentrations of phytates, aluminum, and phytoestrogens that these formulas contain.[6,264] If necessary, a protein hydrolysate formula should be used for preterm infants with protein intolerance. **For term infants, formulas derived from protein hydrolysates should be reserved for infants who are allergic to cow's milk proteins and are not breastfed or do not tolerate soy-derived formulas. Soy formulas have no role in the prevention of atopic disease. In contrast, extensively hydrolyzed formulas may delay or prevent atopic dermatitis in infants at high risk who are not breastfed.**[106] **In general, families with a strong history of cow's milk protein allergy should be encouraged to breastfeed.** The compositions of partially, extensively, and completely hydrolyzed formulas are shown in Table 17.6.

Elemental formulas are used in infants with malabsorption, abnormal GI tracts, or severe protein allergy. The protein in these formulas is derived from free amino acids, 52% of the fat is from MCT oil, and many are lactose free. **Use of elemental formulas generally is indicated in the infant with severe liver disease and fat malabsorption, with short bowel syndrome (e.g., after NEC with surgical resection), or with dysmotility syndromes (e.g., in gastroschisis).** Occasionally, elemental formulas are useful after a severe episode of infectious gastroenteritis with mucosal injury and resulting protein or lactose intolerance. It is not **necessary to use an elemental formula in the routine care of VLBW infants. Formulas with extensively hydrolyzed proteins also have been introduced to treat GI disorders. Hydrolyzed protein formulas are generally well tolerated, but they do not lessen feeding intolerance or the rate of NEC and may result in slower weight gain.**[179,195,243] A variety of other modified formulas are available for infants with special nutritional needs because of inherited enzyme deficiencies.

Caloric delivery and nutritional support can be maintained by increasing the caloric density of feedings when feeding volumes cannot be tolerated or fluid intake must be limited. This can be done by **adding human milk fortifiers to the milk or formula to achieve acceptable concentrations and intakes of nutrients. Liquid formula concentrates, including liquid protein modular, also are used to increase the caloric density of infant feedings. Powdered infant formulas should *not* be used for feeding or fortification in hospitalized newborns in an intensive care unit,** unless no alternative is available, **because of information linking *Cronobacter sakazakii* infections in neonates to the use of powdered infant formulas** (FDA recommendation, 4-11-02). Caloric densities of greater than 24 kcal/oz can be achieved with fortification. However, the cumulative effect of additives to milk, including human milk fortifiers, liquid formula, multivitamins, iron, and sodium chloride supplements, can increase the osmolality of the multiply supplemented milk above the recommended threshold of 450 mOsm/kg in preterm formulas. This **increase of osmolality can be associated with feeding intolerance in the form of reflux, dysphagia, and/or slowed gastric or intestinal motility.**[159] Therefore careful monitoring of

feeding tolerance, electrolytes, fluid balance, and renal function is necessary on a high–caloric density feeding regimen. **The distribution of calories should maintain a balance of protein, fat, and carbohydrate at about 10%, 45%, and 45%, respectively.**

FEEDING TECHNIQUES

Gavage Feeding

Gavage feedings are indicated in infants requiring endotracheal intubation, continuous positive airway pressure (CPAP), or those with an immature, weak, or absent suck, swallow, or gag reflex (Box 17.6). Most infants tolerate intermittent feedings delivered slowly over 30 to 60 minutes, commonly termed *slow bolus feedings*. Studies indicate that such an intermittent "slow" infusion (e.g., 3 hours of volume given over 1 hour out of 3) improves gastric emptying and duodenal motility.[21,80] **Intermittent feedings are given every 2 hours for infants weighing less than 1250 g and every 3 hours for infants weighing 1250 g or more.**[81,86] **Some institutions use continuous feedings for infants recovering from NEC or infants with short bowel syndrome, congenital heart disease, or intolerance of bolus feedings.** However, a summary of randomized controlled trials did not find consistent differences regarding the effectiveness of continuous versus intermittent bolus nasogastric (NG) feedings.[220] **In addition, extended infusion times and pump position may lead to significant (up to 50%) fat and calcium losses when gavage feeding human milk.** Increased exposure of milk to plastic in the form of extension tubing and milk transfer systems, as well as the syringe design, also can contribute to these losses. **Fat and calcium losses are higher with continuous feeding compared with intermittent bolus feeding.**[57] **Positioning electric syringes horizontally or with the tip angled upward, minimizing the length of extension tubing, streamlining feed preparation, and shortening infusion time as medically appropriate can mitigate these losses.**

Regardless of feeding method, gavage tube position must be checked carefully using auscultation over the stomach before every feed. Bedside testing of gastric aspirate pH is often performed on placement of a gavage tube.[197] **If the pH does not confirm gastric position, an abdominal radiograph can be considered to confirm placement.**

For most infants, intragastric feedings are preferred to transpyloric feedings. Current data available do not provide any evidence of benefit of transpyloric feeding for preterm infants, and some evidence for harm exists, including a higher risk of GI disturbances and mortality.[272] **Even when indicated because of severe GER with aspiration, transpyloric feedings have additional complications, including malabsorption and diarrhea, altered gut microbiome, and intestinal perforations requiring surgery. Use of transpyloric feeding should be restricted to short-term use in those infants who cannot tolerate gastric feedings because of excessive GER with aspiration, pneumonia, and apnea.**

Oral Feeding

Development of appropriate neuromuscular coordination is necessary to successfully initiate oral feedings. Criteria for initiating oral feeding must be individualized because components of sucking, swallowing, and respiration and their coordinated activity mature at different rates and times in preterm infants.[12] **Box 17.7 provides an algorithm for oral feeding readiness in those infants greater than or equal to 34 weeks requiring heated high flow nasal cannula or CPAP.** In general, coordination of suck, swallow, and breathing emerges at about 34 weeks of corrected gestational age (range 32 to 36 weeks).[46] **Aspiration is a serious risk in an infant of any gestational age who does not have a neurologically mature swallow, gag, or cough reflex. Tachypneic infants with labored respirations also are at increased risk for aspiration; thus oral feeding usually is not possible unless the respiratory rate is less than 60 breaths/min.**

Use of different nipple shapes and sizes with variable flow rates combined with bottle selection enables infant-driven flow and facilitates progression to safe oral feeding.[204] **Nipple selection is tailored to correspond with infant maturity and underlying medical complexity. Slower flow rates are recommended for the infant with a more immature feeding pattern. As the infant matures and underlying medical issues resolve, the infant can progress to a nipple with a faster flow rate.**

BOX 17.6 GAVAGE FEEDING GUIDELINES

Equipment

1. Breastmilk/formula in syringe (4-hour amount, or unit protocol, maximum)
2. Tape, optional transparent dressing
3. Lubricant, optional
4. Stethoscope
5. For intermittent feeding: infant feeding set with syringe, medicine cup, 4-Fr to 8-Fr gavage tube
6. For indwelling feeding tubes: infant less than 1 kg, 4-Fr tube; greater than 1 kg, 5-Fr to 6-Fr tube (tube size may also depend on placement [i.e., oral versus nasal], amount of feeding, and rate of delivery of feeding). Short-term feeding tube (generally made of polyvinyl chloride [PVC]) should be changed every 24 to 72 hours. Long-term feeding tube (made of polyurethane) should be changed at least once every week. *Note:* Always follow manufacturer's recommendations.
7. Syringe pump and extension tubing as needed

Feeding Tube Insertion

1. Wash hands, and assemble equipment in a clean area.
2. Measure for tube placement by placing tip of feeding tube at the tip of nose, draw to base of ear, then to halfway between the xiphoid process and the umbilicus.[209]
3. Mark tube with indelible ink pen to indicate the distance from the tip of the tube to the corner of the mouth or edge of the naris.
4. Insert tube (swaddling the infant may help with tolerance of this procedure). NEVER FORCE THE TUBE.
   Oral placement (usually preferred for infants less than 1 kg, those on nasal CPAP or ventilator, those with high oxygen need, or those with excoriated nares): insert tip into the oropharynx, gently pushing the tube in a downward arc into the esophagus until reaching the premeasured mark.
   Nasal placement (generally preferred for infants greater than 1 kg with mature or strong gag reflex and infants who are breastfeeding or nippling): moisten tip with water or lubricant. Insert tip gently into one nostril and advance slowly as above.
5. Gastric tube tip placement is verified by auscultation or abdominal radiograph or pH measurement of gastric aspirates. The tube landmark should be checked with every caregiving procedure to determine that it is still visible and at the correct location.
6. Soft Silastic tubes are generally used for transpyloric feedings and require the use of a stylet for insertion. The tube must be inspected visually and by flushing with water before insertion to ensure that it has not been perforated by the stylet. The stylet is removed after insertion and is stored in package by the bedside. Tip placement usually is verified by radiographic imaging.

Securing Feeding Tube

1. Intermittent feeding tubes can be taped to the cheek.
2. Indwelling tubes must be taped securely to the face, leaving the landmark visible. For tubes placed nasally, a narrow piece of tape may be placed along the tubing on the upper lip, with a transparent dressing applied over the tube on the cheek.

Feeding

1. Aspirate entire stomach contents to assess quantity, color, and appearance.
2. To prevent loss of electrolytes, slowly return aspirate to the stomach. Exceptions to this include aspirates that are bloody or "coffee ground," green or bright yellow, or fecal appearing or contain large amounts of mucus. Do not refeed, and discuss the feeding plan with the physician or practitioner. Also report aspirates of undigested formula if the amount is more than one-half of the feeding or occurs more than once, or if there is a change in abdominal assessment. Reducing the feeding by the amount of the refed aspirate is recommended for one or two feedings.
3. Instill human milk or formula via intermittent gavage feeding:
   Detach the syringe from the feeding tube, and remove the plunger; reattach the syringe to the feeding tube. Pour the predetermined amount of milk into the syringe. Flow may begin spontaneously or require a gentle nudge from the plunger. Allow the feeding to run in slowly by gravity. Never push a feeding. The higher the syringe is held, the faster the feeding will flow (about 8 inches is ideal). For most infants, a feeding should run in over 30 minutes. Gavage sets may be rinsed carefully and used for up to 24 hours unless labeled "single use only" or manufacturer's directions indicate otherwise.
4. Intermittent gavage feeding via indwelling feeding tube:
   Check aspirate, and feed as above. When feeding is complete, instill 1 to 2 mL sterile water to clear tubing of residual food, and cap or close off the tube by attaching the syringe with the plunger.
5. Continuous drip feedings via indwelling feeding tube:
   Check feeding tube placement and feeding residuals every 2 to 4 hours using the stopcock, which is placed between the feeding tube and the extension tubing. Check the ink landmark on the feeding tube hourly to ensure proper placement of the tube. Prepare up to 4 hours of breast milk or formula (or amount according to institutional studies of bacterial growth). Fill the syringe with a predetermined feeding amount plus enough to prime the extension tubing. Place the syringe into the syringe pump, and program it to deliver feeding at the desired rate. To help prevent loss of milk fat by settling, place the syringe in an upward vertical position and use minibore tubing.

Care, Assessment, and Documentation

1. Assess the infant's tolerance of feeding tube placement. If gagging occurs, attempt to insert the tube down one side of the oropharynx rather than down the middle. If the infant becomes apneic, bradycardic, or cyanotic during feeding tube placement, pause to allow recovery, or remove the tube and allow the infant to rest before trying again. If these symptoms occur during the feeding, stop the feeding by lowering the syringe or stopping the pump. If recovery occurs quickly, resume feeding slowly and observe. If distress continues or recurs, stop feeding and inform the physician or practitioner.
2. Change short-term (PVC) feeding tube every 24 to 72 hours (or manufacturer's recommendations).
3. Change long-term nasal feeding tube (polyurethane) to opposite nostril weekly. Discard and replace tube after 4 weeks (or manufacturer's recommendations).
4. Document all details of the feeding and the infant's tolerance, proper placement of the indwelling feeding tube, and when feeding tube or equipment is to be changed.

BOX 17.7 ALGORITHM TO ASSESS ORAL FEEDING READINESS FOR INFANTS ≥34 WEEKS REQUIRING HEATED HIGH-FLOW NASAL CANNULA OR NASAL CONTINUOUS POSITIVE AIRWAY PRESSURE

Criteria to Initiate Oral Feeding

1. The infant is showing oral feeding cues defined as the ability to:
   a. Manage oral secretions.
   b. Suck pacifier without desaturation, choking, or requiring increased Fio_2.
   c. Root and bring hands to mouth.
   d. Come to an alert state before/or with cares.
2. The infant is on CPAP 5 cm H_2O or less; HFNC 3 L/min or less
3. The infant has a sustained respiratory rate of <70 breaths/min.
4. The infant can be held in side-lying feeding position while sucking on a pacifier without desaturation or bradycardia.
5. The infant can tolerate tastes of breast milk or formula on a pacifier without desaturation or bradycardia.

Progression of Oral Feeding

1. For mothers who desire to breastfeed:
   a. Let the infant attempt breastfeeding on a pumped breast for 5 minutes, and assess for any sign of intolerance, including choking, desaturation, increased respiratory effort, bradycardia, and increased Fio_2 requirement.
   b. Increase time allowed at breast by 2- to 5-minute intervals.
2. For mothers who do not desire to breastfeed:
   a. Offer small amount (up to 10 mL) of donor human milk or formula in a bottle with a slow-flow nipple, only allowing 5 minutes to take that amount.
   b. Increase the amount of formula by 5 mL, and increase the limit of bottle feeding by 2 to 5 minutes.

CPAP, Continuous positive airway pressure; *HFNC*, high-flow nasal cannula.

Recent evidence has advocated the use of the semi-elevated side-lying (ESL) position when introducing bottle feedings to the preterm infant rather than the semi-elevated supine position (ESU). **ESL positioning better mimics the breastfeeding position, decreases flow of the milk because of decreased hydrostatic pressure, and allows for better coordination of breathing with swallowing**[60,103,207,208] (Fig. 17.7A). **As infants mature, they can be transitioned to ESU positioning. *Semi-demand, cue-based,* or *infant-driven* feedings result in an earlier attainment of full oral feedings in premature infants.**[141,157,176,245] Swallowing exercises, **including placement of a milk bolus (0.05 to 0.2 mL) on the tongue where the bolus rests before entering the pharynx, also facilitate the attainment of independent oral feeding.**[156] Gastrostomy tube placement may be necessary if oral feedings are not adequately established.

Coordination of sucking with breathing is the first lesson for the preterm infant. The ability to suck on a pacifier, fingers, or a gavage tube does not ensure the infant's ability to perform nutritive sucking. **An infant who is successful at oral feeding should exhibit an active suck, coordinated swallow with breathing, minimal fluid loss around the nipple, and completion of feeding within 15 to 30 minutes.**[246] Stress behaviors (e.g., increase or decrease in respiratory or heart rate, decreased oxygen saturation, color change, gagging, choking, emesis, fatigue, irritability, or a "panicked look") should be treated with a rest period or cessation of the feeding. **Provider *pacing* is important until the infant learns to self-pace feedings (see Table 13.13).** Strategies to facilitate oral feedings also include a relaxed caregiver, a quiet environment with subdued light, and a snugly wrapped infant (see Box 13.17) **A too-rapid change to oral feeding can result in insufficient nutrition and potential failure to gain weight appropriately, primarily because the infant tires with feeding and is unable to take a sufficient amount of food.** Diligent attention is warranted, and nipple feedings often have to be limited and gavage feedings continued to prevent dehydration and under-nutrition. Box 17.8 **provides infant-driven feeding scales for readiness score description, quality score description, and caregiver technique score description.**

FEEDING INTOLERANCE AND COMPLICATIONS

Assessment for signs of feeding intolerance is imperative; although some feeding complications are mild and respond to nursing interventions, others are more serious and require more intervention. **Feeding intolerance frequently is the first sign of illness (e.g., hypoxia, dyspnea, congestive**

FIGURE 17.7 The **(A)** semielevated side-lying (ESL) and **(B)** semielevated supine (ESU) positions when introducing bottle feedings to the preterm infant.

BOX 17.8 INFANT-DRIVEN FEEDING SCALES

Infant-Driven Feeding Scales (IDFS) help to determine infant readiness to nipple feed, quality of the feeding, and caregiver techniques used during the nipple feeding. These scales help caregivers determine if infants are ready to nipple feed, a way to assess the quality of the feeding, and what techniques are used to deliver that nipple feeding. The scales may help make nipple feeding more consistent among caregivers and promote feeding success.

Infant-Driven Feeding Scales (IDFS)—Readiness Score Description

1. Alert or fussy before care. Rooting and/or hands to mouth behavior. Good tone.
2. Alert once handled. Some rooting or takes pacifier. Adequate tone.
3. Briefly alert with care. No hunger behaviors. No change in tone.
4. Sleeping throughout care. No hunger cues. No change in tone.
5. Significant change in heart rate, respiratory rate, O_2 saturations/requirements, or work of breathing outside safe parameters.

If the infant receives a score of 1 or 2, the infant is ready to nipple feed. For any score higher than 2, the infant is gavage fed. The nurse would then reassess infant behavior at the next feeding. If nipple feeding readiness is determined, the next two scales are used to document quality of feeding and techniques used during feeding.

Infant-Driven Feeding Scales (IDFS)—Quality Score Description

1. Nipples with a strong coordinated suck, swallow, and breathing (SSB) throughout feed.
2. Nipples with a strong coordinated SSB but fatigues with progression.
3. Difficulty coordinating SSB despite consistent suck.
4. Nipples with a weak/inconsistent SSB. Little to no rhythm.
5. Unable to coordinate SSB pattern. Significant change in heart rate, respiratory rate, O_2 saturations/requirements, work of breathing outside safe parameters, or clinically unsafe swallow during feeding.

Continued

BOX 17.8 INFANT-DRIVEN FEEDING SCALES—CONT'D

Infant-Driven Feeding Scales (IDFS)—Caregiver Techniques Score Description

A. *Modified Side-lying:* Position infant in inclined side-lying position with head in midline to assist with bolus management.
B. *External Pacing:* Tip bottle downward/break seal at breast to remove or decrease the flow of liquid to facilitate SSB pattern.
C. *Specialty Nipple:* Use nipple other than standard for specific purpose (i.e., nipple shield, slow-flow, Haberman).
D. *Cheek Support:* Provide gentle unilateral support to improve intraoral pressure.
E. *Frequent Burping:* Burp infant based on behavioral cues, not on time or volume completed.
F. *Chin Support:* Provide gentle forward pressure on mandible to ensure effective latch/tongue stripping if small chin or wide jaw excursion.

From Waitzman KA, Ludwig SM, Nelson CLA. Contributing to content validity of the Infant-Driven Feeding Scales (IDFS). *Newborn Infant Nurs Rev.* 2014;14(3):88–91. Used with permission.

heart failure, sepsis, NEC). At first, such signs often are subtle; thus, the caregiver should be constantly aware of any change in the infant's overall condition and feeding tolerance.

Residuals

Traditional practice has been to aspirate the feeding tube before a feeding to measure a "residual," or to determine whether gastric emptying is adequate. Incompletely digested aspirates of less than 50% of the previous feeding, 2 to 4 mL/kg, or a 1-hour volume if on continuous feedings may be normal and generally should be refed to the infant. Increasing and persistent residuals in the context of abdominal distention and/or other signs of systemic illness should be further evaluated, as this can indicate ***feeding intolerance, intestinal obstruction, or early NEC.***[185] Recent evidence suggests that routinely checking for residuals in the context of a normal abdominal examination is unnecessary, even counterproductive if residuals are repeatedly not refed to the infant, and potentially harmful, as too high a negative pressure during the aspiration can damage the lining of the stomach.[161] Avoiding routine gastric residual volume before each feeding has been associated with earlier achievement of full enteral feeds in preterm infants.[234,262] An alternative to routine screening of residuals is to measure a prefeed abdominal girth, which also has been shown to decrease the time to reach full enteral feeds.[138,259] Placing the infant in the right lateral recumbent position prone aids in gastric emptying.[58] Because of gastric outlet sphincter incompetence, bile staining of gastric residuals is common in the very preterm infant. Frank blood, increasing bile in progressively increasing residual volumes, bilious emesis, and other signs of intestinal obstruction and/or NEC should be evaluated promptly.

Emesis

Infants with emesis should be evaluated for intestinal obstruction or diseases that produce ileus, such as NEC and sepsis. With persistent emesis or increasing amounts of bilious emesis, feedings should be withheld and the infant should be evaluated for sepsis, NEC, obstruction (including Hirschsprung's disease, malrotation, and midgut volvulus, with or without congenital bands, and microcolon in infants of diabetic mothers), metabolic disorders, or increased intracranial pressure. Postoperative emesis and abdominal distention may indicate a stricture, partial obstruction from subclinical continued NEC, or inflammatory abscess. Emesis also results from an overdistended stomach, severe GER, a poorly positioned feeding tube, gastric irritation from enterally administered medications, drug withdrawal, or overstimulation in a very small infant. Interventions include allowing the feeding to flow more slowly by instilling the feeding over a longer period, decreasing feeding volumes, prone positioning, giving medications at the end of the feeding, or modifying a stressful environment (see Chapter 13). Auscultation, pH testing of gastric aspirates, or abdominal radiographs should be used to assess feeding tube position.

GASTROESOPHAGEAL REFLUX

GER should be suspected in an infant with irritability, emesis, apnea and bradycardia,

respiratory deterioration, refusal to eat, or otherwise unexplained blood in the stools.[3] The use of histamine2 (H2) receptor blocker therapy and/or suppression of the H^+,K^+-ATPase enzyme system at the secretory surface of the gastric parietal cell for GER or feeding intolerance in infants is not supported by good evidence. H2 blockers have been implicated in neonatal sepsis for being permissive to pathologic organisms by eliminating the barrier function of gastric acid.[105] Studies have reported decreased NEC with the acidification of feedings,[202] and there is an association between use of H-2 blocker therapy and NEC.[108,212] Currently, use of such antacids is contraindicated for routine feeding practices.

Abdominal Distention

Abdominal distention with or without palpable or visible loops of bowel is a sign of poor gastric motility, ileus, constipation, or "gas." Variations in abdominal circumference of up to 1.5 cm can occur and, without other clinical signs of illness, may be normal. If the abdomen remains soft and nontender, prone positioning may be comforting, allowing gas and stool to pass. Persistent abdominal distention, pain with palpation, and discoloration of the overlying skin are signs of pathology (e.g., anatomic obstruction or inflammation) and require investigation. An abdominal x-ray examination is indicated in these patients. Abdominal girth is measured every 4 to 8 hours with paper or cloth tape around the abdomen at a consistent point marked on the abdomen to document increased distention.

Abdominal distention is a common complication in infants treated with CPAP.[129] These infants are prone to excess accumulation of air in their stomach and ultimately their intestines, which can present as visible bowel loops. This is a benign condition that can be alleviated by placement of an 8-Fr or larger orogastric (OG) tube to allow for continuous venting of gastric air.[40]

Diarrhea

Diarrhea, or frequent water-loss stools, indicates intolerance of the caloric density of feedings, transient lactase deficiency, use of highly osmotic medications, or other pathology, including, rarely, allergy. Stool culture for bacterial or viral pathogens and stool Clinitest should be performed if the infant also appears ill or if there is blood in the stools. In lactose malabsorption, short-term use of a non–lactose-containing formula or protein hydrolysate formula should result in return to normal stools.

Intermittent Rectal Bleeding/Food Protein–Induced Proctocolitis/ Eosinophilic Allergic Colitis

Asymptomatic and otherwise well newborns can pass stool noted to contain bright red blood. Pathologic factors including NEC, malrotation, Hirschsprung's disease, anal fissures, and blood clotting disorders should be investigated, as indicated. A short period of withholding feeds with supplemental IV fluids can be undertaken. Commonly, the cause is cow's milk protein. If pathology is ruled out, oral feedings can be resumed with a hypoallergenic formula or with mother's own milk after she has been on an elimination diet. The dairy elimination diet in the mother should continue for 2 weeks, but in severe cases up to 4 months, before the suspected allergen is reintroduced.[18,130]

Apnea and/or Bradycardia

Apnea and/or bradycardia frequently occur during or after feeding. These signs are the result of vagus nerve stimulation by the passage or presence of a feeding tube, gastric distention, or GER, or occur with abdominal distention and compromise of lung volumes or airway obstruction. Temporal associations between GER events and apnea/bradycardia events have been found in some studies, but not in other studies.[73,252] In most cases, it is actually the apnea that triggers GER by decreasing lower esophageal sphincter tone.[3] Interventions to decrease vagal stimulation include changing to an OG gavage tube, decreasing feeding volume, and feeding more slowly.

Poor Growth

Growth is an essential requirement for the preterm infant. When normal growth does not occur, all possible factors should be considered, but most commonly, the infant has not been

fed sufficient amounts of nutrition. If this is the case and the infant is not sick in some obvious way, then he or she should be fed more, primarily by increasing protein and energy delivery.[113] **Factors that increase caloric expenditure, such as thermal instability or overstimulation, should be considered as causes of growth failure. Preterm infants always should be cared for in a thermoneutral environment, wearing a hat or other form of head covering (because large amounts of heat are lost from the surface of the head). Additional clothing, bundling or wrapping in soft blankets, supportive positioning, and grouping of care and stimulation to conserve energy often help improve growth.**

Danger Signs

Progressively increasing abdominal distention, bilious emesis, and gross amounts of bile in the gastric aspirate can be signs of significant ileus, obstruction, or NEC. The presence of blood in the stools or gastric aspirate, a tense or tender abdomen, and abdominal wall erythema are more ominous signs of feeding intolerance and may indicate frank NEC (Box 17.9). The presence of these signs and symptoms warrants a careful physical examination and usually **further investigation including x-ray examinations. Feedings should be postponed while these signs and symptoms are being investigated. Other useful studies include a complete blood count with differential to evaluate extent of blood loss, presence of thrombocytopenia (a marker of necrotic bowel), and change in white blood cell count as evidence of infection.** Although feeding of human milk may help protect against developing NEC and 5% to 10% of cases of NEC occur in infants who have never been fed enterally, **NEC can occur in *any* infant. Abnormal abdominal distention or grossly bilious or bloody gastric aspirates should be investigated carefully regardless of feeding status.**

THE PRETERM INFANT

Much progress has been made in providing nutritional support for ELBW (<1000 g) and VLBW (<1500 g) preterm infants. The nutritional requirements of these very small infants are marked, unique, incompletely understood, and frequently inadequately provided for, despite improvements in both the quality and quantity of nutrients in currently used IV and enteral nutrient regimens (Box 17.10). Also, **many of these infants are growth restricted at birth. Thus their nutritional needs for normal rates of metabolism and growth are very likely to differ from those of normally grown infants.** Table 17.9 **shows enteral intake recommendations for stable, growing preterm infants.**

BOX 17.9 CRITICAL FINDINGS

Danger Signs Requiring Immediate Attention

1. Gross bile in the gastric aspirate with evidence of intestinal obstruction
2. Presence of blood in the stools or gastric aspirate
3. Tense or tender abdomen
4. Abdominal wall erythema
5. Unexplained anemia, thrombocytopenia, and neutropenia

BOX 17.10 SPECIAL NUTRITIONAL CONDITIONS IN EXTREMELY LOW-BIRTH-WEIGHT INFANTS

1. Minimal energy reserves (both carbohydrates and fat)
2. Intrinsically higher metabolic rate (greater relative mass of more metabolically active organs: brain, heart, liver)
3. Higher protein turnover rate (especially when growing)
4. Higher glucose needs for energy and brain metabolism
5. Higher lipid needs to match the in utero rate of fat deposition
6. Excessive evaporative rates (immature skin)
7. Occasionally very high urinary water and solute losses (depending on intake and renal maturation)
8. Low rates of gastrointestinal peristalsis
9. Limited production of gut digestive enzymes and growth factors
10. Higher incidence of stressful events (hypoxemia, respiratory distress, sepsis)
11. Metabolic effects of medications used frequently (steroids, antibiotics, sedatives, catecholamines)
12. Abnormal neurologic outcome if not fed adequately

Modified from Thureen PJ, Hay WW Jr. Conditions in preterm infants requiring special nutritional management. In: Tsang R, Lucas A, Uauy R, Zlotkin S, eds. *Nutritional Needs of the Preterm Infant: Scientific Basis and Practical Guidelines.* Baltimore, MD: Williams & Wilkins; 1993.

TABLE 17.9 ENTERAL INTAKE RECOMMENDATIONS FOR STABLE, GROWING PRETERM INFANTS PER 100 kcal*

		CONSENSUS RECOMMENDATIONS BY THE AUTHORS OF THIS CHAPTER				
		INFANT WEIGHT <1000 g	INFANT WEIGHT >1000 g	AAP† <1000 g	AAP† 1000–1500 g	ESPGHAN‡
Water	mL	125–167	125–167	—	—	—
Energy	kcal	100	100	100	100	100
Protein	g	3–3.2	2.5–3	2.5–3.4	2.6–3.8	3.6–4.1 (<1 kg) 3.2–3.6 (1–1.8 kg)
Carbohydrate	g	10–14	10–14	6–15.4	5.4–15.5	10.5–12
Lactose	g	3.16–9.5	3.16–9.8	—		—
Oligomers	g	0–7	0–7	—		—
Fat	g	5–5.5	4.4–5.7	4.1–6.5	4.1–6.5	4.4–6
Linoleic acid	g	0.44–1.7	0.44–1.7	0.467–1.292	0.462–1.309	0.35–1.4
Linolenic acid	g	0.11–0.44	0.11–0.44	—	—	>0.05
18:2/C18:3		>5	>5	5–15	5–15	—
Vitamin A	International units	583–1250 1250–2333	583–1250 1250–2333	467–1154	538–1364	360–740
Vitamin D	International units	125–333§	125–333§	100–308	115–364	800–1000/ day
Vitamin E	International units	5–10	5–10	4–9.2	4.6–10.9	2–10
Vitamin K	mcg	6.66–8.33	6.66–8.33	5.3–7.7	6.2–9.1	4–25
Ascorbate	mg	15–20	15–20	12–18.5	13.8–21.8	10–42
Thiamine	mcg	150–200	150–200	120–185	138–218	125–275
Riboflavin	mcg	200–300	200–300	167–277	192–327	180–365
Pyridoxine	mcg	125–175	125–175	100–162	115–191	41–273
Niacin	mg	3–4	3–4	2.4–3.7	2.8–4.4	3.45–5.0
Pantothenate	mg	1–1.5	1–1.5	0.8–1.3	0.9–1.5	>0.3–1.9
Biotin	mcg	3–5	3–5	2.4–4.6	2.8–5.5	>1.5–15
Folate	mcg	21–42	21–42	17–38	19–45	32–90
Vitamin B_{12}	mcg	0.25	0.25	0.2–0.23	0.23–0.27	0.08–0.7
Sodium	mg	38–58	38–58	46–88	53–105	63–105
Potassium	mg	65–100	65–100	52–90	60–106	60–120
Chloride	mg	59–89	59–89	71–192	82–226	95–161
Calcium	mg	100–192	100–192	67–169	77–200	110–130
Phosphorus	mg	50–117	50–117	40–108	46–127	55–80

TABLE 17.9 ENTERAL INTAKE RECOMMENDATIONS FOR STABLE, GROWING PRETERM INFANTS PER 100 kcal—CONT'D

		CONSENSUS RECOMMENDATIONS BY THE AUTHORS OF THIS CHAPTER				
		INFANT WEIGHT <1000 g	INFANT WEIGHT >1000 g	AAP† <1000 g	AAP† 1000–1500 g	ESPGHAN‡
Magnesium	mg	6.6–12.5	6.6–12.5	53–11.5	6.1–13.6	7.5–13.6
Iron	mg	1.67	1.67	1.33–3.08	1.54–3.64	1.8–2.7
Zinc	mcg	833	833	337–2308	769–2727	1000–1800
Copper	mcg	100–125	100–125	80–115	92–136	90–120
Selenium	mcg	1.08–2.5	1.08–2.5	0.9–3.5	1–4.1	4.5–9
Chromium	mcg	0.083–0.42	0.083–0.42	0.07–1.73	0.08–2.05	0.027–1.12
Manganese	mcg	6.3	6.3	0.5–5.8	0.5–6.8	6.3–25
Molybdenum	mcg	0.25	0.25	0.2–0.23	0.23–0.27	0.27–4.5
Iodine	mcg	25–50	25–50	6.7–46.2	7.7–54.5	10–50
Taurine	mg	3.75–7.5	3.75–7.5	3–6.9	3.5–8.2	—
Carnitine	mg	~2.4	~2.4	~1.9–2.2	~2.2–2.6	—
Inositol	mg	27–67.5	27–67.5	21–62	25–74	4–48
Choline	mg	12–23.4	12–23.4	9.6–12.5	11.1–25.2	7–50

Note: ESPGHAN states that "no specific recommendations are provided for infants with a weight below 1000 g, because data are lacking for this infant group for most nutrients, except for protein needs."

*120 kcal/kg/day was used where conversion was made from per kg recommendations.

†American Academy of Pediatrics Committee on Nutrition. Nutritional needs of the preterm infant. In: Kleinman RE, ed. *Pediatric Nutrition Handbook*. 6th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2014:85–86.

‡European Society of Paediatric Gastroenterology, Hepatology and Nutrition, Committee on Nutrition of the Preterm Infant (Agostoni C, Buonocore G, Carnielli VP, et al.). Enteral nutrient supply for preterm infants: commentary from the European Society for Pediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. *J Pediatr Gastroenterol Nutr.* 2010;50:85.

§Aim = 400 international units/day.

In spite of increasingly aggressive in-hospital nutritional management, the majority of infants born preterm experience postnatal growth restriction during their NICU stay, in large part caused by inadequate nutrient intake.[61,69,87,90,255] In fact, the fraction of these infants who are small for gestational age at discharge is several-fold greater than the fraction at birth (Fig. 17.8).[89] **There is increasingly strong evidence that early nutritional support of preterm and growth-restricted infants can have lasting consequences for improved neurodevelopmental outcome.**[44,85,88] Such observations have important implications. First, we cannot now think of "early" nutrition of these small infants simply in terms of providing immediate nutrient needs just for metabolic maintenance (e.g., glucose to prevent hypoglycemia); we also must consider that early nutrition, both prenatally and postnatally, has biologic effects that have lasting or lifelong significance. Second, we can no longer regard nutritional practices in preterm infants as simply a matter of personal choice. The major impact of sufficient early nutritional support on long-term outcome should be a stimulus to new research that defines consistent approaches to the nutrition of preterm infants to optimize their future health and development.

Concerns about the safety of enteral feeding of preterm infants have frequently delayed the initiation of feedings, despite the fact that there

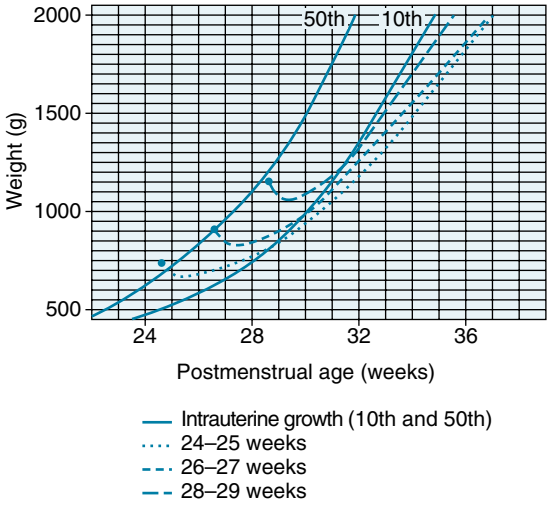

FIGURE 17.8 Average body weight versus postmenstrual age in weeks for infants with gestational ages 24 to 25 weeks *(dotted line)*, 26 to 27 weeks *(short dashes)*, and 28 to 29 weeks *(long dashes)*. The reference intrauterine growth curves were plotted using the smoothed 10th and 50th percentiles birth weight data reported by Alexander G, Himes JH, Kaufman RB, et al. A United States national reference for fetal growth. Obstet Gynecol 1996;87:163–168. (Reproduced with permission from Ehrenkranz RA, Younes N, Lemons JA, et al. Longitudinal growth of hospitalized very low birth weight infants. *Pediatrics.* 1999;104:280–289. © American Academy of Pediatrics.)

BOX 17.11 ADVANTAGES OF MINIMAL ENTERAL FEEDING

- No increase in incidence of necrotizing enterocolitis
- Decreased sepsis
- Decreased permeability of mucosa to foreign antigens
- Increased intestinal peptides and hormones
- Increased mucosal thickness and villi
- Maturation of intestinal motor activity
- Improved feeding tolerance
- Improved bone mineralization
- Earlier achievement of full enteral feedings
- Improved weight gain
- Shorter hospital stay
- Reduced requirement for supplemental oxygen

is little or no evidence that withholding enteral feeding decreases NEC.[187] Furthermore, the absence of enteral feeding leads to GI mucosal atrophy.[192] Evidence is accumulating that strongly supports early initiation (within the first 24 hours of life) of low-volume enteral feedings ("minimal enteral nutrition" or "trophic feeds" or "gut priming"), especially with human colostrum and milk. Minimal enteral feedings represent the administration of small feeds, less than 24 mL/kg/day, over a short but defined period (various feeding advancement protocols among different institutions define how many days to remain on minimal enteral nutrition before advancing to full enteral feeds) to promote GI development, motility, and function in the preterm infant. Enteral feedings are associated with surges in gut hormone production that mediate trophic effects on GI growth and mucosal maturation, including gastrin, enteroglucagon, motilin,[178] and lactase activity.[248] Animal studies have shown that minimal enteral feeding strategies trigger maturation of motor function in the intestine.[32,203] Absorption of nutrients is improved with increased amount and length of villous absorptive surface. Trophic feeding has been shown to improve energy intake, weight gain, head circumference gain, feeding tolerance, and time to reach full enteral feedings.[84,175,178] **The potential advantages of minimal enteral feeding are listed in Box 17.11. Nearly all studies support the use of minimal enteral feedings, although a recent *Cochrane* review could not define specific benefits or exclude harmful effects of minimal or trophic enteral feedings for VLBW infants.[188] Early trophic or gut priming feedings have not, however, increased the risk of NEC, particularly when mother's milk is used, and should be considered the standard of practice. Minimal enteral feedings should begin within the first day of life, range from 6 to 24 mL/kg/day, and be given every 4 to 6 hours for 2 to 5 days in VLBW infants.**

Although older studies indicated that rapid advances to large feeding volumes were poorly tolerated by preterm infants,[33] more recent evidence indicates that progressive feeding advances in both volume and concentration with supplements can proceed more promptly in most preterm infants.[56,135,148,231] A recent *Cochrane* review supported advancing feed volumes at daily increments of 30 to 40 mL/kg/day (compared with 15 to 24 mL/kg/day) in VLBW infants; however, applicability to ELBW infants is more limited.[186] **In the ELBW infant, greater attention should be paid to feeding tolerance, although larger, more mature infants certainly can develop serious feeding intolerance and, in some cases, even NEC.**

TABLE 17.10 EXAMPLE OF FEEDING ADVANCEMENT GUIDELINES

GESTATIONAL AGE (WEEKS)	DOF 1	DOF 2	DOF 3	DOF 4	DOF 5	DOF 6	DOF 7	DOF 8	DOF 9	DOF 10
≤25$^{6/7}$	≤20	≤20	≤20	≤20	≤20	≤50	≤80 Fortify	≤110	≤140	160
26–28$^{6/7}$	≤20	≤20	≤20	≤50	≤80 Fortify	≤110	≤140	160		
29–31$^{6/7}$	≤20	≤20	≤50	≤80 Fortify	≤110	≤140	160			
32–33$^{6/7}$	≤20	≤50	≤80 Fortify	≤110	≤140	≤160				
34–35$^{6/7}$	≤40	≤80 Fortify PRN	≤120	160						

DOF, Day of feeds.

- Intake amounts presented as mL/kg/day.
- Gray shaded boxes represent minimal enteral feedings (trophic feedings).
- Patients may nipple bottle feeds up to the maximum feeding volume, or breastfeed as able. Patients should not initially be placed on ad lib nippling or advanced at higher volumes because of increased risk for feeding intolerance.
- Breast milk is preferred. Donor milk or formula is also acceptable if breast milk is not available or parental choice of formula.
- Infants deemed at higher risk (two or more risk factors) may have feeding amounts reduced or initiated at GI priming volumes with advancement as medically appropriate. *Perinatal risk factors* include 5-minute Apgar score <5, umbilical venous gas or infant's first blood gas with metabolic acidosis (pH <7.2, base deficit >10 mEq/L), nonreassuring fetal heart rate tracing as indication for delivery, asymmetric IUGR or IUGR with reversed or absent end-diastolic flow, monochorionic twin gestation with twin-to-twin transfusion syndrome, severe polycythemia with hyperviscosity.
- *Neonatal risk factors* include significant cardiovascular instability (chest compressions, vasoactive agent requirement, or multiple boluses of crystalloid or colloid), significant apnea (>1 per hour requiring intervention defined as vigorous stimulation with supplemental oxygen and bag-mask ventilation, any >4 per hour, or >6 total in 24 hours requiring intervention), symptomatic patent ductus arteriosus, antibiotic treatment >7 days, prolonged NPO status >7 days.

From K. Hendrickson, MS, RD, CNSC, CSP, in conjunction with NICU Quality Leadership, University of Colorado Health, Aurora, Colorado.

Once the infant is tolerating increasing amounts of enteral feeding (practice is variable, ranging from 20 to 100 mL/kg/day of enteral nutrition), breast milk can be fortified with the addition of human milk fortifiers (see Table 17.3). During this time, parenteral nutritional support is tapered to maintain from birth at least 3.5 g/kg/day protein, 30% to 54% of total calories from fat, and 40% to 60% of total calories from carbohydrate. A recent study showed that fortification as early as first initiation of enteral feeds (20 mL/kg/day) did not delay time to full enteral feeds and increased protein delivery as parenteral nutrition was weaned.[244] The transition from parenteral to enteral nutrition represents a critical period at which VLBW infants are at risk for progressive protein deficit and decreased growth velocity; thus earlier fortification of enteral feeds, if tolerated by the infant, may help to reduce this cumulative protein deficit.[182,241] Reasonable goals for time to achieving full enteral feedings of fortified human milk are 7 to 10 days in VLBW infants and about 2 weeks in ELBW infants. Table 17.10 contains guidelines reflecting a general approach to the advancement of enteral feedings.

Few randomized, controlled trials support any specific feeding strategy; however, several studies support that a defined feeding protocol that is strictly followed by an individual NICU, regardless of the details of the protocol, results in improved growth and reduced incidence of NEC and other morbidities.[71,101,213,256] The process of development and implementation of the

guideline requires reviewing current evidence and increased awareness of feeding tolerance and early signs of NEC by staff. Clinical judgment, however, should be used in following any feeding schedule for an individual patient.

Although most infants benefit from early enteral feeding, those who are asphyxiated with persistent hypoxemia and metabolic acidosis, hemodynamically unstable with a symptomatic PDA, hemodynamically unstable with sepsis, or with evidence of NEC should not be fed enterally. These infants should be managed with aggressive full parenteral nutrition. When infants are receiving indomethacin or ibuprofen for treatment of PDA, there is controversy about whether they should be fed.[169] However, some studies show that it is safe to provide at least minimal enteral feeds to neonates receiving pharmacologic therapy for PDA.[36,63,164]

Late-Preterm Infant

The late-preterm infant, born at $34^{0/7}$ to $36^{6/7}$ weeks of gestation, represents the population of preterm infants now accounting for more than 70% of all preterm births. Although generally these babies are larger and healthier than less mature newborns, NICU admission is frequent for feeding issues. **These infants have intact, functional digestive and absorptive functions, but motility and intestinal colonization may be delayed. Of particular clinical importance is the immaturity of oral motor tone, function, and neural integration. Infants born between 33 and 36 weeks of gestation may initially seem to feed well but cannot maintain successful feeding during the first week of life.** Poor feeding, therefore, is common in this group of babies, potentially contributing to problems of hypoglycemia, hyperbilirubinemia, and excessive postnatal weight loss (see Chapter 5). **The ideal nutrition for these infants, as with those infants born more preterm, is breast milk, preferably mother's own.** A significant amount of brain growth and development occurs between 34 and 40 weeks of gestation, including a 50% increase in cortical volume,[5] which could be compromised if suboptimal amounts of nutrition are delivered. Thus it is **reasonable even in such late-preterm infants to fortify mother's milk or donor human breast milk, or use preterm formulas, particularly if growth is compromised by illness and/or until the infant is taking full enteral feedings appropriate for a term infant.**[217]

THE INTRAUTERINE GROWTH–RESTRICTED INFANT

Many preterm infants have experienced IUGR and thus are born small for gestational age and preterm. Their nutritional needs for normal rates of metabolism and growth are very likely to differ from those of normally grown infants.[77] Nutritional support for the small-for-gestational-age infant requires separate consideration, because decreased size-for-dates occurs with various pathologic conditions or no pathology at all. Small size at birth is related to any number of diseases or abnormalities, both intrinsic and extrinsic to the fetus and newborn. Early events in gestation, including chromosomal and genetic abnormalities or early infection, can lead to symmetric growth restriction. In contrast, asymmetric growth restriction occurs in response to late placental insufficiency or other insults that restrict nutrient supply to the fetus. Many completely healthy and normal infants are constitutionally small. Complicating these issues is the fact that preterm infants often are growth restricted at birth (i.e., whatever led to IUGR also contributed to processes that caused or promoted preterm birth). **Such infants require more individualized management, because they may not tolerate advancing enteral feedings as well as normally grown infants and do not necessarily respond to increased nutrient intake with appropriate rates of growth.**[44,223]

In general, infants with IUGR are likely to have increased energy needs caused by low stores of energy, nutrients, and minerals.[39,77,190,230,263] **Hypoglycemia, hyperglycemia, and increased need for heat production are more likely in the early postnatal period in these infants than in their normally grown peers.**[31,279] **Infants with IUGR take longer to advance to full enteral feeds and have increased incidence of feeding intolerance and NEC.**[8,43] These problems require anticipatory nutritional monitoring and management. Early parenteral glucose, protein, and energy supplementation is necessary while a cautious advance of enteral feedings begins.[268] **Initiation of enteral feeds should not be delayed, however, as early initiation of enteral feeds in**

IUGR infants with prenatal absence or reversal of end-diastolic flow in the umbilical artery had earlier achievement of full enteral feeds with no increase in the incidence of NEC.[158]

CHANGES IN NUTRITIONAL REQUIREMENTS WITH ILLNESS

Studies in adult patients have shown dramatic changes in nutritional requirements depending on type of illness, degree of illness, surgery, and premorbid nutritional status. Although these changes are not well studied in neonates, preliminary data and clinical experience indicate that similar changes should be expected in ill infants. In fact, these patients have even greater nutritional needs because of requirements for growth and development. **The overriding observation from all studies, however, is that ELBW and VLBW preterm infants are underfed during the early postnatal period and that this undernutrition, combined with additional stresses from various diseases, increases the risk for long-term adverse neurologic sequelae.**[228] The value of achieving a specific body composition and growth rate is less certain. There remains a critical need for determining the right quality, as well as quantity, of nutrients for these infants. **The effects of common disease states on the nutrient requirements in preterm and term infants are shown in** Fig. 17.5.

Acute and chronic respiratory diseases are the most common illnesses in neonates. **Acute respiratory problems, such as respiratory distress syndrome, pneumonia, and aspiration, all increase the infant's metabolic needs for energy and protein. Energy requirements are met by increasing carbohydrate and fat delivery.** However, the metabolism of excessive carbohydrate feeding (>12.5 mg/kg/min) may be detrimental to pulmonary status by increasing oxygen consumption and carbon dioxide production, increasing respiratory work, and adding to respiratory failure. **Lipid is a good alternative source of concentrated energy because its metabolism has a lower respiratory quotient and produces less carbon dioxide. Lipids provide dense calories for volume and prevent essential fatty acid deficiency. Protein wasting and catabolism with illness increase the infant's requirement for exogenous support.** Adequate provision of amino acids, especially branched-chain amino acids, prevents catabolism of body protein stores, including respiratory and diaphragmatic muscle protein, and may improve minute ventilation by decreasing carbon dioxide production.

Infants with chronic lung disease and BPD present difficult nutritional problems.[75,189] **Poor nutrition is associated with abnormal lung development, increased toxic effects of oxygen, decreased surfactant production, and increased risk for infection.** Although energy and metabolic demands are increased in these patients, many routine management strategies make the disease process worse. When too much energy is delivered, this can lead to excess adiposity and inflammatory organ (heart and liver) fat deposition. **Excessive fluid volumes increase pulmonary edema and contribute to lung injury. Increased work of breathing limits intake. Steroid therapy and chronic disease have negative effects on protein balance. Diuretic use can waste calcium and potassium.** Feeding ELBW preterm infants with severe respiratory distress and respiratory insufficiency with higher protein-to-energy ratio diets starting with IV nutrition at birth and continuing with enteral feeding is more appropriate and is associated with reduced risk of BPD.[144]

Congenital heart disease, **especially when accompanied by cyanosis or congestive heart failure, significantly impairs nutritional status and growth. These infants have increased *basal metabolic needs* and experience the additional catabolic stress of early surgery.** Nutritional management also is complicated by underlying hypoxemia, diuretic therapy, respiratory distress, malabsorption, and variable fluid balance. Mineral derangement is common postoperatively with diuretic therapy and suboptimal intake. Iron supplementation is necessary to provide for increased erythropoiesis with chronic hypoxemia.

Undernutrition and malnutrition increase the risk of infections, including sepsis. **Good nutritional status can decrease the risk for infection and sepsis, as well as improve recovery in neonates.** Normal immune response depends on adequate protein, energy, micronutrients, and trace elements. Although not well studied in this population, it appears that the **metabolic requirements of septic infants, especially for energy and amino acids, are different from the requirements of otherwise similar, but uninfected, infants.**[225]

The infant with NEC or short bowel syndrome **is at additional risk for malnutrition because of malabsorption and increased nutrient losses. During the acute NEC illness, these infants must receive adequate parenteral nutrition, particularly emphasizing protein to counter the catabolic condition from stress hormones such as cortisol.** Recovery needs to be supported by gradual increases in enteral nutrition and slowly decreasing parenteral supplementation. Of particular concern are excessive water losses with electrolyte imbalance and malabsorption of fats and fat-soluble vitamins. **Infants with short bowel syndrome need to have enteral feeding advanced as soon as possible to avoid total parenteral nutrition (TPN)-related cholestasis.**

Any infant recovering from severe *perinatal hypoxic-ischemic injury* or "asphyxia" with significant evidence of shock (low blood pressure, poor circulation, and metabolic acidosis) should probably not receive enteral feedings for 24 to 72 hours to allow recovery of the bowel from the ischemic injury. Infants with moderate forms of hypoxia-ischemia probably can be given minimal enteral feedings with mother's colostrum or breast milk as soon as the infant is stable in terms of circulation and oxygenation. Minimal enteral feedings potentially could improve gut development after injury and colonize the gut with a more favorable microbiome.

Neonates who have undergone surgery **are at increased risk for nutritional deficiencies resulting from the stresses of illness and surgery and possible abnormal nutrient and water losses.** In these infants, enteral feedings are preferred because they preserve the integrity of the intestinal mucosa and promote continued development of the GI tract. **After a surgical procedure, the infant is often nil per os (NPO) status for 3 to 14 days until the return of intestinal motility and function** (e.g., stooling, lack of abdominal distention, decreased gastric aspirates, absence of bilious aspirates). The method of feeding chosen, rapidity of feeding advancement, formula composition, and type of feeding depend on the infant's general medical condition, GI function, and type of surgery. The choice of formula for the postsurgical neonate depends on bowel integrity. An infant recovering from mild NEC may be started on human milk or regular formula. **With serious or surgically treated NEC, human milk is preferred, but an elemental or protein hydrolysate formula may be used** with MCTs for easily absorbed lipids and glucose polymers for more easily absorbed carbohydrates, as long as they do not produce too high an osmolality in the feeding mixture.

DEVELOPMENTAL SUPPORT

Developmentally supportive feeding is extremely important. Preterm birth resulting in delayed introduction of oral feeding skills, surgical interventions for congenital or genetic abnormalities necessitating alternative feeding methods such as gastrostomy tube feedings, and prolonged interruption of normal feeding patterns for delayed postnatal adaptation in infants with hypoxic-ischemic injuries or early NEC and sepsis, are all examples of the impact that hospitalization can have on patients and their families.[67]

Being aware of the impact that prolonged hospitalization can have on feeding is the first step in being able to provide support and guidance to families of fragile infants. **By using a team approach, the family can help support their infant in attaining and strengthening feeding skills in preparation for discharge** and hopefully prevent or minimize long-term feeding difficulties that often are associated with an extended hospital stay, such as loss of feeding skills and feeding aversion issues.

A *supportive feeding team* should include the parents, physicians, nurse practitioners, lactation specialists, dietitians, occupational and physical therapists, developmental specialists, and nursing staff educated in the developmental support of infants with specialized feeding needs. This support should start as soon as an infant is admitted and continue beyond discharge to promote the best possible outcome with regard to feeding ability.

FAMILY SUPPORT

Parents of the NICU patient may feel overwhelmed by their infant's illness, appearance, and uncertain future. **Loss of control of the infant's care and unclear parental roles make bonding difficult and add to feelings of helplessness, frustration, and isolation.** All members of the health care team must be supportive and facilitate the parents as caregivers. **Parent education about early feeding**

practices in the nursery and anticipated infant growth and development facilitates care by parents. Feeding is an excellent way to involve parents in their infant's care. Parents should be involved in discussions of feeding practices and food choices. **Scheduling oral feedings for parent visits enables active participation in their infant's care. During gavage feedings, parents should be encouraged to hold their infant and support the pacifier to encourage nonnutritive sucking.** Frequent communication about the ups and downs of feeding the sick newborn, as well as weekly progress updates on growth charts, is helpful.

A mother's ability to provide breast milk remains the one aspect of care that she alone can do for her infant. Preterm birth and prolonged illness, as well as the inability to breastfeed the infant directly, are major barriers to successful breastfeeding. **Lactation support in the NICU increases mothers' success at maintaining lactation through discharge from the NICU.** Guidelines for expression and collection of human breast milk, gavage feeding of human milk, and identification of oral feeding readiness all are essential elements of lactation support and success (see Chapter 18).

FEEDING THE PRETERM INFANT AFTER HOSPITAL DISCHARGE

Many preterm infants are still preterm when they are discharged from the NICU, and most are small for their corrected gestational age (i.e., they are growth restricted) and at significant risk for further growth failure in the postdischarge period.[89,151] These infants require continued attention to nutritional support after hospital discharge.[153,199] **Mother's own milk should be used exclusively for the first 6 months of life, with continuation of breastfeeding for 1 year or longer as mutually desired by the mother and infant.**[143] However, postdischarge feeding practices, including the questions of whether and when and how to fortify human milk, vary widely because evidence is conflicting.

For VLBW, formula-fed preterm infants who are of subnormal weight and especially length and head circumference at the time of discharge, expert consensus guidelines support the use of postdischarge transitional formula and close nutritional follow-up.[153,196] These products are intermediate between preterm and term formulas in their energy, protein, calcium, phosphorus, vitamin, and mineral contents (see Table 17.7 for nutritional composition). **These recommendations are supported by some evidence that has shown that providing preterm infants with a formula containing higher protein and energy contents after discharge results in improved growth.**[277] Furthermore, use of a transitional formula for 3 to perhaps as long as 6 months after discharge increases lean mass without increasing percent body fat at 1 year and decreases body fat, truncal fat, and fasting insulin concentrations at 2 years.[70,218] However, few trials have assessed neurodevelopmental outcomes, and those that have do not detect any significant differences in developmental indices at 18 months' corrected age.[24,278] **Thus preterm infants discharged home with a normal weight for postmenstrual age could be fed similarly to term infants of similar gestational age.**[196]

Guidance on how to feed the breastfed preterm infant is scarce. Limited available data do not provide convincing evidence that multinutrient fortified breast milk compared with unfortified breast milk after hospital discharge affects important outcomes, with the exception of a small but significant effect on length at 12 months of age.[277] However, **preterm infants fed their own mother's milk for prolonged periods without fortification, and especially those receiving donor milk with limited fortification, often accrue the greatest nutritional deficits by discharge and are at continued risk of growth deficiencies postdischarge.**[199] Traditionally, mother's milk (22 to 24 kcal/oz) has been fortified with powdered transitional formula, but added nutrition with this method is negligible.[107] **If growth is suboptimal at the time of discharge or in the immediate postdischarge period, consideration can be given to either providing supplemental human milk fortifier in limited amounts or setting a minimum amount of transitional formula feeds to augment breastfeeding until adequate growth is achieved.** Close follow-up by a dietician is recommended. There also are many examples of **former preterm infants growing quite well with increased milk intake from their own mother. Such infants often can take in as much as 200 to 250 mL/kg/day. Prolonged breastfeeding also directly correlates with better neurodevelopmental outcomes.**[25,26,127]

Preterm infants with significant chronic lung disease or other chronic conditions that might increase energy expenditure are likely to need increased protein and energy delivery after discharge to maintain adequate growth. For all preterm infants, attention should be paid to other possible nutrient deficiencies including calcium, phosphorus, iron, vitamins, and LC-PUFAs. **Feeding post-discharge preterm formulas or breast milk with higher concentrations of calcium and phosphorus results in improved bone mineralization.[154] All preterm infants also should receive iron supplementation and close surveillance of iron status.[22] Regardless of milk type, demand feeding should be initiated before discharge to document adequate growth on the chosen feeding regimen. Close monitoring of growth (weight, length, and head circumference for age, indices of body proportionality) and feeding intake should be performed at discharge and regularly after discharge using appropriate growth curves.**

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18 BREASTFEEDING THE NEONATE WITH SPECIAL NEEDS

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Human milk has been recognized as the gold standard for infant nutrition for centuries. Published studies from 1918 on have confirmed that problems develop when human milk is replaced with artificial formulas made from the milk of other species. **Milk of other species that is fed to human infants has been known to contribute to increased infant mortality risk.** Over the years, increasing research has confirmed the presence of anti-infective properties of human milk that protect against infections of the gastrointestinal tract, the upper and lower respiratory tracts, and the urinary tract, as well as against otitis media, bacteremia, bacterial meningitis, botulism, and necrotizing enterocolitis (NEC), leading to lower infant mortality rates.[10,233] In numerous studies, human milk also has been shown to have a protective effect against sudden infant death syndrome, type 1 and type 2 diabetes, obesity, Crohn's disease, ulcerative colitis, lymphoma, childhood leukemia, allergic diseases, asthma, chronic digestive disorders, heart disease, hyperactivity, and hypertension.[154,245] Breastfeeding also enhances cognitive and visual development and neurodevelopment.[27,152,256] Studies show less of a pain response in full-term infants undergoing heel lance when they were breastfed before, during, and after the procedure. **Breastfeeding as a nonpharmacologic intervention for procedure-related neonatal pain is highly recommended**[361] (see Chapter 12). **In preterm infants, human milk provides both short-term and long-term advantages (Table 18.1) in a dose-dependent relationship; the more breast milk the preterm infant receives, the more benefits he or she receives.**[297,301,334,337,387]

Because of a lack of experience and knowledge about breastfeeding, a new mother who is discharged early (24 to 48 hours) from the hospital may find it challenging to initiate breastfeeding for her healthy newborn infant. The mother of a newborn with special needs, such as a preterm infant, a sick term newborn, or an infant with a congenital anomaly, may have even more difficulty in establishing breastfeeding because of the stress of separation and concerns about the infant's well-being (see Chapter 29). The tremendous benefits of providing human milk for all infants, but especially the premature infant, outweigh any apparent difficulties. In 2015, the Centers for Disease Control and Prevention (CDC) found a racial disparity in human milk use in neonatal intensive care units (NICUs) in the United States.[41] Although 80% of infants in reporting NICUs received mother's own breast milk and 10% of infants received donor milk, when NICUs serving a higher percentage of black residents were examined, 72% of their infants received mother's own milk and only 5% received donor milk.[41] **Human milk feedings (i.e., mother's own milk; donor human milk) need to be a priority for all preterm infants in NICUs.**[10,121,297,301]

Healthy People 2020,[445] the health policy statement for the United States, states the following goal about breastfeeding: 81.9% of women breastfeeding in the early postpartum period, at least 60.6% still breastfeeding their infant at 6 months, and 34.1% breastfeeding their infant at 1 year of age. A report published by the Institute of Medicine,[197] the American Academy of Pediatrics (AAP) Section on Breast Feeding,[10] the Academy of Breastfeeding Medicine (ABM),[73] and the U.S. Surgeon General's *Call to Action to Support Breastfeeding*[441] states that **(1) all infants in the**

BLUE type highlights content that is particularly applicable to clinical settings.

TABLE 18.1 ADVANTAGES OF BREASTFEEDING AND HUMAN MILK INTAKE FOR PRETERM INFANTS[295,297,387,433]

BENEFIT	COMMENT
Protection from NEC*	Formula-fed infants developed NEC 6–10 times more often than infants receiving only human milk. Infants ≥30 weeks' gestational age: incidence of NEC 20 times more in formula-fed than in human milk–fed infants. Lower incidence of intestinal perforation and less severity of NEC with human milk intake before NEC. Dose-dependent relationship among human milk intake, reduced risk for NEC, and cost savings (each additional mL/kg/day) of human milk in first 2 weeks of life decreased costs. Exclusive human milk diet fortified with human milk fortifier significantly lowers rates of NEC, severity of NEC, and cost when compared with human milk or formula diet fortified with bovine-based fortifier.[17,420]
Protection from infection or sepsis†	Lowered infection and severity of infections in hospitalized ELBW, VLBW, or LBW infants fed human milk,[334,388,393] resulting in shortened LOS. Skin-to-skin care customizes human milk by production of antibodies against NICU-specific pathogens.[367] Lower intestinal permeability with human milk vs. formula feedings; >75% human milk intake resulted in 3.8-fold lower intestinal permeability compared with <25% or no human milk intake.[425] A dose-response relationship between consumption of human milk and sepsis: every 10-mL/kg/day increase in human milk consumption decreased the risk of sepsis by 19%.[334] Use of mother's milk for oral care of ventilated premature infants was not associated with decrease in ventilator days, LOS; reduced positive tracheal aspirates/positive blood cultures not statistically significant.[426]
Increased feeding tolerance[90,393]	Decreased protection if formula feeding added to human milk feedings. Increased rehospitalization: sevenfold for formula-fed infants compared with 0–1 for infants who are breastfed (both partially and completely). Possible to achieve complete enteral feedings by 6 weeks of age in VLBW infants fed own mother's milk (compared with VLBW infants fed donor milk or formula).[255] Formula-fed infants: increased vomiting, gastric residuals, and longer time to achieve complete enteral feedings.[255]
Earlier attainment of full enteral feedings,[171] which is associated with a significant reduction in late-onset sepsis among extremely premature infants[372]	Preterm infants ≤1250 g receiving at least 50% human milk attained earlier full enteral feedings. Any bovine-based enteral intake in extremely preterm infants results in a longer time to full enteral feedings.[171]
Decreased risk for later allergy	Lower incidence of allergic symptoms (especially eczema) at 18 months in human milk–fed preterm infants.[254]
Improved retinal function[388]	Better retinal function, depending on omega-3 fatty acid concentration (found in human milk, but not previously in formula) in enteral feedings. Less ROP and less severe ROP in human milk–fed compared with formula-fed infants.[270,415,479]
Improved neurocognitive development‡ and brain growth[27,37]	Long-term advantages: higher intelligence quotients at 30 months,[455] and 7–8 years of age;[27] better development at 18–24 months of age;[152,256,454] and better behavioral scores (orientation/engagement, motor regulation, and total scores).[454] Better academic achievement, motor function, and working memory at 7 years of age.[27] Higher IQ and better neurocognitive abilities in adulthood.[384] Increased white matter microstructural organization in the cerebrum and cerebellum.[323] Supplementation with long-chain fatty acids (added to breast milk/formula) significantly improves neurodevelopment at 1–3 years of age.[459] Dose-dependent association between better cognitive scores at 20 months' CA in VLBW infants[337]
Suppression of oxidative stress	Reduced incidence of BPD/CLD in a dose-dependent relationship:[131,170,389,393,415,454] 9.5% reduction in BPD/CLD for every 10% increase in own mother's milk dose; cost savings for every BPD/CLD case prevented.[335] Anti-inflammatory and antioxidant properties of human milk may protect premature infants from white matter injury.[90,232]

Continued

TABLE 18.1 ADVANTAGES OF BREASTFEEDING AND HUMAN MILK INTAKE FOR PRETERM INFANTS[295,297,387,433] — CONT'D

BENEFIT	COMMENT
Reduced health care costs[205,254]	A dose-response relationship between consumption of human milk and cost savings: NICU costs lowest in VLBW infants with the highest intake of human milk in the first 28 days of life.[334] Lower risk of NEC and sepsis (see above). Earlier attainment of full enteral feedings (see above). Shorter LOS.[389,393] Fewer hospital admissions up to 30 months of age.[454]
Reduced heart disease in later life and features predictive of metabolic syndrome[401]	Lower cardiorespiratory levels and LDL to HDL ratios in adolescents born premature who were fed human milk.

*References 90, 248, 255, 270, 354, 456.
†References 90, 95, 295, 334, 388, 393, 425.
‡References 90, 95, 126, 247, 323, 454, 455.
ARA, Arachidonic acid; *BPD,* bronchopulmonary dysplasia; *CLD,* chronic lung disease; *DHA,* docosahexaenoic acid; *DNA,* deoxyribonucleic acid; *ELBW,* extremely low-birth-weight; *HDL,* high-density lipoprotein; *LBW,* low-birth-weight; *LDL,* low-density lipoprotein; *LOS,* length of stay; *HdG,* hydroxy-deoxy-guanosine; *NEC,* necrotizing enterocolitis; *NICU,* neonatal intensive care unit; *PDA,* patent ductus arteriosus; *ROP,* retinopathy of prematurity; *VLBW,* very-low-birth-weight.
Modified from Meier P, Brown L. Breast feeding for mothers and low birth weight infants. *Nurs Clin North Am.* 1996;31:351.

United States should be breastfed, (2) "human milk is uniquely superior for infant feeding,"[197] (3) "infants should be exclusively breastfed for 5 to 6 months,"[10] and (4) "breastfeeding is the ideal method of feeding and nurturing infants."[441] The policy statement by the AAP provides additional recommendations for high-risk infants, including preterm infants. It states that the "hospitals and physicians should recommend human milk for premature and other high-risk infants either by direct breastfeeding or using the mother's own expressed milk." The statement continues by recognizing that maternal support and education, mother-infant skin-to-skin contact, and direct breastfeeding as early as possible are keys to success. State-by-state breastfeeding data on the percentage and length of breastfeeding are available from the CDC in its Breastfeeding Report Card.[66] In 2018, the CDC reported that over one-half of the breastfeeding goals for *Healthy People 2020* had been met by the 2015 data: 83.2% of mothers in the United States breastfed their infants after birth, 57.6% were breastfed at 6 months of age, and 35.9% were still breastfeeding at 1 year.[66]

In 2018, the United Nations International Children's Emergency Fund (UNICEF) and the World Health Organization (WHO) published a revised 10 steps for the Baby-Friendly Hospital Initiative to protect, promote, and support breastfeeding.[439] Although the initial Baby-Friendly steps were intended for full-term healthy newborns and their families, **the revised 10 steps (Box 18.1) are intended to be applied to premature and sick babies as well as healthy breastfeeding neonates.**[439] Quality improvement strategies[332] using 10 steps for promoting breastfeeding for very-low-birth-weight (VLBW)[134] infants and a multidisciplinary approach[35] both significantly improved the rate of breastfeeding with mother's own milk in the NICU at initiation of feedings and at NICU discharge for VLBW infants. Before the start of the World Breastfeeding Conference in 2018, UNICEF and the WHO issued a report that **globally, only 2 of 5 newborns breastfeed in the first hour of life.**[440] Initiation of **breastfeeding later than the first hour of life increases the risk of neonatal mortality by 33%, and initiation after 24 hours of life increases the risk by 50%.**[440]

The goal of this chapter is to give the health care provider the skill and knowledge to support the breastfeeding dyad, especially when it involves the neonate with special needs.

BOX 18.1 REVISED TEN STEPS TO SUCCESSFUL BREASTFEEDING

Critical Management Procedures

1a. Comply fully with the *International Code of Marketing of Breastmilk Substitutes* and relevant World Health Assembly resolutions
1b. Have a written infant feeding policy that is routinely communicated to staff and parents
1c. Establish ongoing monitoring and data-management systems
2. Ensure that staff have sufficient knowledge, competence and skills to support breastfeeding

Key Clinical Practices

3. Discuss the importance of breastfeeding with pregnant women and their families
4. Facilitate immediate and uninterrupted skin-to-skin contact and support mothers to initiate breastfeeding as soon as possible after birth
5. Support mothers to initiate and maintain breastfeeding and manage common difficulties
6. Do not provide breastfed newborns any food or fluids other than breast milk, unless medically indicated
7. Enable mothers and their infants to remain together and to practice rooming-in 24 hours a day
8. Support mothers to recognize and respond to their infant's cues for feeding
9. Counsel mothers on the use and risks of feeding bottles, teats and pacifiers
10. Coordinate discharge so that parents and their infants have timely access to ongoing support and care.

From United Nations International Children's Emergency Fund (UNICEF) and the World Health Organization (WHO). *Implementation Guide: Protecting, Promoting and Supporting Breastfeeding in Facilities Providing Maternity and Newborn Services: The Revised Baby-Friendly Hospital Initiative.* Geneva, Switzerland: WHO Document Production Service; 2018:17.

PHYSIOLOGY OF BREASTFEEDING

Nutritional Value of Breast Milk

The components of breast milk vary with the (1) stage of lactation, (2) time of day, (3) sampling time during a feeding, and (4) extremes of maternal nutrition. In addition, there is variation among individual mothers, especially related to their age and gravity.[245,310,311]

***Colostrum* is produced immediately at delivery and within 5 days gradually changes to transitional milk with increased lactose and finally mature milk by 2 weeks** with an increasing concentration of fat. Colostrum contains higher ash content and higher concentrations of sodium, potassium, chloride, protein, fat-soluble vitamins, amino acids, and minerals than does mature milk. Colostrum has a lower fat content, especially of lauric and myristic acids, than does mature milk. Novel bioactive substances (i.e., irisin, adropin, copeptin) in colostrum may assist the neonate in postnatal adaptation related to thermoregulation, vascular adaptation, glucose metabolism, lung function, and fluid homeostasis.[46] This milk is yellowish, thick, and rich in antibodies, has a specific gravity between 1.040 and 1.060, and contains 67 kcal/dL. During the first day of life, full-term healthy breastfeeding neonates ingest a total of 15 mL (±11 mL) divided among 10 feeding sessions.[386] Multiparas and women who have previously breastfed have more colostrum during the first few days than do women who have not.

***Transitional milk* is produced between 7 and 10 days postpartum,** remains high in protein and fat,[114] and has a dramatic increase in water content compared with colostrum. Among mothers, the high variability of transitional milk accounts for 67 to 75 kcal/dL.

***Mature milk* is produced after 10 days postpartum** and contains 75 kcal/dL. The fat and energy content of mature milk at 30 days after birth is lower when compared with transitional milk.[114] Maternal factors such as age, diet-controlled gestational diabetes, and higher postpregnancy BMI levels, as well as the level of prematurity significantly affect breast milk's macronutrients and energy.[114,235] By the second week of life, maternal milk production averages about 30 mL/hr (i.e., 750 to 800 mL/day). During a feeding, the relative content of protein and the absolute content of fat increases. Morning feedings have a higher fat content than do afternoon and evening feedings. **Foremilk is lower in fat and energy content than hindmilk.** Severely malnourished mothers have been shown to produce less milk, and water-soluble vitamins may be affected by deficient diets, as may occur in strict vegetarians.

Human Milk Versus Cow's Milk

Cow's milk differs significantly from human milk. Cow's milk has 18 parts whey to 82 parts casein, whereas human milk has 60 parts whey to 40

parts casein. Casein is composed of proteins with ester-bound phosphate, high proline content, and low solubility at a pH of 4 to 5. Casein forms curd by combining with calcium caseinate and calcium phosphate. The cysteine and taurine content is low in cow's milk but high in human milk, whereas the methionine content is high in cow's milk and low in human milk (the human infant lacks the enzyme to digest methionine). Human milk also has lower levels of aromatic amino acids, phenylalanine, and tyrosine. Human milk contains 6.8 g/dL of lactose, and cow's milk contains 4.9 g/dL of lactose. Sodium, phosphorus, calcium, magnesium, citrate, and total ash content are higher in cow's milk, but potassium and the calcium:phosphorus ratio is higher in human milk. Formula attempts to mimic human milk but still lacks cholesterol, omega-3 fatty acids, enzymes, antibodies, lactoferrin, and other protective anti-infective properties.

Human milk contains more iron than unsupplemented cow's milk but less iron than supplemented cow's milk. **Only 10% of iron is absorbed from formula, whereas about 80% is absorbed from human milk.** Iron in formula encourages the growth of *Escherichia coli* and inactivates lactoferrin. Cow's milk has a mean pH of 6.8, osmolality of 350 mOsm, and 221 mOsm renal osmolar load. Human milk has a mean pH of 7.1, osmolality of 286 mOsm, and 79 mOsm renal osmolar load.

Cow's milk forms indigestible curds much more easily and thus delays gastric emptying. The newborn cannot handle certain proteins well because cow's milk lacks specific enzymes necessary for metabolism. These enzymes are readily available in human milk. **However, 95% of human milk protein is nutritionally available to term infants, whereas the gastrointestinal immaturity of the preterm infant enables four to six times higher daily losses of human milk protein if human milk is pasteurized or has cow's milk–based fortifier added.** Some human milk proteins are immunoglobulins, which have a protective effect on the gut and are preserved by antiproteases from being digested (i.e., are found in stool). In VLBW infants, the antiproteases persist so there are more immunoglobulins and lactoferrin in the stool early on (i.e., six and four times more immunoglobulin A [IgA] and lactoferrin, respectively). This is a function of the milk of mothers who deliver prematurely, not a deficiency of the VLBW gut. **Iron is more bioavailable in human milk, and iron absorption from human milk is more efficient,** but cow's milk has a higher concentration of zinc and contains more fluorine than does human milk. Human milk, however, contains a ligand specific to zinc absorption, and thus more zinc actually is absorbed and used. Human milk has been used as a therapy for zinc deficiency (see Chapter 17 for other human milk components).

Preterm Versus Term Breast Milk

Significant evidence exists that **there are many differences in the breast milk that a mother produces when she has a preterm infant compared with the breast milk produced for a term infant**[231,273,296,431]: (1) preterm breast milk has an increased protein content that decreases over the first month of lactation; (2) the types of protein, predominantly whey, have a more physiologic balance of amino acids and contain many anti-infective properties; (3) preterm breast milk has higher concentrations of immune proteins; (4) the lipid content in preterm breast milk is more specific for the preterm neonate (i.e., an increased supply of medium-chain to intermediate-chain fatty acids); (5) lactose, the major carbohydrate in breast milk, increases in the first month of lactation and is easily absorbed by preterm infants; (6) docosahexaenoic acid (DHA) and arachidonic acid (ARA) concentrations are similar to full-term breast milk and significantly decrease over the first month of lactation[157,368]; and (7) IgA concentrations are higher (see Chapter 17 for a comparison of preterm and term breast milk). Colostrum from mothers of extremely preterm infants (i.e., 24 to 27 weeks' gestational age) contains significantly lower concentrations of lactose and glucose and higher concentrations of cytokines and immunoglobulins than does mature milk.[305] **By 5 to 7 weeks postpartum, preterm milk changes to resemble term milk, independent of gestational age at premature birth.**[421] A recent study of 40 premature infants given bovine colostrum to supplement mother's own milk in the first 2 weeks of life found that those infants receiving bovine colostrum had increased enteral protein intake.[207] A larger RCT to test the safety and efficacy is needed.

Recent studies of the composition of preterm mother's milk found that mature preterm milk contains more stem cells and immune proteins than preterm colostrum[47,209] and term mother's milk during the first month of life.[163,431] Mother's milk

of premature boys had significantly more sIgA than the breast milk for premature girls; the levels of immune components decrease over time.[163]

In the NICU, four critical exposure periods for premature infants to human milk have been identified: (1) colostrum in the transition from intrauterine to extrauterine life, (2) transition from colostrum to mature milk in the first month of life, (3) the amount of human milk feeding throughout the NICU stay, and (4) human milk feeding after discharge.[295] Colostrum is rich in bioactive factors that promote growth and maturation, as well as protection of the immature intestinal tract of infants.[295,297,431] Mothers of the least mature preterm infants produce the most protective colostrum and produce colostrum for a longer period to protect their vulnerable offspring.[295,431]

The Immunologic Value of Breast Milk

Because human milk protects neonates through its many anti-infective properties, breastfed infants have decreased morbidity compared with bottle-fed infants.[159,306] **The immunologic benefits of human milk depend on dose, duration, and exclusivity.**[173] The main defense factors in human milk are (1) antimicrobial agents, (2) anti-inflammatory factors, and (3) immunomodulators and leukocytes. In addition to providing protective agents, the components in human milk also modulate the development of the newborn's own immune functions.[159] Bacteria in mother's milk and on her areola seed her infant's gastrointestinal system and establish the infant's gut microbiome.[328] **Through breastfeeding, 30% of the beneficial bacteria are provided by breast milk and 10% by skin flora on the maternal nipple.**[328] Formula feeding, as well as cesarean delivery and antibiotic therapy, significantly alter the infant's gut microbiome.[473] **The premature infant is born with an immature immune system, and the provision of human milk reduces the risk of immune system conditions such as infection, inflammation, and allergies.**[250] Bioactive factors in human milk and their functions are listed in Table 18.2.

TABLE 18.2 BIOACTIVE FACTORS IN HUMAN MILK

COMPONENT	FUNCTION
	ANTIBODIES
Secretory IgA (sIgA)	Attaches to mucosal epithelium of the digestive tract, thus preventing attachment of pathogens,[237,371] sIgA against enteric, respiratory, and viral pathogens, as well as specific pathogens to which the mother has been exposed; highest concentration in colostrum peaks during first 3–4 days postpartum; present in mature milk through first year of life.[387] Lower sIgA concentrations in very preterm infant's mother's colostrum than in term colostrum.[65] Antiallergic properties: inhibits absorption of macromolecular antigens from neonatal small intestine.
	MAJOR NUTRIENTS
Protein	
sIgA, IgM, IgG	Immune protection.
Lactoferrin	Higher levels at birth (in colostrum) and at 30 days in premature infants, higher levels at lower birth weights[435] and gestational ages,[6] compared with full-term infants.[296] Higher levels of commensal bacteria in neonatal gut associated with higher lactoferrin levels; may contribute to immunologic maturation and neonatal well-being.[261] Binds iron, thwarts growth of pathogens (e.g., bactericidal, antiviral), modulates cytokine function, and is anti-inflammatory; highest levels in colostrum; present in mature milk throughout first year of life.[237] May attenuate iron-induced oxidation products in preterm infants.[356] Enteral lactoferrin supplementation decreases late-onset sepsis and NEC stages 2 and 3 in preterm infants without adverse effects.[326]

Continued

TABLE 18.2 BIOACTIVE FACTORS IN HUMAN MILK—CONT'D

MAJOR NUTRIENTS	
Lysozyme	Destroys pathogens (e.g., gram-positive and few gram-negative bacteria) by cell wall lysis; human milk contains 300 times the concentration of cow's milk; concentration increases with prolonged lactation.[371] Higher concentrations in preterm breast milk.[431]
Casein	Inhibits microbial adhesion to mucous membranes of respiratory and gastrointestinal tracts. Promotes growth of *Lactobacillus bifidus,* the normal intestinal flora for breastfed infants, and inhibits pathogens[252]; by 1 month of age, *Bifidobacterium* level in infants fed human milk is 10 times that of formula-fed infants.
Adiponectin	Regulates metabolism; possible protection against obesity, by influencing development of body composition.[160]
Fibronectin	Enhances antimicrobial activity of macrophages[371]; assists in repair of intestinal tissue damage by immune reactions.
Carbohydrate	
Oligosaccharides	Bind to microorganisms (microbial ligands), thus preventing pathogens from attaching to respiratory mucosal surfaces.[387] Antimicrobial and antibiofilm properties against *Group B Streptococcus.*[2]
Glycoconjugates mucin and lactadherin	Microbial and viral ligands.[93] Provide receptor site binding for organisms so that the organism is made less harmful or passes from the body in the stool.[371] Lower levels of lactadherin in milk of mothers of very preterm infants.
Fat	
FFAs	Disrupt and destroy lipid-enveloped virus, bacteria, and protozoa.[177] Obese mothers have a proinflammatory fatty acid profile; decreased concentrations of fatty acids and carotenoids influence early visual and neurodevelopment.[327]
MINOR NUTRIENTS	
Nucleotides	Enhance T-cell maturation, antibody response to vaccines, intestinal maturation, repair after diarrhea, and natural killer cell activity; promote growth of *Lactobacillus bifidus.*
Vitamins	
A, C, E, D	Anti-inflammatory: scavenges oxygen radicals. Vitamin D content of breast milk is 25 IU/L or less. For prevention of rickets and vitamin D deficiency, all breastfed infants should be given supplemental vitamin D (e.g., 400 IU/day) beginning in the first few days of life.[312,458]
Enzymes	
Amylase	Digestion of polysaccharides.
Bile salt–dependent lipase	Production of FFAs with antibacterial/protozoan activity. Assists with fat digestion.
Catalase	Anti-inflammatory: degrades H_2O_2.
Glutathione peroxidase	Anti-inflammatory: prevents lipid peroxidation.
Lipase	Breaks down triacylglycerols.
PAF acetyl hydrolase	Degrades PAF, a potent cause of ulceration; protects against necrotizing enterocolitis.
GROWTH FACTORS (HIGHER AMOUNTS OF ALL GROWTH FACTORS IN COLOSTRUM COMPARED WITH MATURE MILK)[310]	
Epithelial growth factors	Enhances maturation of gut epithelial barrier, limiting penetration by foreign antigens, thus decreasing immune stimulation.[371]
Fibroblast growth factor 21	Enhances nutrient absorption and intestinal function.[140] Contributes to improved growth and metabolic profile.

TABLE 18.2 BIOACTIVE FACTORS IN HUMAN MILK—CONT'D

GROWTH FACTORS (HIGHER AMOUNTS OF ALL GROWTH FACTORS IN COLOSTRUM COMPARED WITH MATURE MILK)[310]	
Transforming growth factors	Higher concentrations in extremely preterm infant's mother's colostrum than in term colostrum.[65,431] Alpha: promotes epithelial cell growth. Beta: suppresses lymphocyte function: anti-inflammatory; prevents allergic reaction.
Angiopoietins	Necessary for vessel growth and maturation.[474]
HORMONES	
Prolactin	Enhances B- and T-lymphocyte development; affects differentiation of intestinal lymphoid tissue.
Cortisol, thyroxine, insulin	Promotes maturation of neonatal intestine and development of intestinal host-defense mechanisms.
Erythropoietin	Influences erythropoiesis, gut maturation, apoptosis, neurodevelopment, and immunity.[390] Risk of mother-to-child transmission of HIV inversely related to erythropoietin levels in mother's breast milk.[16]
Leptin	Lower concentration than in plasma. Higher concentration in human milk reflects higher maternal BMI.[235] May contribute to mediating the association between maternal and infant body composition[102] and appetite programming of breastfed infants.[235]
Peptide hormones: adropin, copeptin, irisin, preptin	Present in colostrum; may assist in postnatal adaptation related to thermoregulation, vascular adaptation, glucose metabolism, lung function, and fluid homeostasis.[46]
CELLS	
B lymphocytes	Synthesize IgA and other antibodies targeted against specific pathogens.
Macrophages	90% of cells in breast milk; phagocytize microorganisms and kill bacteria in neonatal intestine; produce lysozyme, lactoferrin, and complement.
Neutrophils	Phagocytize bacteria in neonatal gastrointestinal tract.
T lymphocytes	Phagocytosis against organisms in gastrointestinal tract; mobilize other host defenses; antigens introduced into maternal respiratory and/or gastrointestinal systems stimulate development of antibodies in breast milk; incorporation into neonatal tissue bestows short-term adoptive immunity.[246]
Cytokines	Modulate functions and maturation of immune system.
Proinflammatory: interleukins 1-beta, 6, 8, 12; interferon-gamma; tumor necrosis factor–alpha	Enhances inflammation. Higher levels of interleukin-6 and lower levels of interleukin 8/10 and TNF-α in colostrum after preterm birth.[65] Interleukin-8 levels decline with stage of lactation; no significant difference in concentration between premature and term mother's milk.[346]
Anti-inflammatory: interleukin 10; tumor growth factor–beta	Suppresses function of macrophages, natural killer cells, and T cells.

BMI, Body mass index; *FFA,* free fatty acid; *HIV,* human immunodeficiency virus; *Ig,* immunoglobulin; *IU,* International unit; *NEC,* necrotizing enterocolitis; *PAF,* platelet-activating factor; *sIgA,* secretory immunoglobulin A; *TNF-α,* tumor necrosis factor-α; *TGF-β,* transforming growth factor-β.
Modified from Hamosh B. Bioactive factors in human milk. *Pediatr Clin North Am.* 2001;48:69.

The highest concentration of immunoprotective factors is found in colostrum, which should be pumped, preserved, and fed to a neonate with special needs.[177] **Pumped milk should be labeled chronologically so that it is fed to preterm infants in the same sequence in which it was collected. In this fashion, the preterm infant receives the high concentration of protective qualities that have been shown to protect the gastrointestinal and respiratory systems. Clinical guidelines for colostrum feeding in the NICU are presented in** Box 18.2.[295]

BOX 18.2 CLINICAL GUIDELINES FOR COLOSTRUM FEEDING IN THE NICU

- Colostrum should be the first feeding received by the newborn infant.
- Colostrum may be used for minimal enteral nutrition (trophic feeds).
- Colostrum can be safely administered to the oropharynx either before or with minimal enteral nutrition.
- Give exclusive colostrum feedings for the first 3 to 4 days; then alternate colostrum with fresh mature human milk (to protect the infant from NICU organisms through the enteromammary pathway).
- Store colostrum in small, sterile, food-grade containers that are easy to recognize in the refrigerator/freezer.
- Number the colostrum containers in the order of pumping; feed to baby in the order of pumping.
- Dilute small, expressed drops of colostrum with 1 to 2 mL of sterile water so that drops of colostrum are removed from container and/or to achieve desired feeding volume. Dilution of colostrum is not necessary for any other reason.
- Do not mix colostrum with formula or fortifier.
- Pumping colostrum may be facilitated by a combination of hand expression and breast pumping.
- Avoid formula feeding during the introduction and advancement of colostrum. Formula may exert a separate detrimental effect on gastrointestinal integrity during this critical time.

Modified from Meier PP, Engstrom JL, Patel AL, et al. Improving the use of human milk during and after the NICU stay. *Clin Perinatol* 2010;37:217.

Providing colostrum to the oral cavity of the preterm infant stimulates the development and response of the neonate's own immune system. A pilot study of 5 extremely low-birthweight (ELBW) infants (mean birth weight 657 g and mean gestational age 25.5 weeks) receiving 0.2 mL of oral colostrum every 2 hours for 48 hours beginning at 48 hours of age found that the colostrum was easy to administer, inexpensive, and well tolerated.[369] In 48 extremely preterm infants (<28 weeks of gestation), oral colostrum resulted in increased levels of immune protective factors (i.e., secretory immunoglobulin A and lactoferrin) and an inhibition of proinflammatory cytokines.[249] Another study compared administration of colostrum to the buccal pouch of VLBW infants every 2 hours for 48 hours with standard NICU care. At 48 and 96 hours, there was a marked change in the oral microbiota between the two groups.[408] **Oropharyngeal colostrum is safe and associated with higher rates of breast milk feeding in the NICU and through discharge.**[407] A 5-year, multicenter, double-blind, randomized controlled trial to evaluate the safety and efficacy of oropharyngeal mother's milk on the incidence of late-onset sepsis, NEC, and death in a large cohort of extremely premature infants is ongoing.[370] Box 18.3 is an adapted protocol for oral care with colostrum.

BOX 18.3 ORAL CARE WITH COLOSTRUM[146,295]

Teach the mother hand expression, and place colostrum in small breast milk containers.
Use fresh colostrum if possible; otherwise, refrigerated/frozen colostrum can be used.
Use colostrum in the order that it was pumped.
Using universal precautions, saturate a sterile cotton swab with colostrum (about 0.2 mL).
Before feeds or with scheduled cares if on nothing-by-mouth status: Parent/nurse paints the tongue, gums, and cheeks with colostrum.
Document.

Enteral intake in the first month of life constitutes the second critical period when benefits listed in Table 18.1 **are seen in VLBW and ELBW preterm infants in a dose-dependent relationship to human milk intake.**[295,337] The normal microflora found in the neonatal gastrointestinal tract is the first line of defense against many pathogenic bacteria. After birth, the first exposure of the neonatal gut is to the maternal vaginal flora, and colonization continues with development of an environment of flora by 1 week of age. Colonization of the gastrointestinal tract of preterm and sick neonates is altered by cesarean birth, antibiotics, delayed enteral feeding, separation from the mother, and presence in an NICU. **With breastfeeding or provision of breast milk, containing both prebiotics and probiotics, the dominant flora are *Bifidobacterium* and *Lactobacillus,* which suppress pathogens.** Breast milk has been shown to be effective in reducing the colonization with *Klebsiella, Enterobacter,* and *Citrobacter.*[125] In addition, paracellular pathways between enterocytes in the preterm infant's intestine are closed, thus inhibiting the passage of bacteria and toxins from gut lumen to the bowel wall. When infants are provided formula, the growth of bifidobacteria is very slow, and there is only one-tenth the concentration at the end of the first week compared with that in infants fed breast milk. During this critical period, even small amounts of formula interrupt both of these processes.[295]

There are conflicting results from research as to whether reduction of anti-infective activity occurs with the use of breast milk fortifier. Older studies showed that fortifier does not decrease anti-infective properties of human milk,[179,246,389] whereas a more recent study showed that human milk fortifier with iron reduced the bacteriostatic action of the fortified breast milk against *E. coli,* in vitro.[59] Continued surveillance in the use of fortifiers is recommended.[389]

The fourth critical period of human milk intake for preterm infants is the total amount and/or exclusive human milk feeding during their NICU stay.[295] Research shows that extremely premature infants (i.e., ELBW, VLBW) exhibit benefits of human milk intake listed in Table 18.1 based on their total intake of human milk. Those infants with the highest doses benefited most in both short- and long-term outcomes.[28,388,389,396,454,455] A recent study of pumping practices among[129] mothers in two NICUs found that only 50% of their infants exclusively received their mother's own breast milk and that two-thirds of the mothers had inadequate expression practices (i.e., ≤6 times/day).[196] **The goal of breast pumping is to establish a full milk supply (≥500 mL/day) by the end of the neonate's first 2 weeks of life.**[189] Attaining a full milk supply by 14 days is the strongest indicator of VLBW infants receiving own mother's milk at NICU discharge.[188]

Banked human milk (donor milk) can be used if the mother is unable or unwilling to provide sufficient quantities of breast milk.[10,121] Human milk banks in the United States have rigorous guidelines for donations and adhere to strict quality controls.[10]

Normal Lactation

Breast development during pregnancy is stimulated by luteal and placental hormones—lactogen, prolactin, and chorionic gonadotropin.[315] Production of breast milk depends on both mammogenesis and lactogenesis. Mammogenesis is the growth and development of the glandular tissue of the breast and the differentiation of secretory epithelial cells or lactocytes during pregnancy.[181] **Estrogen stimulates growth of the milk collection (ductal) system, whereas progesterone stimulates growth of the milk production system.** These hormones, however, inhibit the initiation of breast milk production in significant quantity. With the birth of the infant, the hormones of pregnancy decline abruptly when the placenta is delivered, permitting the initiation of milk secretion. There is some speculation that mammogenesis and lactogenesis stage I may be truncated with the birth of preterm infants, especially the VLBW premature infant. In addition, cesarean delivery may affect lactogenesis stage II as it affects the hormone balance stimulated by labor. Breast growth varies greatly during pregnancy, and it is unclear how much breast tissue is necessary to support full lactation. Many factors other than breast size affect milk production, such as stress and fatigue, both of which are increased when a preterm infant is born.

If a woman aborts as early as 16 weeks, her breasts secrete colostrum; therefore mothers are prepared to breastfeed any viable infant.[245]

Estrogen and progesterone function as inhibitors to actual milk production because they inhibit the breast receptors for prolactin. Therefore stimulation of the breast before delivery does not create milk but may induce uterine contractions because oxytocin is released. Once the infant and placenta are delivered, stimulation of the nipple becomes effective in producing milk.

Stimulating the nipple by the infant's sucking action causes an increase in the prolactin released in the bloodstream and induces the synthesis and release of oxytocin, which is initiated by nipple stimulation and other sensory pathways (Fig. 18.1). The amount of prolactin is directly related to the quantity and quality of nipple stimulation; because prolactin stimulates the synthesis and secretion of milk, the surges in prolactin levels are related to the quantity of milk. **A decrease in the quality of stimulation causes a decrease in prolactin surges and thus a decrease in milk production.** Studies show that **overweight/obese mothers have a diminished prolactin response to infant sucking** (e.g., less milk production) in the first postpartum week.[359] **The prevalence of delayed milk production among obese mothers in a recent study was 57.9% with milk "coming in" delayed until the sixth day of life.**[350] These mothers may benefit from earlier lactation counseling and support that will enable them to continue breastfeeding and prevent their infants from excessive weight loss and formula supplementation.[350,359,405]

Adequate prolactin secretion controls the maintenance of milk supply. The sooner the infant nurses, the sooner the milk comes in and becomes established. Initially, production of milk is on a more consistent basis because the basal level of prolactin is very high immediately after birth. Maintenance of milk depends on adequate stimulation of the breast and removal of milk on

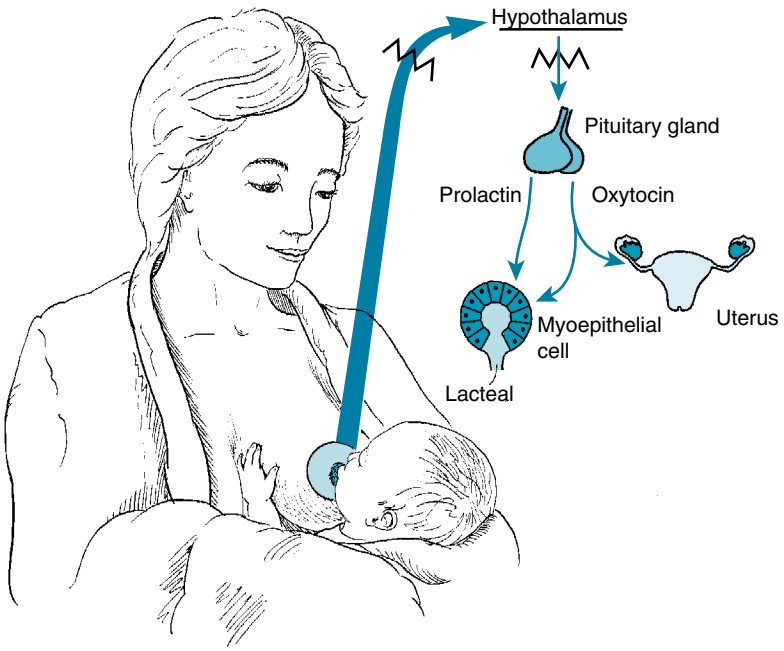

FIGURE 18.1 Ejection reflex arc, or letdown reflex. Infant suckling stimulates mechanoreceptors in the mother's nipple and areola that send the stimuli along the nerve pathways to the hypothalamus. Stimulation of the posterior pituitary gland releases oxytocin that (1) stimulates myoepithelial cells of the breast to contract and eject milk and (2) stimulates the uterus to contract. Stimulation of the anterior pituitary gland releases prolactin, which is responsible for milk production in mammary alveoli. (Modified from Lawrence RA, Lawrence RM. *Breast Feeding: A Guide for the Medical Profession.* 5th ed. St Louis, MO: Mosby; 1999.)

a regular and frequent basis. By the second week of lactation, 92% of mothers of healthy term neonates are producing *at least* 440 mL/day of breast milk for their infants.[221,222] Initially, a newborn needs to nurse for a longer time to stimulate milk production and letdown. As the infant grows, sucking becomes more efficient, with the infant stimulating sequential letdowns early in the nursing period, thereby shortening the length of nursing. Establishing a generous milk supply is critical in long-term maintenance. **Research has demonstrated that for mothers who are separated from their infants, pumping both breasts simultaneously stimulates a higher prolactin surge with increased milk supply than pumping one breast at a time.**[206]

PSYCHOLOGICAL VALUES OF BREASTFEEDING

The short-term advantage of breastfeeding is early mother-infant contact. The en face position of breastfeeding enhances this contact. During the first 1 to 2 hours after birth, the infant's sucking and touching of the mother's areola increases maternal attentiveness to the baby's needs for at least the first week of life. Because several studies show that maternal analgesia alters the infant's initial breastfeeding behavior, the mother's behavior may also be altered. Early contact—whether by breastfeeding or another physical means—sometimes must be delayed or modified in a sick neonate. **Prolactin and oxytocin affect the initiation of maternal behavior and are involved in stress management in humans.** Oxytocin has been shown to reduce depression and anxiety in lactating mothers compared with nonlactating mothers.[282] Feldman and Eidelman found that providing breast milk functions to initiate a more optimal bonding process between mothers and their premature infants by operating on physiologic, behavioral, and representational (mood) systems.[126] **Maternal depression as measured by the Beck Depression Inventory was reduced significantly when mothers provided more than 75% of breast milk nutrition for their**

preterm infant.[126] Two more recent studies also show that breastfeeding is associated with a reduced risk of postpartum depression that is maintained over the first 4 months of the postpartum period.[175,423]

The long-term psychological effect for the mother of unrestricted nursing is a more even mood cycle as a result of elevated prolactin, oxytocin, and endorphin levels,[445] which enhance coping mechanisms associated with caring for a new family member by diminishing maternal stress responses to physical, intrapersonal, or interpersonal stress.[164] Providing her own milk, including pumping and gavaging breast milk and eventual feeding at the breast, enhances maternal attachment and maternal behaviors[164,216,427] and enables the mother to contribute to her infant's care[195] (see Chapter 29). Proximity of the mother and infant, as well as the infant's initial experience at the breast, contributes to maternal and infant regulation and the establishment of innate behaviors and emotional and social ties between the mother and infant.[429] Kavanaugh et al. described rewards to the mother from breastfeeding as follows[216]:

- Knowing that she is providing the healthiest nutrition
- Enhancing closeness between her and her preterm infant
- Perceiving her preterm infant's contentment and tranquility during breastfeeding
- Convenience for the mother
- Giving her a tangible claim to her preterm infant

All physicians and nurses who admit infants to the NICU should educate, encourage, support, and assist mothers who wish to breastfeed their infants.[295,303] Use of kangaroo care at birth (see Chapter 5) and in the NICU (see Chapter 13) facilitates early initiation of breastfeeding and increases maternal confidence, competence, and breastfeeding duration. If the infant is able to take oral nourishment, he or she can be breastfed at 1000 to 1200 g and about 28 weeks' gestational age (see Chapter 13, Table 13.2).

Neurobehavioral Development in Premature Infants

The positive impact of breastfeeding on neurobehavioral and cognitive development in infants has been posited for several decades. Two theories have been proposed to explain improved neurobehavioral development: nutritional content of breast milk that improves neurologic growth, and the effect of breastfeeding on the mother-infant relationship that indirectly supports cognitive development. Evidence continues to mount demonstrating positive effects of human milk in the preterm infant. Breastfeeding increases maternal responsiveness and higher levels of synchrony observed between mothers and preterm infants, hence leading to higher cognitive outcomes. A study of 86 preterm infants with a mean gestational age at birth of 30 weeks and an average birth weight of 1300 g found that the amount of breast milk provided made a significant impact on the neurodevelopment of the infant when assessed at 37 weeks and 6 months' corrected age. The preterm infants who received more than 75% of their nutrition from breast milk demonstrated a more mature neurodevelopmental profile at 37 weeks' corrected age and higher mental and psychomotor skills at 6 months' corrected age.[126] An observational cohort study of the relationship between breastfeeding, early weight gain, and neurodevelopment resulted in an "apparent breastfeeding paradox."[377] In the studied cohorts, only 16% and 19% of very preterm infants breastfed at discharge from the NICU. On follow-up, the breastfed infants' initial weight gain was characterized as "suboptimal," but their neurodevelopmental outcomes were more favorable than the very preterm infants who were not breastfed.[377]

FACILITATING SUCCESSFUL BREASTFEEDING

Although breastfeeding is a normal, natural function, it is not a reflex but, rather, a highly complex interaction and interdependence between mother and infant. To be successful, the breastfeeding dyad must synchronize their behavior and physiology and receive support from their environment. Delayed breastfeeding may be as successful as immediate feeding when (1) problems are prevented, (2) the mother receives support and encouragement in maintaining her milk supply, and (3) everyone is patient and knowledgeable about teaching the infant to suckle. Initiating breastfeeding as early

as possible is important to prevent problems. Thorough evaluation of the effectiveness of the nursing couple is important in achieving adequate nutrition and breastfeeding success. Knowledgeable health care providers and licensed, certified lactation consultants, where available, can perform these evaluations.[348] **Development of an evidence-based and mother-friendly breastfeeding service has been shown to dramatically improve the volume of mother's milk that is available and to prolong the duration of milk provision for preterm infants.**[297]

Sucking

Sucking is a primitive reflex appearing as early as 15 to 16 weeks of gestation. **Although isolated components of feeding behaviors (e.g., root, suck, swallow, gag) are all present early in gestation, they are not effectively coordinated for bottle feedings before 32 to 34 weeks' gestational age (see Chapter 13, Table 13.2).** The infant can coordinate suck and swallow while breastfeeding as early as 28 weeks of gestation. Two distinct types of sucking, nonnutritive and nutritive, develop in the human infant.

Nonnutritive Sucking

Nonnutritive sucking (NNS) is sucking activity in which no fluid or nutrition is delivered to the infant. Characterized by short bursts of rapid motion, pauses, and few swallows, NNS has a stabilizing effect on physiologic responses (i.e., better oxygenation; quieter, more restful behavior; decreased tension; increased insulin and gastrin secretion that may stimulate digestion and storage of nutrients; and improved readiness for oral feedings) (see Chapter 13). Because there is no bolus of fluid to swallow, NNS results in an alternation of inspiration and expiration without the regular apneic periods of nutritive sucking. However, even in NNS when the occasional swallow of saliva is necessary, there is a maturational progression of swallow-breathe interaction from central apnea to obstructive apnea to attenuated breathing.[365] A sensorized pacifier has been developed to give a complete pressure profile of sucking patterns with NNS and possibly used to monitor sucking skills of premature infants.[158]

Nutritive Sucking

Nutritive sucking, used by an infant when fluid or nutrition is available, is characterized by an organized, rhythmic pattern that is about one-half the rate of NNS (i.e., one per second). During nutritive sucking, each milk expression is followed by a reflexive swallow and an occasional brief pause. In a term neonate, rates of sucking range from 40 to 60/min. Nutritive sucking provides the neonate with positive reinforcement, which encourages a steady level of behavior. A variety of factors affect nutritive sucking, including maternal anesthesia and/or analgesia, length of labor, type of delivery, gestational age, birth weight, age (in hours), severity of illness, infant state, type of fluid, disorders of the central nervous system, and individual variations.★

Although nutritive sucking is associated with faster heart rate (when bottle feeding), little information is available describing energy requirements of nutritive sucking. The findings of one study suggest that, during bottle feeding, preterm infants expend significantly less energy to suck the same volume than do full-term infants.[202] **Bottle feeding requires *more* energy than breastfeeding in all infants.**[202]

Two patterns of nutritive sucking have been identified: continuous sucking and intermittent sucking.[269] ***Continuous sucking* occurs at the beginning of bottle feeding, when the suck is strong and continuous for at least 30 seconds.**[266,269] ***Intermittent sucking,* an alternation of sucking bursts with periods of pause/no sucking,**[266,269] **occurs first during breastfeeding, followed by continuous sucking (with breast milk letdown).**[268,289] **Breathing and oxygenation are affected more during continuous sucking than during intermittent sucking,**[428] even in full-term infants who can exhibit apnea and bradycardia with feeding.[265]

An increasing level of organization of nutritive sucking occurs with increasing gestational age, maturity, and experience.†

Preterm sucking patterns exhibit a higher sucking-to-breathing ratio (2:1 to 4:1) than the well-coordinated ratio of full-term newborns (e.g., 1:1).[342] By 32 to 34 weeks' postconceptual

★References 49, 135, 241, 268, 278, 282, 283, 319, 342, 400
†References 135, 241, 268, 278, 282, 283, 319, 342, 400

age (PCA), there is a change in sucking bursts (i.e., increase in number of sucks, number of suck bursts, and pressure; decrease in time between sucking bursts). This developmental maturation enables nutritive sucking to take less time and is less tiring. For infants having feeding difficulties or a preterm infant who is not progressing as expected in feeding ability, there is a quantitative instrument, the Medoff-Cooper Nutritive Sucking Apparatus (M-CNSA), that provides a continuous record of the negative pressure generated during a 5-minute feeding assessment. The M-CNSA augments clinical evaluation as it objectively measures nutritive sucking parameters and enhances clinical decision making.[461]

Nutritive sucking requires coordination between sucking, swallowing, and breathing. During coordinated sucking bursts, suck-swallow-breathing occurs in a 1 sec:1 sec:1 sec sequential pattern. Recent research has found highly variable suck-swallow-breathe patterns ranging from 1:1:1 to 12:1:14.[382,383] The lack of a coordinated suck-swallow-breathe ratio of 1:1:1 contributes to a preterm infant's apnea with feeding, a reflexive protection of the airway.[268,348,365,428] Although suck-swallow is achieved by 32 weeks of gestation,[284] respiration may still not be well coordinated, so the preterm infant may develop apneic episodes with bottle feeding.[348,365,428] With increasing PCA and neuromuscular maturity, *consistent* coordination of suck-swallow-breathe (with bottle feeding) occurs by 35 to 37 weeks' PCA.[135]

Sucking patterns of full-term, preterm, and preterm infants with bronchopulmonary dysplasia (BPD) have recently been studied. **All full-term infants had a normal sucking pattern soon after birth, but bottle feeding was found to contribute to arrhythmic sucking over a 10-week period after birth.[96]** Small-for-gestational-age (SGA) preterm infants were found to develop normal sucking patterns later than appropriate-for-gestational-age (AGA) preterm infants; **by term-equivalent, no SGA infants and 38% of AGA preterm infants had normal sucking behaviors.[97]** Abnormal sucking in the SGA infants included incoordination and dysfunctional sucking patterns. Compared with preterm infants without BPD, those with BPD had more incoordination of sucking, swallowing, and breathing (36% vs. 15%).[98]

A randomized study of early introduction of oral (bottle) feeding (e.g., within 48 hours of full tube feedings) found the following[400]:

- Transition time to all oral feedings was significantly shorter.
- Oral feeding was introduced 2.6 weeks earlier.
- Total oral feeding was achieved at earlier postmenstrual age (PMA) (e.g., 54% of 33-week-PMA infants vs. 12.5% of control group infants).
- Weight gain and discharge weights were similar in both groups.
- Episodes of feeding-related bradycardia and desaturations were similar for both groups.
- The early feeding group was discharged 10 days earlier than the control group.

In this study and others, researchers postulate that **feeding opportunities in young infants provide them with practice and *experiential* opportunities to develop their oral motor skills and coordination of suck-swallow-breathe.[133,276,400]**

Human nutritive sucking is composed of five separate yet interrelated processes: rooting, orienting, sucking, expressing, and swallowing (Fig. 18.2).[40] *Rooting,* the tactile stimulating of the infant's face and lips, elicits the head to turn toward the stimulus. Stimulation of the center of the lower lip enables the infant to root by coming forward extending the tongue, drawing in the nipple and areola, and latching on, rather than turning the head to one side. *Orienting,* or *latching on,* occurs when the tongue draws the nipple and areola into an elongated teat and compresses it against the hard palate (Fig. 18.3).

Sucking, the application of negative pressure in the infant's mouth with lowering of the tongue/mandible, elongates the nipple and transfers milk from the breast.[116,304,357] At the beginning of breastfeeding, a strong suction stretches and shapes the nipple, but only moderate suction is necessary to maintain adequate grasp of the nipple.[60] During the feeding, occasional bursts of sucking enable milk to be expressed. *Expressing* milk occurs when negative pressure is applied to the breast with closure of the mandible that compresses milk ducts, slowing or stopping milk flow allowing for safe swallowing and breathing[116,141,357] (Fig. 18.4). The lips should be flanged out to create a seal.

Swallowing milk occurs as peristaltic motion of the posterior pharynx (reflexive swallowing) and

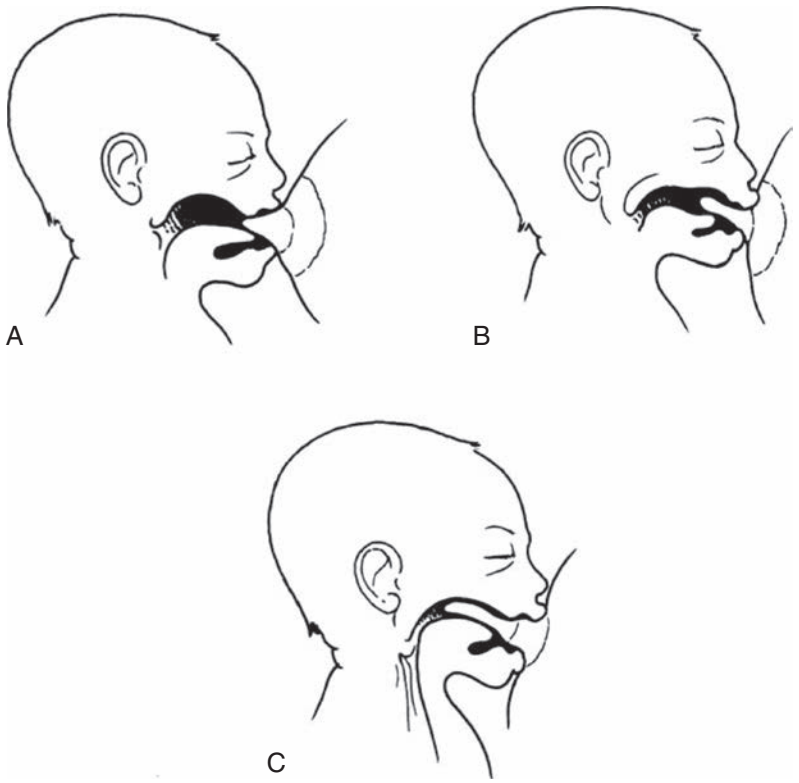

FIGURE 18.2 Normal suckling. **A,** As the infant grasps the breast, the tongue moves forward to draw in the nipple. **B,** The nipple and areola move toward the palate as the glottis still permits breathing. **C,** The tongue moves along the nipple, pressing it against the hard palate and creating pressure. Ductules under the areola are milked, and flow begins as a result of peristaltic movement of the tongue. The glotis closes. Swallow follows. (From Lawrence RA, Lawrence RM. *Breast Feeding: A Guide for the Medical Profession.* 8th ed. Philadelphia, PA: Elsevier; 2016.)

propulsion of milk down the esophagus. These peristaltic motions coordinate suck and swallow so breastfeeding infants do not choke, unless the letdown reflex is excessive. Swallowing milk also inhibits respiration (thus protecting the airway), and reflexively initiates the expression cycle of jaw and tongue movements. Therefore nutritive sucking is primarily expression and swallowing of milk. During nursing, just enough suction to keep the nipple in proper position is used, even during the expressive phase of sucking. **Breastfeeding is an infant-regulated system; milk flow depends on active sucking by the infant. When an infant pauses to regain physiologic stability, the flow of milk from the breast ceases.**

Ultrasonographic studies[145] of full-term infants' breastfeeding note (1) an elongation to twice the resting size of the maternal nipple[358]; (2) the formation of a passive seal by the neonate's oral cavity[358]; (3) milk ejection coinciding with the downstroke of the tongue and jaw, creating negative pressure by oral cavity enlargement[358]; (4) multiple milk ejections during breastfeeding that may not be sensed by the mother[358]; and (5) milk ejection characteristics that are consistent within women during different breastfeeding and pumping sessions,[138] as well as across consecutive lactations.[139]

Artificial nipples have also been shown to vary in their rate of milk flow.[262,264,266] Nipple hole size, rather than the type of nipple,[262,267] has been found to be the major determinant of the variability in

milk flow.[264] With an artificial nipple, fluid flows into the posterior oropharynx by gravity (Fig. 18.5). Artificial nipples and bottles are gravity-regulated systems requiring the infant to actively inhibit milk flow to permit swallowing and breathing. In an attempt to regulate milk flow and prevent choking or gagging, infants may clench their jaws or obstruct the nipples' holes with their tongues in a thrusting motion. Orthodontic nipples result in physiologic stability and more effective feeding behavior in some infants.[109] A study comparing breastfeeding and bottle feeding with two delivery systems (soft-walled and rigid-walled bottles/nipples) found better coordination of suck-swallow-breathing, better oxygen saturations, and a feeding pattern more like breastfeeding when the soft-walled system was used.[155]

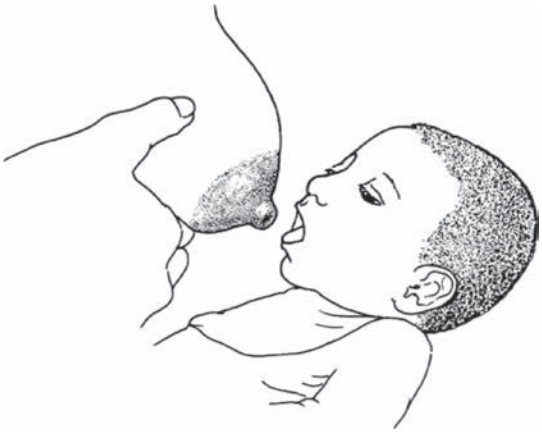

FIGURE 18.3 Latch-on response. In response to stimulating the infant's lower lip with the nipple, the mouth opens wide. This response has been called the *oral searching reflex*. It is part of the circumoral rooting reflex. (From Righard L, Alde MO. Sucking technique and its effect on success of breastfeeding, *Birth* 1992;19:185; Lawrence RA, Lawrence RM. *Breast Feeding: A Guide for the Medical Profession*. 8th ed. Philadelphia, PA: Elsevier; 2016.)

An RCT of a novel feeding nipple that only allows milk to flow when a preterm infant creates a vacuum showed that length of stay in the NICU was shorter, and less formula was fed at discharge to infants using the novel nipple.[399] A more recent study of the new nipple found tongue actions the same as those used in breastfeeding, with a higher volume of milk intake while using an intraoral vacuum that was lower than the pressure used in breastfeeding.[144] With further research, this system could be used to provide supplementary oral feedings when the premature infant's mother is unavailable and may assist the preterm infant in learning the sucking dynamics necessary for successful breastfeeding.[144]

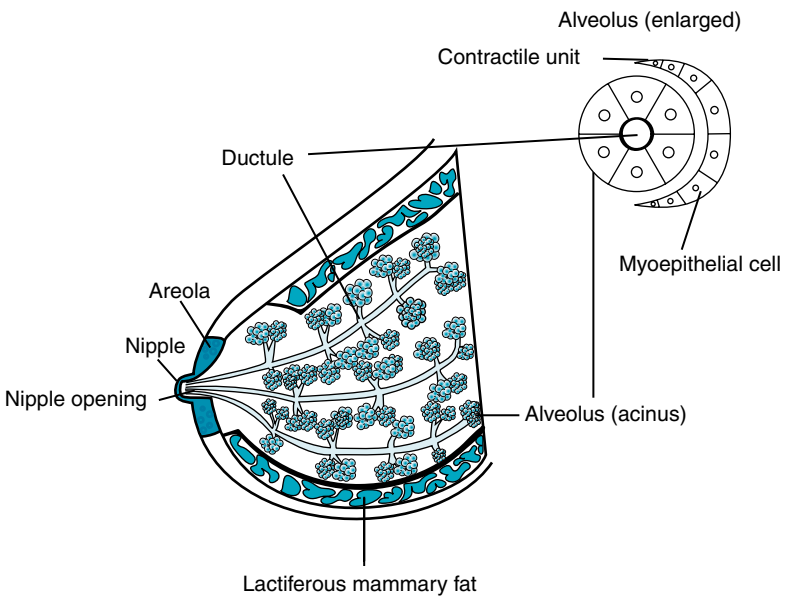

FIGURE 18.4 Structure of human breast during lactation based on ultrasound findings. (Redrawn from Ramsey DT, Kent JC, Hartmann RA, et al. Anatomy of the lactating breast redefined with ultrasound imaging. *J Anat*. 2005;206:525. With permission from Wiley-Blackwell Publishing.)

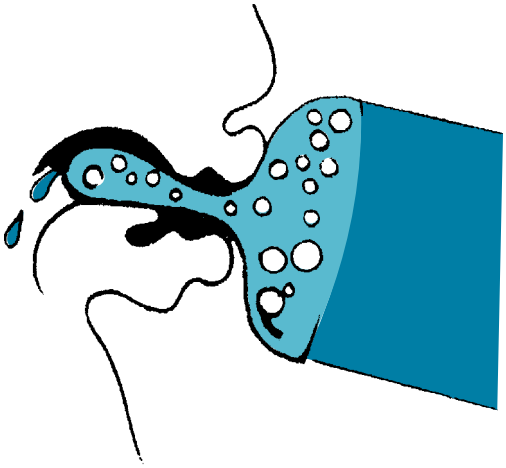

FIGURE 18.5 Artificial nipple. Infant sucking on artificial nipple, which fills the mouth and thus prevents tongue action and provides flow without tongue movements. Flow occurs even if the lips are not tight around the rubber hub. (From Lawrence RA, Lawrence RM. *Breast Feeding: A Guide for the Medical Profession*. 8th ed. Philadelphia, PA: Elsevier; 2016.)

PREVENTION OF BREASTFEEDING PROBLEMS

Problems with breastfeeding may be with the mother or with the neonate or may arise from a combination of problems in the dyad. Lack of information about common problems in the early weeks of breastfeeding is a common reason for breastfeeding failure.[108,410] In descriptive studies addressing breastfeeding problems, mothers frequently identified concerns related to sore nipples, breast discomfort, and inadequate milk supply.[57,108] Breastfeeding problems should be prevented. To solve a breastfeeding problem, the mother must be observed feeding the infant.

Maternal Problems

INADEQUATE MILK SUPPLY

An inadequate milk supply is production *of less than* 440 mL/day by the 11th day of lactation.[221,222] Breast milk production in the first 4 weeks after birth in healthy, full-term infants shows a high frequency of inadequate milk production: (1) two-thirds of mothers produced less than 440 mL/day between days 11 and 13, and (2) one-third of mothers between days 14 and 28 produced less than 440 mL/day.[221] **Assessment for adequate milk supply is essential to assist mothers in correcting low supply early in lactation and preventing early cessation of breastfeeding.**

Inadequate milk supply, a major problem for both the mother and infant, is the most commonly cited reason for discontinuation of breastfeeding in the NICU and after discharge.[57,185,215,287,452] Predictors of maternal perception of inadequate milk supply at 8 to 12 weeks postpartum (after preterm birth) include inadequate milk supply at 6 weeks postpartum, unemployment, and infant hospital discharge after postpartum day 42.[185] **Initially, some neonates with special needs are unable to breastfeed. In this common situation, the most compelling breastfeeding issue is establishing an adequate milk supply without the neonate's assistance[184,295] (Table 18.3). Preterm mothers are three times more likely to produce an inadequate milk supply at 6 weeks than are full-term mothers.[184] Because low milk volume in the first week of life is related to continued low production,[184] developing a very early program of education and support for the mother will help her establish an early milk supply and prevent low milk volume.**

Initiating, establishing, and maintaining a milk supply must be accomplished mechanically when the infant is unable to breastfeed. Because milk production depends on adequate and frequent expression, maternal education is the key to establishing an adequate supply (see Table 18.3). Mothers should be encouraged to provide their milk for their compromised infants and should be educated about the benefits of human milk feedings for their fragile infant so they are able to make an informed choice and decision.[288,297,303,410] A parent-focused video about the importance of human milk and the science that supports human milk as the best source of nutrition is available.[378]

The mother who wants to or is willing to breastfeed should be instructed about initiating and maintaining a milk supply until the infant can breastfeed. In general, instruction includes information about pumping, which is individualized to the mother's situation. **Milk production through pumping should be encouraged early and regularly to (1) collect colostrum, which is rich in anti-infective properties; (2) ease the initial engorgement associated with lack of regular stimulation and**

TABLE 18.3 CRITICAL FINDINGS FACTORS THAT INFLUENCE THE MOTHER'S MILK SUPPLY AND SUCCESSFUL BREASTFEEDING OF THE PRETERM INFANT

ENHANCES	REDUCES	COMMENTS
Early skin-to-skin contact regardless of method of delivery[172,242]; early initiation of pumping,[329] preferably with a double-pumping setup and breast massage[206,412]	Immediate separation at birth, delayed initiation of pumping (associated with cesarean birth, male gender, higher gestational age at birth, poor maternal psychological well-being, and previous NICU experience)[196] or feeding at the breast[45,313]	If possible, initiate within 1–2 hr of birth (first hour after birth for mothers of VLBW preterm infants)[329]; pumping both breasts simultaneously is associated with higher prolactin levels, milk yield, fat concentration, and maternal preference.[206,295] Provide volume-based containers for storing milk from each pumping episode.[295]
Frequent milk expression with complete breast emptying at each session	Failure to express frequently or incomplete emptying of the breasts	5–8 expressions/day (every 3–4 hr)[188,412]: duration of pumping >100 min/day (about 15–20 min with double-pump setup); longest nonpumping interval <6 hr. Maintain a pumping log.[412] A password-protected website with educational information and ability to track pumping volumes actively involves mothers.[36]
Rest, relaxation, and stress management (see Chapters 29 and 30)	Fatigue, anxiety, stress (i.e., maternal illness; stress, noise and lack of privacy in NICU; return to work; more commitments in and outside the home; maternal dislike of breastfeeding)[45,313]	Inverse relationship between maternal anxiety scores and milk volume for mothers of preterm infants; uninterrupted sleep of at least 6 hr.[245,445] Privacy for breast pumping: 55% of mothers preferred to pump at home for more privacy; more mothers pumped in their preterm infant's single-family room.[110]
Adequate nutrition	Inadequate nutrition	At least 60% of recommended daily allowances produces milk of adequate quantity and quality to promote infant growth.[68]
MEDICATIONS		
Use of galactogogues[51] (metoclopramide, oxytocin, reserpine, phenothiazines, domperidone[167])	Bromocriptine, antihistamine, oral contraceptives (especially estrogen and progesterone combination)	Knowledge of maternal medication use enables effective counseling. More pump-dependent mothers achieved a 50% increase in human milk volume with the use of domperidone.[20]
HERB		
Fenugreek		Two or three capsules two or three times per day; maternal diarrhea; lowers blood glucose; may increase asthma symptoms; maple syrup smell to sweat, urine, milk; colic.[173] Less weight loss and greater milk volume at 3 days of age in infants whose mothers took fenugreek.[436]
Positive feedback to mother regarding infant growth;[63] infant's condition improving	Worsening infant's condition	Mothers report feeling rewarded by infant's growth while receiving expressed mother's milk by gavage[287]; Mothers continue to provide breast milk when preterm infant has good growth velocity.[63]
Educate mothers about fortification and why it is necessary with premature infants.	Mother thinks fortification of her milk needed because her milk is not "good enough"	Parents understand how mother's milk changes and special needs of preterm infants for growth.
Skin-to-skin contact (kangaroo care)[86,248,412] in the NICU	Parental separation	Maternal reinforcement of lactation, maternal behaviors, confidence, and attachment; ensures maternal exposure to pathogens in NICU so that her immune system is stimulated to produce environmentally specific antibodies that are passed in maternal milk and protect the preterm infant.

Continued

TABLE 18.3 CRITICAL FINDINGS FACTORS THAT INFLUENCE THE MOTHER'S MILK SUPPLY AND SUCCESSFUL BREASTFEEDING OF THE PRETERM INFANT—CONT'D

Educational information (e.g., video, brochure) readily available for both mothers and fathers [73,406,412,422] of preterm infants within the first 24 hr after birth[422]	No verbal or written information for parents; conflicting opinions and advice about breastfeeding[288,295]	Decision about type of pump, frequency; written instructions on collection and storage per NICU protocol; information about maternal rest, fluid intake, and nutrition. Positive effects of breastfeeding, advantages of human milk to preterm infant; how to interpret infant cues and behaviors.[245,317]
Knowledgeable professional care providers (e.g., primary nurses, lactation specialists, physicians, peer support) who educate, support, and assist[73,132] through consistent, practical advice[248,288,295]	Nonsupportive care providers and/or inconsistent advice and information; no alignment between NICU routines and parents' needs	Prevention of maternal problems (e.g., inadequate supply,[45] sore nipples,[45] engorgement)[29] through self-education and professional interaction and education enhances success and prevents discontinuation of breastfeeding.
Initiation of breastfeeding before bottle feeding	Initiation of bottle feeding before breastfeeding[45] Small size, fragility, medical complications of premature infant[313]	Early breastfeeding is less stressful than early bottle feeding[135,285–287,289,471] because of difference in the patterns of sucking and breathing; during bottle feedings, preterm infants alternate short bursts of sucking with breathing and do not breathe within sucking bursts; during breastfeeding, breathing is integrated within sucking bursts.[286] Test weighing (i.e., weighing before and after breastfeeding, with differences in weight representing milk intake [1 g = 1 mL]) using electronic scales is a reliable method of documenting milk intake in preterm infants.[291,295] For specific problems, maximizing milk intake may be assisted by lactational support devices (i.e., nipple shields; lactation supplementer) and/or breast pump stimulation of the opposite breast during infant feeding.[245,287,295]
Simultaneous feeding and caregiving schedules for multiples (see Chapter 13)		For multiples: Introduce simultaneous feeding as soon as possible, encourage maternal independence with position suggestions, comfort measures, experimenting, and verbalizing what mother needs or wants.[318] Need for privacy, taking babies out of NICU, rooming-in with father to assist with care and feeding.[318] Lactation support devices and/or breast pump stimulation of the opposite breast during infant feeding.[388]

NICU, Neonatal intensive care unit.
Modified from Schanler R, Hurst N. Human milk for the hospitalized preterm infant. *Semin Perinatol.* 1994;18:476.

maintain continued stimuli to produce milk; (3) provide quality nutrition for the neonate; and (4) alleviate concerns about available volume once the infant begins breastfeeding. The early postpartum period in the hospital is the optimal time to teach pumping methods, while support and encouragement are readily available.

BREAST DISCOMFORT

Maternal problems include engorgement, painful nipples, and cracked nipples. A primipara is at high risk for developing engorgement. Frequent emptying of the breast is the best prevention.

Engorgement occurring in the early postpartum period is characterized by general breast

swelling, usually in both breasts in a well, afebrile woman. A little engorgement is normal. Areolar engorgement blocks the nipple and makes grasping the areola difficult for the infant. **Gentle breast massage and manual expression of a small amount of milk soften the areola so the infant is able to "latch on."** When the body of the breasts and the areolae become excessively engorged and painful, **the goal of management is to make the mother comfortable so that nursing may continue. Supporting the breasts is crucial, and the mother should wear a well-fitting but adjustable brassiere 24 hours a day.**[245] **Applying cold packs between nursing decreases pain and swelling. Pain relievers also may be prescribed. In a recent study, application of herbal compresses relieved the pain of engorgement better than hot compresses.**[223] **Applying heat (packs or a warm shower) and expressing some milk before feeding help initiate milk flow. A nursing infant, manual expression, or an effective pump helps initiate and maintain milk flow.** Breast massage before and during breast pumping/feeding also facilitates milk flow. Therapeutic breast massage in lactation (TBML) is effective in reducing the breast pain of engorgement and for management of future episodes.[469]

Prenatal stimulation of the nipple by pulling or rolling (to toughen it for breastfeeding) is not recommended because of the possibility of initiating uterine contractions and premature labor.[245]

Nipple pain occurs by the seventh postpartum day in 9.6% of breastfeeding women, with primiparity being a predisposing factor. Causes of nipple pain include (1) inappropriate positioning and latching (72.3%); (2) ankyloglossia (tongue-tie) (23.2%); and oversupply of milk (4.4%).[352] Other causes of nipple pain include infection, flat/inverted nipples, mastitis, vasospasm, and neonatal palatal anomaly.[220] With prompt recognition and appropriate interventions, recovery occurs within 2 weeks and does not reduce exclusive breastfeeding rates.[352]

Breastfeeding should *not* be painful. When it is, the problem is most often an incorrect latch. Sore nipples are another major discomfort and concern for the new mother. The initial grasp of the nipple by the infant or with pumping can be uncomfortable. **Poor positioning of the infant, however, can cause painful and eventually cracked nipples. Prevention and treatment involve educating the mother about careful positioning of the infant facing the mother, looking directly at the breast, and tummy-to-tummy with her (Fig. 18.6). Changing the infant's position on the nipple at different feedings is helpful.**

FIGURE 18.6 Proper positioning for breastfeeding infant tummy-to-tummy facing the mother.

Positioning the infant correctly at the breast assists in the prevention of sore nipples. There are three common positions that can be used with breastfeeding: the cradle hold (see Fig. 18.6), the football hold (Fig. 18.7), and lying down. Initially, the cradle or football hold allows the most control for the mother and infant to learn breastfeeding. Breastfeeding in the lying-down position becomes easier once latch-on techniques are developed.

Nipple care involves keeping nipples clean and dry. Clear water (no soap or alcohol) is all that is necessary to keep the nipples clean. Drying nipples well, not using plastic nursing pads, and exposing nipples to air and dry heat (sunlight, light bulb, sauna, or a low setting on a hair dryer) are comforting. **Using ointments may be helpful, especially**

FIGURE 18.7 Football hold in breastfeeding. Pillows may be used for support.

in dry climates. If used, a small amount (i.e., one drop) should be gently massaged into the nipple after the feeding. Purified lanolin (if there is no allergy to wool), A&D ointment, or vitamin E may be used to treat, but will not prevent, sore nipples. An RCT comparing the use of hydrogel dressings with lanolin ointment in the prevention and treatment of sore nipples found a greater reduction in pain, no infections, and earlier discontinuation of therapy in the hydrogel dressing group.[105] A more recent RCT found maternal satisfaction with use of lanolin, but its use did not reduce nipple pain or improve breastfeeding outcomes.[200] Combining treatment with breast milk and a breast shell was more effective than using lanolin for nipple trauma and pain.[450] The most recent Cochrane review states that **applying nothing to painful nipples or treatment with expressed breast milk (EBM) may be equally or more beneficial than ointments such as lanolin.**[103]

Severe and/or persistent nipple pain may be caused by a bacterial or yeast infection, which should be promptly treated. Yeast infection of the breast (Table 18.4) **manifests as a burning sensation in the nipples, stabbing pain throughout the breast, and edema/shiny skin or flaking skin on the nipple/areola.**[307] A significant risk factor for yeast infections of the breast and oral thrush in the baby is the use of bottles in the early postpartum period.[236] In one study, yeast infection was associated with cessation of breastfeeding (in 65% of infected mothers) by 9 weeks postpartum because of pain with feeding.[307]

Another recognized cause of nipple pain is **Raynaud's phenomenon of the nipple,** which is often misdiagnosed and mistreated as a yeast infection.[13] Twenty percent of childbearing-age women may have Raynaud's phenomenon, and symptoms are exacerbated by cold temperatures.[13] **Raynaud's phenomenon of the breast, associated with a history of breast surgery, is characterized by extreme or severe nipple pain with breastfeeding; nipple blanching, cyanosis, or erythema; and accompanying throbbing pain, burning, and paresthesia.** Treatment includes (1) preventing and/or decreasing exposure to cold and emotional stress, (2) avoiding vasoconstrictive drugs (e.g., nicotine), (3) using nifedipine for its vasodilator effects (see Table 18.7), and (4) including fish oil and evening primrose oil in the mother's diet.[245] **If the mother does not have Raynaud's of the fingers or toes, it is unlikely that she has it of the breast.**

In the past, nipple shields were not recommended because they are awkward for the mother, are confusing for the infant, and decrease milk production by 50%. Modern ultrathin nipple shields concentrate the immature (preterm or late preterm) infant's suction pressure in the tunnel of the shield, stimulate milk flow, and stimulate milk removal.[291,295] **Use of silicone nipple shields has been found to be a useful tool in treatment of sore nipples and latch-on problems and as a bridging technique to direct breastfeeding.**[410] One study showed that for preterm infants, use of a nipple shield increased breast milk intake and promoted longer duration of breastfeeding.[290] Although use of nipple shields is associated with weaker intraoral vacuum pressures, vacuum strength was not associated with milk intake, rather higher milk intake was caused by longer sucking.[142] **Breast pumping after use of nipple shields is necessary to express residual milk, maintain adequate milk supply, and obtain milk for supplemental feeding.**[297,410] Nipple shields are also helpful if the mother's nipple is too large for her infant's mouth. Use of nipple shields to facilitate and support breastfeeding is certainly preferable to cessation of breastfeeding.[77]

TABLE 18.4 PERINATAL COMPLICATIONS AND BREASTFEEDING

COMPLICATIONS	BREASTFEED YES	BREASTFEED NO	COMMENTS
MATERNAL COMPLICATIONS			
Cesarean delivery	X		Regional anesthesia enables contact and feeding in recovery room. Pain medication is best given after feeding so levels peak before next feeding. Use of breast pump (pressure of ~150 mm Hg) quickens onset of lactation, increases daytime milk supply, and improves maternal confidence.[478]
Pregnancy-induced hypertension	X		Preterm or small-for-gestational-age infants may be delivered, making delayed breastfeeding and pumping necessary. Maternal drugs may affect infant (see Table 18.7).
Venous thrombosis and pulmonary embolism	X		Depending on mother's ability; radioactive materials may be used for diagnosis, and pulmonary embolism anticoagulants may be used for therapy (see Table 18.7).
BACTERIAL INFECTIONS			
Urinary tract	X		Choice of antibiotics is important (see Table 18.7).
Mastitis[12]	X		Continued emptying of breast (i.e., nursing baby or breast pump), bed rest, antibiotic therapy that is safe for infant, application of heat and cold, and use of analgesics are therapeutic.
Sexually transmitted diseases	X		No contraindication once mother is treated appropriately.
Tuberculosis	X	X	Culture-positive mothers must be separated from their infants regardless of mode of feeding; may pump and provide breast milk because tubercle bacillus is not passed through milk but through respiratory contact.[246]
	X		After therapy, when it is safe for mother to contact infant, it is safe to breastfeed directly.
Diarrhea	X		Proper handwashing should be done and breastfeeding continued.
VIRAL INFECTIONS			
CMV	X		Both virus and protective antibodies occur in breast milk. Anti-CMV activity in breast milk from mothers of preterm infants that varies with stage of lactation and serologic maternal status.[106] Anti-CMV activity may attenuate CMV excreted in milk and reduce risk of maternal to neonatal transmission.[106] Incidence of acquired infection in preterm newborns at 4%, with 82% of those having CMV-positive breast milk[25] Freezing (for 72 hr)-thawing method effectively reduces CMV viral load in human milk of mothers of preterm infants.[191] Pasteurization, but m=not freeze-thawing, eradicates CMV from human milk. 8% of ELBW infants developed CMV after freeze-thawing[475]
Enterovirus	X		Maternal antibodies in breast milk protect infants from enteroviral infections, especially if the infant was breastfed for >2 weeks.[381]
Rubella	X		Isolate infected infant from other infants and susceptible personnel. Mother is not contagious postpartum and need not be isolated from infant. Rooming-in may be considered.

Continued

TABLE 18.4 PERINATAL COMPLICATIONS AND BREASTFEEDING—CONT'D

COMPLICATIONS	BREASTFEED YES	BREASTFEED NO	COMMENTS
Rubella immunization	X		There is no known adverse effect on infant.
HSV	X	X	May breastfeed if there is no active lesion on breast. Strict handwashing and covering of genital lesions is necessary. Rooming-in supports breastfeeding while isolating infant from others in nursery.
Varicella (chickenpox)	X	X	If mother has chickenpox within 6 days of delivery, isolate mother and do not allow her to breastfeed until she is no longer contagious. Infant should be separated regardless of mode of feeding.
Measles (rubeola)	X	X	If infant has measles, may isolate mother and infant together and allow breastfeeding. Mothers with postpartum measles have breastfed, and neonates have acquired mild disease. Secretory antibodies are probably present in milk in 45 hr. Mother exposed before delivery without active disease should be isolated from infant, because 50% of infants contract disease.
Hepatitis	X		Hepatitis A: may breastfeed as soon as mother receives gamma globulin.
	X		Hepatitis B antigen has been found in breast milk, but transmission by this route is not well documented. Both infants of chronic HBsAg carriers and those with acute hepatitis should receive high-titer hepatitis B immunoglobulin and hepatitis vaccine, and breastfeeding is permitted.
	X		Hepatitis C virus (HCV) infection rate is 4% in both breastfed and bottle-fed infants; breastfeeding permitted: HCV-positive women do not increase the infection risk to their infants.
HIV, AIDS	X		WHO recommends that mothers who receive ARV therapy while breastfeeding should: (1) exclusively breastfeed for the first 6 months, (2) introduce complementary foods and continue breastfeeding after the first 6 months, (3) if not exclusively breastfeeding or breastfeeding for less than 12 months, mixed feeding is acceptable with ARV therapy, and (4) breastfeed for 12–24 months.[472]
Human T-cell leukemia virus type I (HTLV-I) or type II (HTLV-II)		X	Infected lymphocytes found in breast milk; unknown if able to cause disease. Current US position: breastfeeding is contraindicated.[9,10]
West Nile virus	X		Transmission through human milk occurs but is rare;[186] breastfeeding recommended by CDC.[69]
Zika virus	X		Virus transmitted through breast milk and infected a newborn.[38] After third-trimester Zika infection, virus persists in breast milk (33 days after maternal infection; 9 days after delivery)[409] CDC recommends breastfeeding in Zika areas because benefits outweigh risks, and no reports of health problems in infants breastfed from a mother with infection.[70]
PARASITIC INFECTIONS			
Toxoplasmosis	X		No transmission of toxoplasmosis has been demonstrated in humans. Antibodies are present in breast milk.
FUNGAL INFECTIONS			
Candida albicans infection of the nipple/breast	X		Antifungal topical medication (nystatin) for the mother and simultaneous oral nystatin for the infant. Persistent yeast infections are treated with oral fluconazole (see Table 18.7).

TABLE 18.4 PERINATAL COMPLICATIONS AND BREASTFEEDING—CONT'D

COMPLICATIONS	BREASTFEED YES	BREASTFEED NO	COMMENTS
OTHER INFECTIONS			
Trichomoniasis		X	Metronidazole is contraindicated for infant; milk may be pumped and discarded until therapy is completed. Mother's dose can be modified so she can pump and discard milk for 24–48 hr.
OTHER MATERNAL COMPLICATIONS			
Anemia	X		Severe maternal anemia, but not mild to moderate anemia, adversely affects the iron status of breast milk. Maternal nutritional status significantly influences fetal iron status but not breast milk iron content.[236]
Diabetes	X		Lactation is antidiabetogenic. Lactosuria must be differentiated from glycosuria.
Thyroid disease	X	X	Radioisotopes and thiouracil are found in breast milk and may adversely affect infant. Mother who is taking propylthiouracil can breastfeed. Neither hypothyroidism nor hyperthyroidism is contraindication alone.
Cystic fibrosis	X	X	May cause nutritional drain on mother. Milk composition is normal. The Cystic Fibrosis Association has guidelines for lactation.
Smoking	X	X	Nicotine interferes with letdown and is excreted in milk. Approximately 50% of women who cease smoking during pregnancy resume after birth.[362] Of mothers who smoke, breastfed infants are healthier than bottle-fed infants. Second-hand smoke increases the risk of SIDS and respiratory illnesses.
Opiate withdrawal	X		One small study. See "Methadone" in the "Other Substances" section in Table 18.7.
Bariatric surgery	X		Breast milk adequate in energy, macronutrients, and vitamin A during first 6 weeks of lactation.[203]
NEONATAL COMPLICATIONS			
Medical			
Diarrhea	X	X	Maintain breastfeeding in infectious diarrhea unless milk is source of infection. Congenital lactase deficiency is rare but requires lactose-free formula.
Respiratory disease	X	X	Breast milk by gavage may be used if infant's condition permits.
Galactosemia		X	Galactose (lactose)-free diet is required.
Inborn errors of metabolism (e.g., phenylketonuria)	X	X	Combination of breast milk and special formula may sometimes be used. Careful monitoring of blood and urine levels of the amino acid is required.
Acrodermatitis enteropathica	X		Low plasma zinc levels are corrected by human milk and zinc sulfate supplementation.
Down syndrome	X		Hypotonia and poor suck reflex contribute to poor letdown and inadequate supply. Proper positioning, manual expression to begin feeding, and supporting the breast so infant does not lose nipple are helpful. Support from another mother with an infant with Down syndrome is helpful.
Hypothyroidism	X		Enough T_3 may be ingested to avoid serious symptoms.
Hyperbilirubinemia	X		May have slightly higher bilirubin than bottle-fed infant. There is no evidence that supplements are beneficial (see Chapter 21).
Breast milk jaundice	X	X	Uncommon occurrence; diagnosis of exclusion; if all other causes are excluded, a temporary cessation of breast milk may be indicated (see Chapter 21).
Cystic fibrosis	X		Increased losses of and lower electrolyte content of breast milk may cause electrolyte imbalance, which is less likely than with formulas.
Sepsis/rule out sepsis	X		NICU admission for presumed early-onset sepsis caused by maternal chorioamnionitis is associated with reduction in discharge breastfeeding rates in asymptomatic term neonates.[395]

Continued

TABLE 18.4 PERINATAL COMPLICATIONS AND BREASTFEEDING—CONT'D

COMPLICATIONS	BREASTFEED YES	BREASTFEED NO	COMMENTS
Surgical			
Cleft lip and/or palate	X		Associated lesions, size, and position of defect influence successful feeding. Positioning and stabilizing breast in infant's mouth may help seal defect.[364] Consult plastic surgeon.
Gastrostomy	X		If gastrostomy feedings are used, expressed breast milk is appropriate.
Partial obstruction (meconium plug, ileus, Hirschsprung's disease)	X		If oral feedings are indicated, breast milk is feeding of choice because of digestibility and mild cathartic effect. After GI surgery, 100% breast milk diet associated with earlier full enteral feedings, shorter length of TPN use, and shorter LOS[396]
Necrotizing enterocolitis	X		Breastfeeding may be partially protective and may be used when feeding resumes.
Gastrointestinal bleeding	X		Most common cause is maternal bleeding from nipple. Perform Apt test to differentiate fetal from adult hemoglobin.
Central nervous system	X		Weak suck and uncoordinated suck and swallow may be problems; however, infants with malformations may breastfeed more effectively than bottle feed.
Omphalocele repair	X		If oral feedings are indicated, breast milk is feeding of choice because of digestibility.[411]
Congenital diaphragmatic hernia	X	X	Breastfeeding is deferred until surgery and ECMO are completed. Mother initiates pumping and storing until baby is able to have enteral nutrition.[413]

AIDS, Acquired immunodeficiency syndrome; *ARV,* antiretrovirals; *CDC,* Centers for Disease Control and Prevention; *CMV,* cytomegalovirus; *ECMO,* extracorporeal membrane oxygenation; *GI,* gastrointestinal; *HIV,* human immunodeficiency virus; *HSV,* herpes simplex virus; *LOS,* length of stay; *NICU,* neonatal intensive care unit; *SIDS,* sudden infant death syndrome; *TPN,* total parenteral nutrition; *WHO,* World Health Organization.

Data from American Academy of Pediatrics. *Report of the Committee on Infectious Disease.* 29th ed. Elk Grove Village, IL: The Academy; 2012; Lawrence RA, Lawrence RM. *Breast Feeding: A Guide for the Medical Profession.* 8th ed. Philadelphia, PA: Elsevier; 2016.

Flat or inverted nipples may be difficult for the infant to grasp and result in maternal engorgement, decreased milk supply, infant frustration, and suboptimal infant breastfeeding behavior (Fig. 18.8). Inverted nipples may be treated by using a breast pump to draw out the nipple before attempting to latch the baby onto the nipple.

Neonatal Problems

Ideally, no term or preterm infant who will be breastfed should ever be fed with an artificial nipple, but this is not always possible, especially for a sick premature infant who requires prolonged hospitalization. However, teaching a premature infant to suck often starts long before nutrition is obtained from a nipple. **When a premature infant is gavage fed, swabbing the cheeks, tongue, and gums with colostrum familiarizes the infant with the taste of mother's milk and provides oral immune therapy.[146] In addition, stable preterm infants who are gavage fed should be held for feedings and offered a pacifier, which may teach the infant to equate satiety with sucking. Using a pacifier provides NNS that calms and soothes the preterm infant and also provides the opportunity to develop sucking skill.** A recent study of preterm infants randomized to pacifier use versus no pacifier use in the NICU found significant advantages among those preterm infants using a pacifier: (1) shorter time to full transition to breastfeeding, (2) shorter time to discharge, (3) lower weight at full breastfeeding, (4) lower weight at discharge, and (5) better sucking skills.[217]

When the mother is present for gavage feeding, she can administer oral colostrum,[146] hold the infant, and offer the breast instead

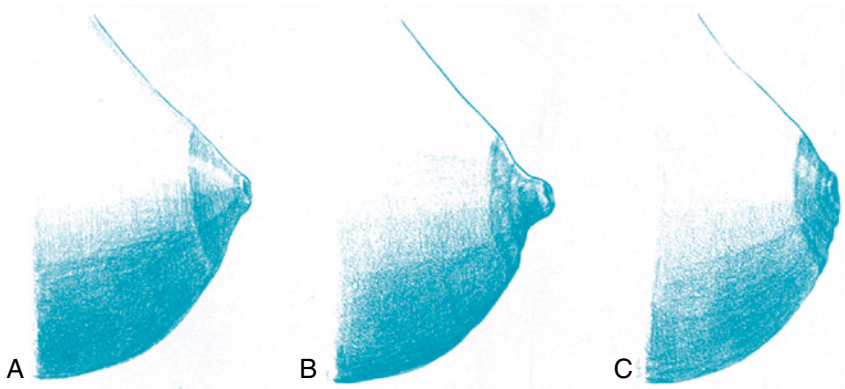

FIGURE 18.8 Inverted nipples. **A,** Normal and inverted nipples may look similar when the nipple is not stimulated. **B,** The normal nipple protrudes when stimulated. **C,** The inverted nipple retracts when stimulated. (Courtesy Jimmy Lynne Scholl Avery.)

of an artificial nipple. If it is necessary to avoid swallowing any fluid, the breast can be prepumped. **Placing the infant in direct skin-to-skin contact with the mother's breast enables nuzzling and licking behaviors and teaches that relief from hunger and the breastfeeding position are associated. Because increased stimulation creates an increased milk supply, it is possible to breastfeed multiple infants. In the early weeks, it is difficult and time-consuming, but eventually it can become faster and more convenient than bottle feeding. Two infants can be fed at the same time, in the cradle position or in the football hold position (Fig. 18.9).** A study of breastfeeding twins found that mothers preferred simultaneous feeding using the football hold (possibly because of the bias of the observers because not all mothers of twins agreed).[318] Infants should change breasts with each feeding because one may have a stronger suck than the other, and each breast should receive an equal amount of stimulation.

Understanding the mechanisms of sucking is essential to preventing, assessing, and intervening in neonatal sucking problems. Infants are born ready to suckle the breast.[96] Arrhythmic sucking has been found in full-term infants who bottle feed.[96] Nipple confusion describes the difficulty of infants who have been fed with artificial nipples before learning to breastfeed.[480] The infant who has learned to feed from a bottle nipple often sucks incorrectly at the breast, preventing milk flow.

The infant's confusion creates frustration and crying, which may inhibit milk letdown. The best means for preventing nipple confusion is to enable the infant to learn breastfeeding *before* bottle feeding is established[480] (see Table 18.3).

Assessment of the problem includes evaluating the method of feeding and possibly using alternative nutritional methods (gavage feedings) until the cause is determined. If the infant is bottle fed, choking may be a result of a soft nipple, a fast flow that the infant cannot control, or a nipple that is too long for the infant's (particularly the preterm infant's) mouth. If the mother is breastfeeding and the ejection is strong, the first rush of milk could cause choking, which may be prevented by manual expression of a small amount (several spurts) of milk before offering the nipple to the infant. Collins et al.[84] studied the effect of bottles, cups, and dummies (pacifiers) on breastfeeding in preterm infants using an RCT. Included in the study were 319 preterm neonates born at 23 to 34 weeks of gestation, with 303 included in the final analysis. The primary outcome measure was continuation of any breastfeeding on discharge home from the NICU. **The results demonstrated that there were no significant differences with the use of a pacifier.** However, infants randomized to cup feeds were more likely to be fully breastfed on discharge home but had a longer length of stay in the hospital (cup = 59 days; bottle = 48 days). Cup feeding did not show a difference in the incidence of any breastfeeding at discharge.

Studies of pacifier use and impact on breastfeeding in premature and term infants show conflicting results. **Howard et al.[192] found in a cohort of 750 healthy newborns that early use of a pacifier**

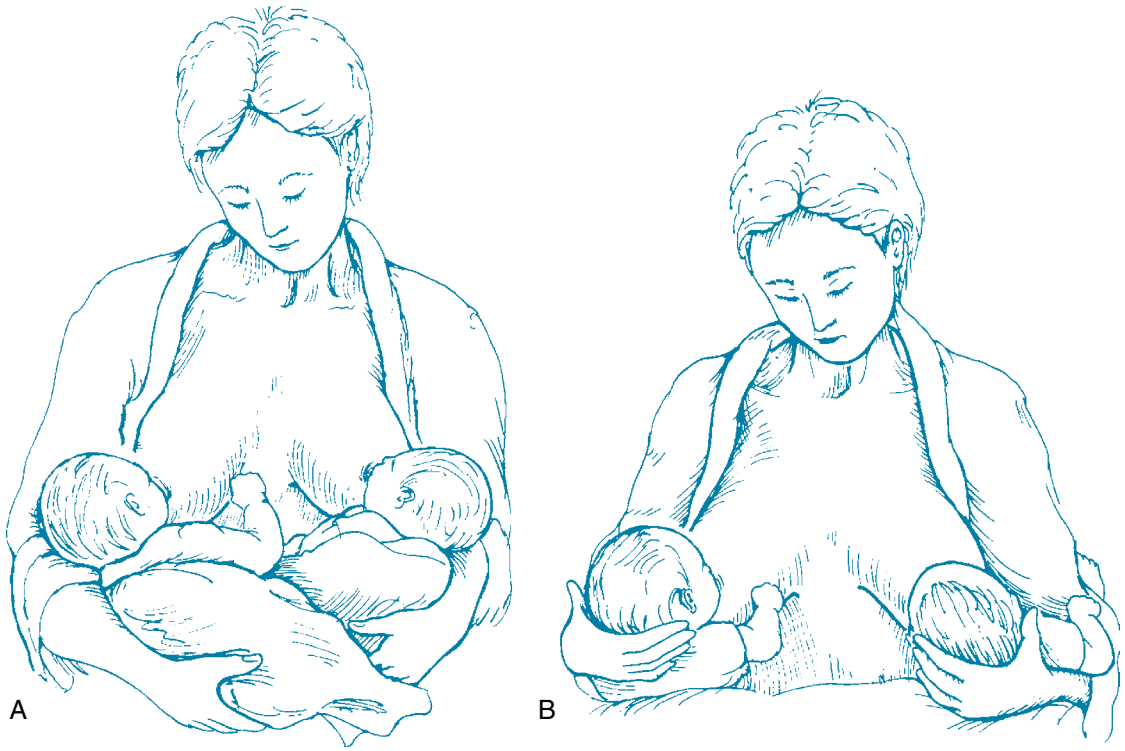

FIGURE 18.9 Breastfeeding twins. **A**, Cradle position. **B**, Football hold position.

did decrease success and duration of breastfeeding through 1 year. Another study of pacifier restriction in term newborns, without restriction of formula use, resulted in a drop of exclusive breastfeeding rates to 68% from 80% when pacifiers were routinely used.[213] Among new mothers with a high risk for postpartum depression, pacifier use may help protect against early breastfeeding cessation.[402] A secondary analysis of the CDC Pregnancy Risk Assessment Monitoring System (PRAMS) data from 10 states assessed the relationship between pacifier use in the hospital and breastfeeding (continuation and exclusivity).[211] **Pacifier use by neonates admitted to the NICU was not associated with less breastfeeding (duration and exclusivity), whereas pacifier use by neonates in the well-newborn nursery was independently associated with a decrease in breastfeeding and exclusive breastfeeding by 10 weeks of age.**[211] A Cochrane review of restricted pacifier use (from birth or after lactation was established) in healthy full-term infants found no significant effect on the prevalence or duration of exclusive or partial breastfeeding from birth to 4 months of age.[198] Benefits of NNS for preterm infants are listed in Chapter 13, Box 13.15.

The most recent Cochrane review of cup feeding newborn infants evaluated five studies of cup feeding versus bottle feeding for supplemental nutrition in breastfeeding infants.[129] The majority of studied infants were premature, so the recommendations are only for preterm infants. For late-preterm infants (LPIs), there may be some benefits on breastfeeding rates at 6 months of age. Although premature infants of younger gestational ages spent 10 more days in the hospital, more mature preterm infants who did not start cup feeding until 35 weeks of gestation did not have longer lengths of stay (both groups average a length of stay of 26 days). The reviewers also reported problems with the studies that may have included overreporting of breastfeeding exclusivity and compliance with supplemental feeding. Before larger RCTs are undertaken, the reviewers recommend that consideration of the issues of noncompliance with cup feeding, blinded outcome assessment, and 100% follow-up are needed.[129] Another recent

Cochrane review of 7 studies of low-to-moderate quality using cups, tubes, and nipples for supplementation of breastfeeding found that use of cups increased the extent and duration of breastfeeding.[85] The safety of cup feeding has not been established so that noncompliance with cup feeding may be the result of fear of aspiration by the neonate.

Some sucking problems result from the sequelae of perinatal events (e.g., low Apgar score, preterm low-birth-weight [LBW] infant, small-for-gestational-age [SGA] infant, large-for-gestational-age [LGA] infant, LPI, infant of a diabetic mother [IDM], and multiple births)[201] or from physical disorders (e.g., hyperbilirubinemia, hypoglycemia, cardiorespiratory conditions, sepsis, neuromotor/developmental problems, and structural abnormalities of the oral cavity)[98,245,259] and represent developmental delays. **These sucking difficulties require diagnostic evaluation of the underlying cause and appropriate intervention.**[245,259]

LPIs ($34^{0/7}$ to $36^{6/7}$ weeks' gestational age; see Chapter 5) are often poor feeders because of their developmental immaturity in coordination of suck-swallow-breathe and because they are awake less frequently, give fewer if any cues of readiness to feed, and are easily fatigued and fall asleep before a feeding is completed.[48,300,343] A retrospective review of factors predicting the time and age at which the LPI (32 to 36 weeks' gestational age) initiated and attained full oral feedings found that the median time to the first oral feeding was 1 day, and the median time to full oral feedings was 12 days.[199] In this study, no LPI attained full oral feeding before 33 (±3) weeks PMA, and factors such as gestational age, birth weight, medical conditions, and location of the NICUs was significantly associated with the time to first oral feeding and full oral feeding in 6 NICUs in Baby-Friendly accredited hospitals.[199]

Being an LPI or an early term infant is an independent risk factor for breastfeeding difficulties and lack of exclusive breastfeeding at 1 month and 4 months of age.[168,253,300,314] All of these problems contribute to poor stimulation of the breast, incomplete breast emptying, and inadequate milk production. While in the hospital, lactation assistance should focus on strategies to initiate and maintain maternal milk supply and provide adequate fluids and calories for the LPI. When supplementation is needed by the LPI, use of human milk rather than formula does not increase length of stay and supports breastfeeding until hospital discharge.[274] **Hallmarks of breastfeeding the LPI include proper positioning; use of breast pump, nursing supplementer (Fig. 18.10), or nipple shield; waking every 2 to 3 hours to feed (for 8 to 12 breastfeedings per day); use of skin-to-skin care; weights before and after breastfeeding; use of alternative methods of enteral nutrition; lactation support during hospitalization and after discharge, and peer support groups.**[39,48,62,150,212,253,300,343,360]

FIGURE 18.10 Lact-Aid Nursing Trainer. (Courtesy Lact-Aid International, Inc.)

Collaboratively creating a feeding plan with parents that they understand and are able to carry out at home is essential before discharge.[18,39,48,117,300] A Canadian study of LPIs and term infants found a longer hospital stay for LPIs, initial breastfeeding difficulties, and higher readmission rates by 4 months.[277] Although this study found earlier cessation of breastfeeding at 4 months,[277] another Canadian study, in the same region, found that being an LPI and readmission were not factors influencing the predominance of breastfeeding at 2 months, especially if parents had a positive encounter with a health care provider about breastfeeding.[281]

Maternal factors also contribute to breastfeeding problems with LPIs, but research shows contradictory results. One study showed that admission

of LPIs to the NICU was not associated with early breastfeeding cessation,[210] and another study showed that mothers of LPIs in the NICU were as likely to initiate breastfeeding but less likely to still be breastfeeding at 10 weeks postpartum.[178] In the first study, lower breastfeeding rates at 10 weeks was associated with being a single mother, having only a high-school education, and maternal obesity.[210] In the second study, mothers of LPIs in the NICU were less likely to breastfeed in the hospital, less likely to be told to feed on demand, and more likely given a breast pump while in the NICU.[178] A Swedish study found that higher maternal self-efficacy, measured by The Breastfeeding Self Efficacy Scale—Short Form (BSES-SF), was positively associated with exclusive breastfeeding of their LPI at 40 weeks, and 3 months corrected age.[149] Maternal breastfeeding self-efficacy and breastfeeding success of moderately and late preterm infants is being studied by a mixed-methods protocol in a family integrated care setting.[50]

Maternal emotional well-being is altered with a late-preterm birth and for the first month postpartum.[44] During both of these periods, mothers had elevated anxiety, depression, posttraumatic stress symptoms, and worry about their infant's health. Mothers were coping with their altered birth and postpartum experiences after giving birth earlier than planned. A more recent study corroborates these findings and found that **maternal distress over giving birth prematurely affected both initiation and duration of breastfeeding.**[477]

A Canadian quantitative and qualitative study about maternal and public health nurses' perceptions about breastfeeding LPIs found that 50% of the mothers (n = 61) breastfed their LPI after discharge.[107] Only 10 of these mothers exclusively breastfed their infants, and 51 partially breastfed. Qualitatively, three themes emerged from maternal interviews: **(1) significant difficulty with breastfeeding, (2) failing to recognize their infants' disorganized behavior and feeding distress, and (3) parental stress caused by their infants' multiple feeding issues.** Qualitatively, public health nurse interviews found corollary themes of challenges initiating and during breastfeeding as well as the need for breast stimulation during breastfeeding. This same research team followed these **mother-infant pairs for the first 2 months after birth of an LPI and found maternal depression and declining maternal confidence.**[349] **Declining maternal confidence was caused by (1) demanding needs of the LPI, (2) the ever-looming prospect of rehospitalization, and (3) interactions with public health nurses.**[349] In this cohort, maternal depression resulted in less maternal confidence when compared with nondepressed mothers. Multidisciplinary lactation teams of health care professionals with special education to assist mothers of LPIs are recommended.[434] Providing parental education and anticipatory guidance about the challenges of breastfeeding an LPI; providing ongoing support with initiation and continuation of breastfeeding; promoting maternal skills with the LPI; assisting mothers in their own self-care; and assisting mothers with strategies to support breastfeeding are all essential with this population of high-risk mothers and neonates.[107,349,434]

Some mothers may not establish or may have difficulty maintaining an adequate milk supply, yet infants with problems require an easily obtainable milk supply. **The Lact-Aid Nursing Trainer system (see Fig. 18.10) addresses a variety of breastfeeding problems, including sucking defects.**[21] EBM or formula is contained in a presterilized, disposable bag suspended between the mother's breasts by a cord, and the liquid is delivered by a thin, flexible tube attached to the bag. The end of the tube is placed against the mother's nipple to enable the infant to suckle the tube and nipple at the same time. **This device provides the correct rate of flow and volume of liquid that elicits the reflexes of swallowing and expression. The Lact-Aid trainer provides oral therapy and nutritional supplementation for the infant and the mammary stimulus necessary to enhance the mother's lactation.**[245] **It is effective in managing low milk production in the mother that has resulted from separation, delayed breastfeeding, poor technique, or other correctable problems, and the device gives nutritional and oral therapy to an infant who is slow in gaining weight or has a sucking dysfunction.**

CAUTION: To prevent the spread of serious infections, the Lact-Aid trainer should never be borrowed, rented, or loaned from another mother.

Problems with the letdown reflex may originate with the mother, the neonate, or both. Often, especially in breastfeeding a premature infant, this is because of fear of failure or a lack of privacy. Knowledge of the mechanisms of lactation can help the mother avoid a fear of failing. **Give the mother as much privacy and the least stressful**

environment possible when she is pumping her breasts and breastfeeding. If a mother experiences a weak or delayed letdown, she should massage the colostrum or milk down to the nipple before putting the infant to the breast. Infants with a poor suck, such as preterm infants or infants with Down syndrome or a neurologic deficit, understimulate the breast and do not trigger the letdown reflex. **Use of the Lact-Aid trainer provides oral therapy, improves these infants' sucking ability, and facilitates a successful nursing relationship. The breast also can be stimulated with a good pump between feedings to increase the milk supply.**

DATA COLLECTION AND INTERVENTION

Establishment of Breastfeeding

AVAILABLE FEEDING AND SUCKING NEONATE

Infants who have been admitted to the NICU often present a dilemma to care providers as to the most favorable time to begin putting the infant to the breast. Research shows that direct breastfeeding, especially for the first oral feeding in the NICU, is associated with an increase in (1) frequency of later breastfeeding, (2) duration of breast milk feedings, (3) success with breastfeeding in the hospital, and (4) breast milk feedings at discharge.[344] **A more recent study of direct breastfeeding as the first feeding in the NICU found a shorter time to transition to oral feedings, a younger age of attainment of full oral feedings, and earlier NICU discharge.**[419] Because combination human milk and formula feedings have been shown to result in earlier breastfeeding cessation, prompt initiation of breastfeeding in the NICU benefits the mother-infant breastfeeding dyad.[190] A randomized study of oral stimulation (15 minutes for at least 10 days before oral feeding) provided to preterm infants resulted in significantly higher breastfeeding rates (70% vs. 45.6%) at discharge.[23]

In the NICU, the infant's current physical status, plus considerations of nutrition and energy expenditure, helps determine the decision to initiate enteral feedings.[229] In a national survey, criteria used to determine readiness for oral feedings included the following: (1) 75% used gestational age (e.g., 34 weeks by 60%) or weight (e.g., 1500 g by 50%) and (2) infant behavioral cues (e.g., sucking behaviors).[397] Table 18.5 presents the research basis for readiness to initiate oral feedings. A more recent survey of enteral feeding practices found that gestational age was the leading criteria used to initiate feedings.[159] **Few empirical data support the contention that either weight or gestational age affects the ability of a preterm infant to suckle effectively because the suck and swallow will automatically be coordinated by the peristaltic motion at the breast.** In the earlier survey, a majority (85% to 93%) responded that bottle feeding is started first, before breastfeeding.[397] **Professional caregivers believe and teach parents that breastfeeding is too stressful and requires more energy and exertion than bottle feeding.**[462] Contrary to physiologic evidence, progression of nutritional support for the preterm infant has proceeded from intravenous fluids → total parenteral nutrition → gavage (continuous → intermittent) → bottle feeding (at 1500 to 1800 g or 34 to 35 weeks' PCA) → breastfeeding (after bottle feeding without distress). **Problems arising from this approach include the following*:**

- Delay in initial oral feedings and slower attainment of full oral feedings
- Establishment of a sucking method that may not easily transfer to breastfeeding (i.e., bottle feeding alone has been found to contribute to arrhythmic sucking in full-term infants)[96]
- Initiation of breastfeeding when discharge is imminent so the mother receives little, if any, breastfeeding assistance and support
- Each additional week of hospitalization reduces the likelihood of the infant transitioning to direct breastfeeding by 14%

An ***Early Feeding Skills (EFS) Assessment*** checklist has been developed to assess both oral feeding readiness and oral feeding skills in preterm infants.[429] To individualize interventions, an infant's developmental stage regarding specific feeding skills (e.g., the ability to remain engaged in feeding; to organize oral-motor functioning; to coordinate swallowing and breathing; and to maintain physiologic stability) is profiled. Content validity and intrarater and interrater reliability have been established. The EFS is being tested for predictive, concurrent, and construct validity.[429] Other tools to evaluate readiness for oral feedings are the Premature Infant Oral Motor Intervention (PIOMI) and the

*References 135, 174, 287, 400, 410, 462

TABLE 18.5 CRITICAL FINDINGS READINESS FOR INITIATION OF ORAL FEEDINGS: RESEARCH BASIS

BREASTFEEDING	CRITERIA	BOTTLE FEEDING
	←Gestational/ Postconceptual Age→ ←Weight→	
Preterm 28–32 weeks: Better able to coordinate suck, swallow, and breathing.[285,286,289]		**Preterm** 34–35 weeks: PCA is a developmental guideline—based on belief that sucking pattern is similar to that of full-terms*; infants may be ready at an earlier age (i.e., 28–34 weeks).[228,284] Coordination of respirations with sucking and swallowing is consistently achieved by infants >37 weeks PCA.[201,278,342,449]
<1500 g: Better able to coordinate suck, swallow, and breathing.[285–287,289]		1500–1800 g: Traditional criteria without research basis.
Full-Term Ultrasound study shows human nipple elongates to twice its resting length; neonatal cheeks act as a passive seal for the oral cavity. Sucking pressures of –50 to –155 mm Hg[351]; and –64 to –145 mm Hg.[143] Peak vacuum pressures highest at initiation of nutritive suck then decreases.[60] More milk removed with stronger vacuum and faster application rate[60]	←Mechanics of Sucking→	**Full-Term** Higher maximum pressure and number of sucks or bursts; greater suck widths and greater intake/suck. Able to alter sucking to accommodate nutrient composition, nipple, and hole size to minimize energy expenditure[268] and autoregulate milk flow by controlling pressure generated during sucking.[268] Regulates sucking pressure by coordination of various oral motor structures so that intraoral pressure is controlled to enable milk flow in a manageable fashion.
Preterm Sucking pressures of –2.5 to –15 mm Hg.[351] Generate intraoral pressure in same manner as term infants; higher milk intakes associated with longer, more efficient and a greater proportion of sucking during a feeding and not with vacuum strengths[142]		**Preterm** Burst width (interburst and intersuck width) similar to that of full-term infant.[202,282,283] At the beginning of a feeding, preterm infants generate weaker sucking pressure within the oral cavity that changes over time to pressures and duration in the same range as for term infants, because of neural maturation and sucking experience.
Full-Term 50% of feeding obtained in first 2 min; 80%–90% by 4 min; last 5 min, minimal obtained from each breast.[351]	←Energy Expenditure→	**Full-Term** 86% of feeding obtained in first 4 min of sucking.[241] Generate larger negative pressure with sucks with higher energy expenditure.[202] Able to alter sucking to accommodate nutrient composition, nipple and hole size to minimize energy expenditure[268] and autoregulate milk flow by controlling pressure generated during sucking.[268]

TABLE 18.5 CRITICAL FINDINGS READINESS FOR INITIATION OF ORAL FEEDINGS: RESEARCH BASIS—CONT'D

BREASTFEEDING	CRITERIA	BOTTLE FEEDING
Preterm After 34 weeks: 70%–80% of feeding ingested in first 6 min, then intake sluggish, rest periods increase; and sucking and nourishment decrease. At 36–37 weeks: Sucking standards are similar to those in mature neonate.[319] The younger the gestational age, the higher the variability.[319] Longer duration of breastfeeding than bottle feeding.[285,289] No differences in duration of breastfeeding versus bottle feeding. At 35 weeks' CA: Small volume of milk intake in same duration of feeding; fed less efficiently and with fewer suck bursts.[135]	←Energy Expenditure→	**Preterm** 40% of total volume ingested in first min, less energy to suck same volume as full-term infant.[202] Infants born 26–29 weeks' gestational age benefit from restricted milk flow (i.e., milk is obtained only with active sucking; no milk flows to infant by gravity or high-low nipples during rest periods). At initiation of oral feeding (with restricted milk flow), an intake of 1.5 mL/min and a proficiency of 30% (e.g., intake of 9 mL in first 5 min; intake of 30 mL in 20 min) are indicative of earlier attainment of full oral feeding.[241] Consumes an average of 2.6 mL/min of feeding.[342] At 35 weeks' CA: Greater volume of milk intake in same duration of feeding with more sucking bursts; fewer single sucks, better nipple seal.[135]
Preterm Skin temperature higher (than when bottle feeding) because of bodily contact with mother.[76,285,289] No temperature change before feeding (ac) or after feeding (pc).	←Temperature→	
Preterm Less weight gain after breastfeeding compared with bottle feeding.[174]	←Weight Gain→	**Preterm** No difference in weight gain between experimental self-demand feeding protocol and control group (standard care).[276]
	← Heart Rate→	**Preterm** Bradycardia occurred with bottle feeding but not breastfeeding; bradycardia possibly related to faster milk flow and interference with breathing;[285,289] apnea and bradycardia with bottle feeding in otherwise healthy preterm infants.[278]
Full-Term Swallowing occurs nonrandomly between breaths and does not interfere with breathing.[155] With age and experience become more efficient by extending suck bursts, pausing less, applying weaker vacuum levels and increased oxygen saturation and decreased heart rate.[383]	← Coordination of Suck, Swallow, and Breathing→	**Full-Term** Suck, swallow, breathe in a 1:1:1 pattern.[278] Alteration of breathing pattern—prolongation of expiration and shortening of inspiration.[269,289] No difference in sucking frequency or pressure when bottle feeding expressed milk or formula. Differences in sucking and/or breathing patterns attributed to nutrient delivery rather than nutrient composition.[267] Soft-walled delivery system results in significantly higher oxygen saturation, better coordination of suck-swallow-breathe, and feeding behaviors more like breastfeeding than use of hard-walled delivery system.[155]

Continued

TABLE 18.5 CRITICAL FINDINGS READINESS FOR INITIATION OF ORAL FEEDINGS: RESEARCH BASIS—CONT'D

BREASTFEEDING	CRITERIA	BOTTLE FEEDING
	← Coordination of Suck, Swallow, and Breathing→	
Preterm Different patterns of sucking bursts and better coordination, breathing is integrated within sucking bursts.[286]		**Preterm** Initial feedings at 32–34 weeks are characterized by periods of apneic suckle alternating with respirations; as PMA increases, the percentage of apneic swallows decreases and suck-swallow-breathing is more synchronized.[449] High-flow nipples result in apnea[268,394] or bradycardia.[262–264,266] Do not breathe within sucking bursts but in alternate short bursts of sucking with breathing.[289] Consistently achieved by infants 36–37 weeks' PCA.[449] Use of orthodontic nipples results in physiologic stability and effective feeding behavior in some preterm infants.[109] At 34 weeks' PCA, sucking pattern primarily expression component; with maturation, experience, endurance, and strength gains, there is a shift to more frequent use of term sucking pattern.[400] Not necessary to wait for full-term sucking pattern for successful oral feeding.[133,400]
Full-Term No desaturation with feeding.[176] 18% of pc saturations <90%.	← Oxygen Saturation→	**Full-Term** No desaturation with feeding[269] 29% of pc saturations <90%. More oxygen desaturations (<90%) than breastfeeding.[267]
Preterm No difference in oxygenation with breastfeeding versus bottle feeding;[285,289] no pc decline of oxygenation; oxygenation more stable than with bottle feeding—fewer desaturations.[109] Desaturations (<90%) in 21% of breastfeedings.[76] With BPD, saturation higher than with bottle feeding.[76]		**Preterm** Decreased oxygenation during initial sustained sucking, but oxygenation increased as sucking pattern modulated.[373] 32–36 weeks: Range of 94%–97% with feeding, with sucking decreased saturation from 2.5%–16% (range 80%–100%).[284] Fluctuations and sharper decrease in saturation with bottle feedings versus breastfeeding;[76,285,289,373] 10 min pc saturation 50% below baseline.[76] Desaturations (<90%) in 38% of bottle feeding.[76] Desaturation in VLBW infants at discharge: average of 10.8 events during feeding; 20% of feeding time with saturations less than 90% Behavioral cues of desaturation are unreliable; changes in breathing and sucking pauses to regulate breathing pattern and increase oxygenation may occur.
	←Hypercapnia→ (elevated P_{CO_2})	**Preterm** 34–35 weeks: Increased P_{CO_2} depresses sucking and swallowing so that respirations may supersede feeding in preterm infants with increased respiratory drive (e.g., BPD).

TABLE 18.5 CRITICAL FINDINGS READINESS FOR INITIATION OF ORAL FEEDINGS: RESEARCH BASIS—CONT'D

BREASTFEEDING	CRITERIA	BOTTLE FEEDING
Preterm 32 weeks: Increased feeding in active alert and quiet alert state.	**←Behavioral Cues→** ←Quiet alert→state before and during feedings associated with more successful feeding behaviors.[162,276,278,279] Offer pacifier for NNS ac to promote awake behavior at beginning of feeding.[342,348] NNS ac associated with better oral feeding ability.[40] ←NNS pattern of sucking develops before nutritive pattern; mature NNS pattern not reliable cue for readiness to orally feed.[241,342] ←Cues include[10,278,400]→ Oral behaviors—sucking on pacifier, fingers, feeding tube. Rooting reflex, hand-to-mouth behaviors, mouthing movements. Presence of gag reflex. ←*Behavioral State*→ Changes—arousal from sleep, quiet alert state ac.[279] Exhibits stability in autonomic, motor, and behavioral states. Able to self-regulate, interact, and tolerate outside stimuli.[278] ←Crying→fussing and demanding to feed—a late sign.	**Full-Term and Preterm** Motor behavior: Change in arm posture (flexion) with feeding.

*References 133, 241, 276, 278, 284, 342.

ac, before feeding; *BPD,* bronchopulmonary dysplasia; *CA,* corrected age; *NNS,* nonnutritive sucking; *pc,* after feeding; *PCA,* postconceptual age; *PMA,* postmenstrual age; *VLBW,* very-low-birth-weight.

Supporting Oral Feeding in Fragile Infants (SOFFI), which are briefly discussed in Chapter 13. The latest Cochrane review of RCTs or quasi-RCTs of instruments for assessing readiness to commence oral feeding in preterm infants concluded that there is no evidence that supports any instrument or that informs practice.[94] Recent research has found five genes involved in the essential developmental pathways for feeding readiness present in neonatal saliva.[225] Hunger signaling proteins in saliva are quantifiable and in the future may be used to assess oral feeding readiness in the premature neonate.[225]

Use of a breastfeeding protocol[418] without use of bottle feeding (either before breastfeeding or to supplement breastfeeding) is associated with the longest duration of breastfeeding. An RCT of this protocol in which nasogastric (NG) supplementation was compared with bottle feeding for a transition to feeding at the breast found that NG supplementation was associated with feeding from the breast at discharge, 3 days, 3 months, and 6 months compared with preterm infants supplemented with bottle feeding.[230] In this same study, earlier age at initiation of breastfeeding also was

associated with successful and longer duration of breastfeeding.[230] If the first oral feeding is direct-to-breast, preterm infants in the NICU are more likely to still be receiving breast milk at discharge.[63] Other protocols for transitioning from gavage to breast have been proposed but not tested in an NICU population. **After discharge from the NICU, mothers wean their preterm infants from the breast because of (1) infant resistance to latching on, (2) weak suck, (3) refusing the breast, and (4) difficulty with latch-on.**[183] **If the sucking pattern learned with bottle feeding impedes breastfeeding, health care providers should promote early, exclusive breastfeeding to prolong the duration of preterm breastfeeding after discharge.**[230,348,465]

Maturation of feeding skills depends on developmental changes in the infant's central nervous system coupled with experiential learning.★ "Successful infant feeding is a complex process that requires integration of physiologic function and neurobehavioral ability."[61] Experiential learning through a prefeeding oral stimulation program has been shown to improve preterm infants' sucking behaviors before actual oral feeding.[23] A recent randomized study of oral stimulation (15 minutes for at least 10 days before oral feeding) resulted in significantly higher breastfeeding rates (70% vs. 45.6%) at discharge.[23] **Studies show that preterm infants are able to breastfeed far earlier (less than 1500 g or 28 to 36 weeks' gestational age) than they can bottle feed.**[285-287,289,410] **VLBW infants (at 28.7 + 2.8 weeks' gestational age) who were fed their first oral feeding at their mother's breast were more likely to be receiving breast milk at discharge from the NICU.**[64] A comparison of studies of breastfeeding and bottle feeding shows less oxygen desaturation, warmer skin temperature, no bradycardia, and better coordination of sucking and breathing with breastfeeding compared with bottle feeding (see Table 18.5). According to these research data, **the ability of the preterm infant to breastfeed without alterations in homeostasis occurs *before* the ability to safely bottle feed.** Oxygenation is more stable with breastfeeding, because the type of sucking pattern (e.g., intermittent) and the flow of milk at the beginning of breastfeeding may be easier for the VLBW infant to control and regulate.[263,394] In VLBW infants, breathing is compromised (e.g., desaturations, increase in heart and respiratory rates) more during continuous sucking than during intermittent sucking.[394]

When an NG tube is in place, a VLBW infant has even poorer oxygenation, shallower breathing, and inability to increase tidal volume.[394] **The postfeeding period enables recovery of oxygen saturation and end-tidal CO_2 to the prefeeding levels.**[394]

Health care providers and parents should closely observe VLBW infants during the continuous sucking period (e.g., the first minute of bottle feeding,[428] **with letdown during breastfeeding) for apnea, oxygen desaturation, and heart rate changes. Recommendations for continuous sucking periods include (1) not allowing breathing pauses of more than 10 seconds, (2) monitoring oxygen saturation and heart rate for continuous sucking of more than 30 seconds, and (3) interrupting sucking by withdrawing the nipple for breathing pauses and desaturations.**[394] **Desaturations, especially in the first minute of bottle feeding, during the continuous sucking period, still occur in VLBW infants nearing discharge.**[428]

Skin-to-skin (kangaroo) care provides a safe, effective alternative method of caring for premature infants (see Chapters 5 and 13). Use of kangaroo care has been shown to improve lactation for mothers of preterm infants.[135,317,410] **During skin-to-skin contact, the infant may initiate NNS at the breast.**[297,412] **NNS time at the breast is used to accustom both the mother and baby to each other and the pleasant sensory stimuli at the breast. The smell of a premature infant's own mother's milk persistently decreases salivary cortisol levels, even after the breast milk odor has been removed.**[271] **NNS at the breast improves maternal letdown, enhances attachment and bonding, and shortens transition time to and lengthens the duration of breastfeeding.**[348,410] As the preterm infant matures, NNS is replaced by hunger cues, latching on, and effective nutritive sucking. Both AGA and SGA infants (700 to 2450 g) benefit from early (sometimes starting at birth) (see Chapter 5) and sustained breastfeeding as follows (see Chapter 13):

- More mothers breastfeed and are more confident.
- More frequent feedings are given.
- More milk is produced.
- Infants breastfeed longer (e.g., at 1 month after discharge, breastfeeding rates increased from 11% to 50%).
- There is less bradycardia than with gavage or bottle feeding.
- There is better weight gain and earlier discharge.

★References 133, 278, 319, 342, 348, 400, 410, 418

Both maternal and neonatal responses to breastfeeding should be monitored.[348,410] Adequate milk volume is available when the milk ejection (letdown) reflex occurs. Breast massage may assist in bringing down the milk, thus making it easier for the infant to obtain. Letdown may be felt by the mother or observed as a change in the rhythm of infant sucking and audible swallowing. After letdown is established, the infant expends little energy in sucking. He or she only needs to coordinate swallowing and breathing with an occasional burst of sucking. The nurse should be available during the initial breastfeeding to provide support to the mother, to ensure that the infant exhibits no signs of distress (e.g., color changes, bradycardia, oxygen desaturation, drop in temperature), and to provide guidance for the mother if the infant chokes with letdown. The nurse also needs to reinforce to the mother that the infant's sucking pattern will be a pattern of bursts and pauses. The pauses are present in all infants and provide rest periods for the infant.

The infant's respiratory status should be reviewed. Infants requiring supplemental oxygen can breastfeed. If the infant requires 35% oxygen or less, oxygen may be delivered through a nasal cannula to ensure adequate, consistent oxygenation. This will eliminate another source of concern for the mother: having to worry about juggling the blow-by oxygen line. If the infant has not been placed on a nasal cannula previously, the nurse should initiate the cannula and then assess oxygenation using a pulse oximeter before the feeding begins. The infant's temperature status requires review. Attention should be directed toward preventing hypothermia with infants who require significant thermal support. The infant should be swaddled, and a hat should be placed on his or her head to prevent heat loss.

Duration of breastfeeding should be based on cues of satiety, such as sucking cessation or falling asleep, or cues of physiologic instability or fatigue. Frequency of breastfeeding can be progressed, as can frequency of bottle feeding: from one breastfeeding per day to one per shift to every other breastfeeding. If the mother is available for this progression, bottle feeding may be deferred until breastfeeding is well established, or bottle feeding may be avoided altogether. When the infant is taking all nutrition orally, the mother can be encouraged to breastfeed as often as possible and institute an ad lib schedule.[288,410] If the mother is available, the infant should breastfeed as often as necessary, and supplementation should not be provided. However, if the breast milk supply is insufficient, using a Lact-Aid Nursing Trainer provides nutritional supplementation and mammary stimulation to increase maternal milk supply. Total intake should be estimated to ensure adequate calories.

If the infant weighs less than 1500 g, it is necessary to augment calories, protein, and calcium with human milk fortifiers (fortifiers made from human milk are preferred to cow's milk fortifiers) (see Chapter 17).[1,104,238,385] Advantages of an exclusive human milk diet are listed in Table 18.1. Exclusive use of human milk, fortified with human milk fortifier, results in less feeding intolerance[385] and lower rates and severity of NEC in extremely premature infants compared with the use of human milk or preterm infant formulas with bovine milk fortifier.[420] A standardized feeding protocol using an exclusive human milk diet and early fortification with human milk–based fortifier resulted in improved growth, significantly less NEC, and no effect on NEC of the early fortification in preterm infants less than or equal to 1250 g.[194] High protein intake of fortified human milk in preterm infants less than or equal to 1250 g resulted in less postnatal growth restriction and better neurologic outcomes at 24 months corrected age.[33] There are limited data to support multinutrient fortification of human milk after hospital discharge and little data to show that important outcomes are affected, including growth rate during infancy.[476] Fortification also interferes with feeding at the breast.[476]

Families and staff often fear that the infant will not get enough during a breastfeeding. This concern is especially predominant when infants have been hospitalized for prematurity and fluids and calories have been scrutinized closely. Health professionals should be sensitive to such concerns and refrain from employing methods such as weighing infants before and after feedings or using gavage tubes to attempt to determine the exact amount of breast milk ingested during the feeding. With today's electronic NICU scales, however, test weighing (before and after feeding) (see Table 18.3) is accurate, if necessary.[174,291,297] Test weighing reassures mothers (and professionals) that preterm infants are receiving adequate intake while nursing and is associated with a higher exclusive breastfeeding than merely estimating breastfeeding intake.[119,295]

Health care professionals should also focus on cues that can be used during and after hospitalization by both caregivers and the family.[174] These cues include the infant's satisfaction after the feeding (asleep or fussy), the frequency of feedings, voiding pattern (minimum of six to eight wet diapers per day, weighing diapers, and checking specific gravity), and palpation of the mother's breasts before and after feeding. Trends in weight gain also can demonstrate the success of the mother-infant dyad in breastfeeding.

A small infant may have difficulty taking a large nipple into the mouth. The mother should shape her nipple by compressing behind the areola to allow more of the nipple to be placed in the infant's mouth. The thumb and index finger or the first two fingers should be parallel to the infant's nose and chin. The breast must be soft enough to be compressed in this manner. The mother should hold the infant close for the comfort of both, with the infant's entire body, not just the head, turned toward the mother's body (see Fig. 18.6).

A nipple shield allows the infant to get a nipple in the mouth but increases the amount of sucking necessary to obtain milk and decreases the amount of stimulation received at the nipple. Supervised temporary use of silicone nipple shields has been found to be a successful bridging technique for the infant to transfer to direct breastfeeding (after only a few sessions of shield use).[290] Use of a nipple shield should be followed by breast pumping to express residual milk, maintain adequate milk supply, and obtain milk to freeze for supplemental feeding.

Because NNS does not stimulate prolactin secretion and milk production, infants should not be placed on an empty breast to feed. Without positive reinforcement (i.e., milk) for their efforts, infants soon learn that the breast does not give milk, become frustrated, and refuse to feed. The Lact-Aid Trainer may be used to initiate proper suckle and supplement intake in a small premature infant who is able to nurse (see the Prevention of Breastfeeding Problems section earlier in this chapter).

Supplementing breastfeedings with bottle-fed formula is inefficient in terms of energy and calories, because the infant expends energy, and thus calories, to feed twice. More energy-efficient and calorically efficient methods of initiating breastfeeding include offering smaller, more frequent feedings; supplementing by gavage feeding[100]; and using a lactation supplementing device. Breast milk fortifiers (see Chapter 17) should be used when the mother's milk is not nutritionally adequate for the infant's requirements.[104] Breast milk substitutes, such as donor milk, should be used when the mother does not provide sufficient volume; donor milk also needs fortification to meet the nutritional needs of VLBW premature infants[470] (see Chapter 17). A recent RCT showed that standard fortification of donor milk does not increase the incidence of NEC in preterm infants.[3]

UNAVAILABILITY OF A FEEDING OR SUCKING NEONATE

If premature birth or neonatal or maternal illness delays the onset of breastfeeding, the mother experiences a decrease in her milk production. Depending on how long breastfeeding has been delayed, mammary involution and the return of menstrual hormonal cycles may inhibit breastfeeding. A preterm infant or one who is ill may be weak and tire easily, and thus adequate lactation is not established.

If a neonate is unable to feed at the breast, breast milk must be produced through artificial stimulation of the breast. The mother should establish a regular routine of breast massage[206,410] and pumping soon after the infant's birth. A comfortable chair with armrests or a pillow often helps, and the mother should be assured of privacy during breastfeeding and breast pumping. It is often necessary for the care provider to help the mother start and to encourage her routine. Each breast should be pumped every 2 to 4 hours, preferably with a double pumping system to enhance milk supply.[206] Mothers should increase pumping time up to 15 to 20 minutes as the milk comes in, with the suction pressure increased as tolerated. At the beginning of pumping, mothers should awaken to pump at night to establish a good milk supply. Sleep and rest are necessary for good milk supply; however, the mother should not sleep when breasts are engorged because this will decrease the supply. Mothers should be advised that if their infant were with them, they would be feeding every 2 to 4 hours around the clock and therefore should develop that pattern to establish an adequate supply.

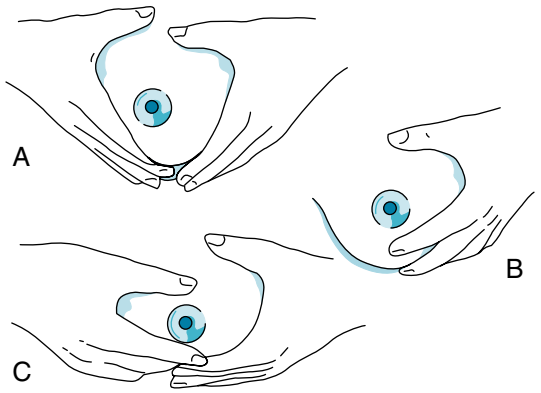

FIGURE 18.11 Breast massage. **A**, Place hands with palms toward the chest at the breast. Encircle the breast with the fingers and thumbs. **B** and **C**, Applying pressure, move hands forward, overlapping as they near the nipple. Stop posterior to the areola. Continue for 1 to 2 minutes or until milk is on nipple. Repeat on the opposite breast. (From Lawrence RA, Lawrence RM. *Breastfeeding: A Guide for the Medical Professional.* 6th ed. St Louis, MO: Mosby; 2005.)

CAUTION: Mothers should be counseled about the potential risks of using breast shells or breast pump kits that have been used by other women. Breast shells, breast pump kits, and lactation aids are intimate-care items and are meant for use with one mother and one baby. Breast pump attachments and collection devices must be appropriately cleaned.[67]

Induction Aids. Various induction aids using tactile and mechanical principles are available to assist the mother in lactating and relactating. Knowledge of the different systems and their advantages and disadvantages enables the health care provider to help the mother choose the most helpful aid.

Breast massage (gentle, tactile stimulus usually in a circular motion using increasing pressure) before breastfeeding or pumping may help unplug breast ducts and enable milk to flow more easily.

Breast massage during pumping provides the important tactile stimulation that is missing without the infant's nursing and facilitates prolactin release and milk yield.[245]

Hand Expression. Once the breast milk supply has been established, hand expression (Fig. 18.11) is the simplest and most cost-effective way to collect milk; however, prolactin secretion and milk yields are less than with a pulsatile breast pump.[481] Combining hand expression of colostrum and hands-on pumping results in greater milk production for pump-dependent mothers of preterm infants.[308] A comparison of exclusive hand expression versus electric breast pump expression in mothers of VLBW infants in an NICU found significantly lower cumulative daily breast milk production during the first 7 days postpartum in the hand expression group that lasted throughout the first 28 days.[257] Some mothers find hand expression esthetically unsatisfactory, and they should use other methods.

Mechanical Devices. Breast pumps work by application of negative pressure (e.g., −50 to −155 mm Hg) and compression in a suck-release pattern (e.g., rate of 40 to 50 suck-release cycles/min) by fitting the nipple cup (or flange) over the maternal nipple and areola.[299] Nonautomated or manual pumps are regulated by the number of times the mother manually exerts and releases pressure; they are best for occasional use. Automated pumps (battery, mini-electric, double electric, and hospital-grade) exert more negative pressure, permit the greatest number of cycles per minute, and are the pumps of choice for establishing and maintaining lactation for a preterm or sick infant.[299,410] Breast pumps that mimic the sucking pattern of the human infant result in greater amounts of pumped milk and are more efficient, comfortable, and convenient.[293,347] Automated pumps are available in the NICU and for home rental use. Health insurance (both public and private) may reimburse for pump rental.

Serum prolactin levels and increased milk yield more closely parallel those with natural infant sucking when an intermittent, pulsative pump is used.[481] Just as nursing twins simultaneously results in a greater prolactin response, pumping both breasts simultaneously is more convenient, provides higher prolactin release (and higher milk yield), and saves time.[481]

To increase milk supply when the infant is not nursing, the pump should be used frequently (see Table 18.3). Because the breast pump is not as efficient as the suckling infant (a healthy neonate removes ~80% of the total ingested breast milk volume in 4 minutes,[351] and an efficient breast pump removes 85% in 15 minutes[292]), the mother may find that tactile

stimulation and breast massage before initiating pumping help increase the milk supply. Looking at the infant's picture or listening to a recording of the infant's cry stimulates the mother's milk production with a pump.

Beginning on the low or normal pump setting and carefully breaking the suction at the breast with a finger will help prevent sore nipples. Painful engorgement is relieved by pumping each breast just enough to obtain relief. Nipple or areolar engorgement must be relieved so that the infant is able to grasp and suckle the nipple.

Lactoengineering.

To increase caloric density of EBM to improve growth/weight gain in VLBW infants, the pumping process can be altered to increase lipid content. Because the lipid content of hindmilk (e.g., milk expressed after letdown or later in the pumping session) is two to three times higher than the lipid content of foremilk, selectively feeding hindmilk to VLBW infants has been shown to increase growth and weight gain.[387] For VLBW infants with a consistent weight gain of less than 15 g/kg/day, hindmilk feedings may be initiated until a consistent weight gain of more than 30 g/kg/day is achieved.[446]

To express hindmilk, breast pumping is interrupted an average of 2 to 5 minutes after milk ejection has begun. This milk is collected and labeled "foremilk." Pumping is resumed until about 2 minutes after milk flow has ceased. This milk is placed in a separate container labeled "hindmilk." Another method of lactoengineering is to individualize the milk fractionation procedure by use of a "creamatocrit" that accurately estimates lipid and caloric content of EBM.[161,294] A small sample (<1.0 mL) of pumped breast milk is aliquoted into two capillary tubes that are sealed and centrifuged for 5 minutes. The lipid and cream layer rises to the top of the tubes and can be quantitated as a percentage of breast milk volume using a hematocrit reader and converted to estimates of lipid concentration and caloric density using published regression equations.[294] One study showed that mothers are able to cost-effectively and accurately perform creamatocrit assays; the mothers enjoyed the responsibility and increased involvement in their infant's care.[161] It is interesting to note that low-income mothers with fewer years of formal education and skilled rather than professional occupations were the most accurate in their performance of creamatocrits.

DONOR HUMAN MILK

Human milk banks that collect, store, and distribute milk to infants other than those of the donating mother exist around the world. This support is not available to some NICUs; others intentionally choose not to store or use donor milk.[26,330] In England, a wide variation in the use of donor milk was ascribed to clinical uncertainty.[26] The reservations about storing/using donor milk in the NICU generally involve lack of knowledge (i.e., advantages, concerns about adequate nutrition, safety, parental receptiveness, cost).[26,121,330] Parental reluctance to use donor milk for preterm or term infants correlates with education, ethnicity, religion, and a desire to have the infant receive only mother's milk because "donor milk is somebody else's milk."[54,122,224,355]

Recognition of human milk as the best nutrition for preterm infants has increased research into donor milk and the growing use of pasteurized donor human milk in NICUs worldwide.[10,121,330] One study showed a marked increase in the use of donor milk for preterm infants, especially in the first 2 weeks of life, from 8% to 77% in two urban US hospitals from 2006 to 2011.[101] There is also increasing use of donor human milk in larger, higher-level care NICUs that are in close proximity to a milk bank in the Midwest and western United States, in facilities with the highest rates of mothers' own milk feedings, and those participating in the Baby-Friendly Hospital Initiative.[330,339] Level 3 and 4 NICUs that participate in the Vermont Oxford Network and have a high number of VLBW admissions use more donor human milk.[169] According to the CDC, disparities exist in the provision of donor milk in NICUs where more black patients are cared for; less donor milk is used, which may be a result of hospital policies, personnel, distance from a milk bank, and/or lack of maternal knowledge.[41] **For preterm infants, use of donor milk dramatically increases human milk intake, decreases formula intake, does not alter the mother's milk intake,[101] and is associated with higher rates of exclusive breastfeeding of VLBW preterm infants at discharge.[121,331,432,466]** A systematic review of 10 studies of the use of donor milk in neonatal units found mostly positive effects.[464] However, one single-center study in the systematic review found less own mother's milk use on days 1 to 14 and 1 to 28 days of life.[123]

Use of donor milk is also increasing in well-baby, level 1 nurseries. A survey in Massachusetts found that 29% of birthing hospitals and 43% of hospitals served by a human milk bank used donor milk in the well-baby nurseries.[28] **Use of donor milk increased exclusive breastfeeding at discharge (77% vs. 56%).** Donor milk utilization for healthy term newborns in one academic center in Massachusetts increased from 0.4% to 4.7%, mainly for excessive weight loss/dehydration and parent/caregiver request.[392]

The WHO, UNICEF, AAP,[8] ABM,[73] European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN),[121] and World Association of Perinatal Medicine all endorse the use of donor human milk.[301] The increased use of donor milk has increased the importance and existence of human milk banks.[121,219,321] Adequate screening of human milk donors (for cytomegalovirus [CMV], human immunodeficiency virus [HIV], and other viruses) is essential **because of the possibility of milk-borne pathogens (e.g., CMV, HIV, herpes simplex virus, human papillomavirus, hepatitis B and C viruses).**[240,321] **All donor milk must be pasteurized, which eradicates bacteria with 93% of pooled samples sterile after pasteurization in one study.**[240] Milk banks ship human milk when necessary. A list of human milk banks is available at www.hmbana.org.

Donor human milk for use in the NICU should *only* be provided by a human milk bank.[10,121,321] Two studies of purchases of human milk from the Internet found microbial contamination[218] and milk arriving above the recommended frozen and refrigerated temperatures.[147,148] Seventy-four percent (74%) of the Internet milk was colonized with gram-negative bacteria or had too high an overall bacterial count.[218] No samples were HIV positive, but 21% of the Internet samples were positive for CMV DNA.[218] **Parents should be cautioned that human milk obtained without adequate screening, use of proper collection and storage techniques, and pasteurization poses an increased risk as a source of acquired infection for their preterm and/or medically compromised neonate.**[147,148,218]

For healthy term neonates, informal milk sharing should also *not* include Internet-based acquisition of human milk because the donors are unknown and the milk often arrives without proper storage and temperature. The ABM recommends that if human milk is shared for term healthy neonates that the donor be medically screened and that safe milk handling practices be used.[416] The ABM position statement provides guidance for health care providers to educate their patients about informal milk sharing.

Nutritional analysis of donor human milk may optimize its use in feeding of preterm infants[88,121] **(Box 18.4).** The nutritional composition of donor human milk is influenced by mammary gland maturity, stage of lactation that donor milk replaces or supplements the mother's own milk, and freezing and thawing.[296] In addition, the method of administration of donor human milk alters its nutritional content. When three feeding methods (bolus/gravity gavage; syringe pump gavage over 1 hour and 2 hours) were compared, lipid loss was significant in the timed feedings compared with the bolus method.[52]

Outcomes of premature infants fed donor human milk are compared with outcomes from mother's own milk and formula in Table 18.6. Use of donor breast milk to feed preterm infants and the resulting decrease in the incidence of NEC is a cost-effective and clinically effective strategy.[136,430] A recent meta-analysis of RCTs did not demonstrate that feeding very preterm infants their mother's milk supplemented with donor human milk decreased the incidence of BPD/CLD. However when a meta-analysis of observational studies was done by the same reviewers, **there was a reduction in BPD/CLD with mother's milk supplemented with donor human milk.**[453] **Use of donor human milk after birth in one study resulted in a decrease in BPD/CLD (36.1%) when compared with the preterm formula group (70.4%).**[227]

Reimbursement for donor milk varies among third-party payers and from state to state. Although the cost of donor milk to the hospital and families may be a barrier to wider use, pasteurized donor human milk is a low-cost intervention compared with other NICU interventions and has numerous short- and long-term benefits that are cost-effective.[8,55,414]

COMPLICATIONS OF BREASTFEEDING

Many complications other than prematurity may pose difficulties with breastfeeding. **Information on perinatal complications and breastfeeding**

BOX 18.4 NUTRITIONAL ANALYSIS OF DONOR HUMAN MILK COMPARED WITH MOTHER'S OWN MILK[121,298]

Differs from Mother's Own Milk

- Oligosaccharide amount and content[260]
- Lower protein levels[88]
- Pasteurization:
  - Decrease in cytokines, lactoferrin, lysozyme, leukocytes, lymphocytes, phosphatases, and growth factors[82,298,363]
  - Inactivation of maternal T and B cells, macrophages, neutrophils[82]
  - Reduction of secretory immunoglobulin A (sIgA) by 28% to 60%[82]
  - Reduction of immunoglobulin A and G by 33% to 40%[321]; reduction by 30% to 60%[4]
  - Reduction in minerals (Ca, P, K) and electrolytes (Na)[81]
  - Reduction in lysine and DHA[447]
  - Reduction in nutritional antioxidants by 18% to 53%[180]
  - Modest decrease in protein (6%) and fat (8%)[82]; reduction of fat absorption by infant recipient
  - Reduction in protein, fat, and carbohydrates[4]
  - Higher concentration of free fatty acids than in fresh milk[82]
  - Kills bacterial pathogens such as *Staphylococcus aureus, E. coli,* etc.
  - Inactivates cytomegalovirus
  - Slightly affects content of vitamins (A, D, E, B_2, and B_6); choline, niacin, and pantothenic acid[5]; significant reduction (10% to 20%) in vitamin D compounds[156]
  - Significantly decreases thiamine (25%), biotin (10%), and vitamin C (35%)[5]
  - Reduces nitrogen retention[5]
- After first year of lactation[340]:
  - Increased concentration of lysozyme
  - Decreased concentration of zinc and calcium

Similar to Mother's Own Milk

- Does not meet nutritional requirements of preterm infants; fortification required
- Pasteurization:
  - No decrease in cytokines, chemokines, and growth factors[165]
  - No change in long-chain polyunsaturated fatty acids (DHA/ARA),[22] monoglycerides/free fatty acids, and linoleic/alpha-linoleic acid[321]
  - No change in oligosaccharide amount and content[31]
  - No effect on protein, fat, and carbohydrate levels[82]
  - No difference in trace elements (Zn, Cu, Se, Mn, I, Fe, Mo, Br)[424] or Mg[81]
- After first year of lactation[340]:
  - Stable concentrations of protein, lactose, iron, copper, lactoferrin, and secretory immunoglobulin A (sIgA)

Br, Bromine; *Cu,* copper; *Fe,* iron; *I,* iodine; *Mn,* manganese; *Mo,* molybdenum; *Se,* selenium; *Zn,* zinc.

TABLE 18.6 OUTCOMES OF PREMATURE INFANTS FED DONOR HUMAN MILK*

	COMPARED WITH MOTHER'S OWN MILK	COMPARED WITH PRETERM FORMULA
Growth	Higher rates of SGA at discharge if received >75% donor milk[83] Slight and nonsignificant difference in growth[258] Similar growth[272,388] Slower regaining of birthweight and higher length and head circumference at discharge[113] Every 10% increase in donor human milk intake slowed growth velocity by 0.17g/kg/day and head circumference by 0.01cm/week[53]	Slower in-hospital rates of increase in weight gain but length and head circumference similar[258] Slower in-hospital rates of increase in weight gain, length, and head circumference;[87,227,354] and higher risk of NEC,[354] no significant difference in any of these parameters at 36 weeks' PMA[227] Slower growth[43,53,272] Slower growth in weight and head circumference[256] Very early fortification associated with significantly higher early extrauterine weight gain and head growth in VLBW infants.[153]
Feeding Tolerance	Slower initiation of breastfeeding by 2 weeks[112]	Better feeding tolerance[463] Shorter time to full enteral feeding[234] Same time to achieve full enteral feedings[91]

TABLE 18.6 OUTCOMES OF PREMATURE INFANTS FED DONOR HUMAN MILK* — CONT'D

	COMPARED WITH MOTHER'S OWN MILK	COMPARED WITH PRETERM FORMULA
Incidence of NEC	More NEC when compared with exclusive mother's milk group[388] Less NEC: 4.3% vs. 5.3%[404] Similar intestinal microbiome[333] Intestinal microbiome with a high number of *Enterobacteriales*[87]	Less NEC[17,89,280,354,420]: • Decreased by 79%[43] • 4–6.5 times less likely[280] • 3% vs. 21%[93] • Decreased by 2.6%[214] • 3.9% vs. 11%[430] • 2.8% vs. 38.9%[227] • 4.3% vs. 11.4%[404] Meta-analysis of four studies: not protective against surgical NEC[398]
Incidence of Infection	More infection when compared with exclusive mother's milk group[388] Similar intestinal microbiome as when fed mother's own milk[333]	No difference in incidence of serious infection, NEC, and mortality[89,388] Lower incidence of sepsis: 11% vs. 23%[234]
Length of Stay	Longer LOS when compared with exclusive mother's milk group[388]	No difference in LOS[388] Fewer days of TPN and nonsignificant decrease in LOS[93] Longer LOS[89,437] Less time receiving supplemental oxygen and mechanical ventilation[448]
Neurodevelopmental Outcomes	Lower cognition scores at 1 and 2 years of age[272]	Similar outcomes when unfortified donor milk group compared with preterm formula group[256] Better outcomes when donor milk group compared with term formula group[256] Less responsive at 37 weeks' PMA to inanimate stimuli[437] No significant developmental difference (cognitive, language, motor) at 18 months CA[113,256,320] Lower cognition scores at 1 and 2 years of age[272]
Cost-effectiveness		Costs to 18 months CA did not differ, but postdischarge costs lower in donor milk group[430] Exclusive human milk diet decreases LOS, shorter time to full feedings, and lower hospital and MD costs for extremely preterm and VLBW infants.[17]

CA, Corrected age; *LOS,* length of stay; *MD,* physician; *NEC,* necrotizing enterocolitis; *PMA,* postmenstrual age; *SGA,* small for gestational age; *TPN,* total parenteral nutrition; *VLBW,* very-low-birth weight.
Modified from Gardner SL. Current use of donor human milk in the NICU: "evidence-based practice." *NICU Curr.* 2017;7(1):1.

is shown in Table 18.4.[10,245] Because of the significant benefits of breast milk, infants with special needs should be encouraged and mothers should be assisted in breastfeeding. Many principles used with the preterm infant and other variations of feeding styles and techniques may help facilitate these infants and their mothers in enjoying a successful breastfeeding experience.

Consultation with or referral to a certified licensed lactation consultant or specialist also may be helpful.[348] Many NICUs have such an expert on their staff.

Misappropriation of Breast Milk

Misappropriation of breast milk (giving the wrong EBM to the wrong infant) does occur.

As a distillate of human blood, human milk may contain infectious bacteria (e.g., *Klebsiella, Streptococcus,* methicillin-resistant *Staphylococcus aureus*) and viruses (e.g., HIV, hepatitis virus, CMV, herpes virus) to which the infant given the wrong milk may be exposed. Both staff and parents involved in such an event experience psychological stress and anxiety.[111] Human milk has also been mistakenly administered by the intravenous instead of the enteral route, resulting in a range of consequences from no sequelae to death.[379] **Unit practices to prevent these occurrences include the following**[111,127,275,379]:

- **Ensure centralized milk preparation** with trained milk technicians.
- **Use tubing for enteral feedings** that is incompatible with intravenous tubing/connections.
- **Check milk containers for two identifiers.**
- **Have two nurses verify** the milk for administration; both nurses should sign that verification has occurred.
- **Have two nurses verify and sign** (that the milk has been verified) at transfer and at discharge.
- **Use commercial bar-coded devices.**

A quality improvement project in a large tertiary NICU resulted in a reduction of human milk administration errors over a 6-year period.[324] Using an electronic breast milk tracking system, the project reduced the total number of errors from 97.1/1000 bottles to 10.8/1000 bottles. Reduction of errors occurred in the following areas: (1) expired milk errors from 84/1000 bottles to 8.9; (2) preparation errors from 4.8/1000 bottles to 2.2; and (3) wrong-milk–to–wrong-infant from 8.3/1000 bottles to 2.0.[324] The quality improvement team concluded that the major contributors to their success were use of bedside scanners (rather than centralized scanners) and dedicated staff (i.e., milk technicians) rather than bedside nurses to handle milk.

Drugs in Breast Milk

Table 18.7 **provides information about specific drugs excreted in breast milk.**[245,380] **The most current and comprehensive information about the transfer of drugs and therapeutics into human milk is available at LactMed at www.toxnet.nlm.nih.gov.** Protein binding, degree of ionization, molecular weight, and solubility of drugs influence the passage of drugs into milk. Protein-bound drugs and drugs of large molecular weight (greater than 200) are less likely to pass into milk. Conversely, lipid-soluble drugs pass more easily into the milk. Because breast milk is slightly acidic compared with plasma, weakly alkaline compounds are present in equal or greater amounts in breast milk compared with plasma. Weakly acidic compounds have a higher concentration in plasma than in breast milk.

Several factors influence the drug effect on the infant. **Most drugs appear in milk, but drug levels usually do not exceed 1% to 2% of the ingested dose and do not depend on the milk volume.**[245] The clinical dose of a drug to the infant can be calculated by the following formula[173]:

$$\text{D} - \text{infant} = \text{Drug concentration in milk (at C} - \text{max, or C} - \text{av)} \times \text{Volume of milk ingested}$$

Drug transfers through breast milk may be minimized by feeding the infant before taking oral medications. Many variables, such as gastric emptying, pH, and effects of intestinal enzymes, affect absorption. Finally, the chronologic and gestational ages of the infant affect the maturity of the systems involved in excretion and detoxification (see Chapter 10).

PARENT TEACHING

Parent teaching has been discussed throughout this chapter because it is essential to a successful breastfeeding experience for both the mother and infant (Box 18.5). Postnatal education for parents about breastfeeding is significantly associated with improvement in knowledge, changed attitudes, and better exclusive breastfeeding rates at 6 months.[309]

Before a premature or sick infant is actually nursed at the breast, the colostrum and breast milk may have to be pumped and fed to the infant. If the mother's production is adequate, no supplementation is necessary. **Before collecting the mother's milk, perform the following:**

- Screen the mother (by history) for disease.
- Screen the mother (by history) for drugs that she has taken.
- Instruct the mother in sterile technique.

Proper collection and storage must be discussed with each family so that stored milk does not cause infections. Breast pumps can be a potential source of contamination, and therefore instructions on proper cleaning are paramount. After the death of a 29-week-old infant in an NICU as a result of a contaminated breast

TABLE 18.7 DRUGS EXCRETED IN BREAST MILK

DRUGS	BREAST MILK	CONSIDERATIONS IN INFANT
	ANALGESICS	
Heroin, codeine, meperidine, fentanyl, morphine, tramadol, pentazocine, oxycodone, dextropropoxyphene	Appears in variable amounts. FDA warning recommends against use of codeine and tramadol by breastfeeding women.[443] FDA warning[442] about mothers who rapidly metabolize codeine (because of a genetic predisposition), resulting in increased morphine levels in their breast milk and morphine overdose to breastfeeding infants. Mothers who rapidly metabolize codeine will become so sleepy that they are unable to care for themselves or their infant. Rapid metabolizers of codeine include (1) 1%–10% in whites; (2) 3% in blacks; (3) 1% in Asians and Hispanics; (4) 16%–28% in North Africans, Ethiopians, and Saudi Arabians; and (5) those positive for *CYP2D6* genotype with genetic testing.	Symptoms of depression and floppiness have been associated with these drugs.[208,239] Sleepiness, difficulty breastfeeding, limpness, hypotonia, and respiratory distress. Severe, life-threatening events (respiratory arrest) caused by morphine overdose have occurred.
Aspirin	Safe on a single-dose schedule, although it passes into milk in low concentration.	In a deliberate overdose, metabolic acidosis resulted from an accumulation in the infant; use cautiously because of the risk for Reye syndrome.
Acetaminophen	Appears in small amounts.	Well tolerated.
Ibuprofen	Appears in small amounts.	Well tolerated.
Sumatriptan succinate	Appears in small amounts.	Well tolerated.
	ANTIBIOTICS AND SULFA DRUGS	
Sulfa drugs	Appear in breast milk and may interfere with bilirubin binding in neonate; infants with G6PD deficiency may develop hemolysis.	Should not be used for breastfeeding mother in the first month if infant is jaundiced or if infant has G6PD deficiency.
Chloramphenicol	Appears in breast milk.	Contraindicated in nursing mother because infant may accumulate drug and develop "gray baby syndrome."
Penicillins (ampicillin, amoxicillin)	Small amounts in breast milk.	Disruption of gastrointestinal (GI) flora, allergic sensitization/reactions. Observe for thrush, diarrhea, and rash. Breast milk assists recolonization of normal gut flora.
Tetracycline	Appears in breast milk at 50% of serum level.	Infants may develop stained and mottled teeth when therapy exceeds 10 days; should be given only for life-threatening maternal infections. Discontinue breastfeeding during treatment.
	ANTIFUNGALS	
Metronidazole/tinidazole	Appears in breast milk in levels equal to serum levels.	Side effects include decreased appetite, vomiting, blood dyscrasia, and animal evidence of tumorigenesis. Mother's dose can be modified (e.g., 2 g single-dose therapy) so she can pump and discard milk for 24 hr.
Antimalarial (chloroquine)	Very small amounts appear in breast milk.	Observe for GI symptoms (vomiting, diarrhea); hypotension.

Continued

TABLE 18.7 DRUGS EXCRETED IN BREAST MILK—CONT'D

ANTIFUNGALS		
Cephalosporins (cephalexin, cephalothin)	Very small amounts appear in breast milk.	Rash and sensitization are possible. Also may affect bacterial flora—diarrhea, thrush.
Fluconazole (Diflucan)	Excreted into breast milk in small amounts (1% of the maternal dose; <5% of the therapeutic pediatric dose).	Considered safe for nursing infants.
Fluoroquinolones (levofloxacin, norfloxacin, ofloxacin, ciprofloxacin)	Varying levels in breast milk—use with caution.	Pseudomembranous colitis—observe for GI symptoms (vomiting, diarrhea). Tooth discoloration; phototoxicity. Arthropathy in animals.
ANTICHOLINERGICS		
Atropine, scopolamine, synthetic quaternary ammonium derivatives	Atropine appears, but quaternary ammonium derivatives do not appear in breast milk.	The neonate of nursing mother receiving atropine should be observed for tachycardia, constipation, and urinary retention.
Cimetidine	Appears in higher concentration than in serum.	No reported effects, although may suppress gastric activity, inhibit drug metabolism, and produce central nervous system stimulation. Use with caution until more information about antiandrogenic effects.
ANTICOAGULANTS		
Heparin and warfarin (Coumadin)	Do not appear in breast milk.	
ANTITHYROIDAL AGENTS		
Iodide	Passes into milk. May affect thyroid activity and cause goiters.	Not contraindicated during breastfeeding.
Thiouracil	Higher concentration in maternal milk than in blood.	Neonatal problems include suppression of thyroid activity and agranulocytosis. If breastfed, infant should be given thyroid supplement, and thyroid function should be followed.
Propylthiouracil	Appears in small amounts (<0.3% of maternal dose).	No reported effects on infant. Follow with T_3, T_4, and TSH.
ANTICONVULSANTS		
Phenobarbital, phenytoin, carbamazepine (Tegretol), and valproic acid (Depakene)	All appear in small amounts.	Sedation is possible, but rarely are clinical symptoms significant enough to cause adverse effects. Accumulation may occur because of long half-life of valproic acid.
Lamotrigine	Mean milk-to-plasma ratio 41.3% with a nonsignificant trend toward higher levels in breast milk 4 hr after maternal dose.[316]	Infant plasma concentrations were 18.3% of maternal plasma concentrations, with a theoretical infant dose of 0.51 mg/kg/day and a relative infant dose of 9.2%.[316] Mild thrombocytosis was the only adverse event noted.

TABLE 18.7 DRUGS EXCRETED IN BREAST MILK—CONT'D

CARDIOVASCULAR DRUGS		
Digoxin	Appears in small amounts.	Appears to be safe.
Reserpine	Appears in breast milk.	Symptoms include diarrhea, lethargy, nasal stuffiness, bradycardia, and respiratory difficulties; contraindicated in breastfeeding.
Propranolol, metoprolol, labetalol	Appear in breast milk in varying degrees; safest beta blockers with breastfeeding.	Observe for beta blockade—respiratory depression, bradycardia, or hypoglycemia.
Verapamil, diltiazem	Appear in varying amounts in breast milk.	Appear to be safe.
Nifedipine	90% of the dose unavailable for transfer to breast milk because of binding to plasma proteins.[13] Low levels (<1–10.3 mcg/L) appear in breast milk 1–3 hr after maternal dosing.[173]	Appears to be safe.
CATHARTICS		
Aloin, cascara sagrada, and anthraquinone preparations	Appear in breast milk.	Colic and diarrhea are possible side effects.
CONTRACEPTIVES		
Birth control pills (combined; progestin only; minipill)	Appear in breast milk with peak levels 2 hr after intake.	Combined: may alter the quality and quantity of milk—suppress lactation, shorter breastfeeding, and slower weight gain. Progestin only or minipill: no alteration of milk volume or infant weight gain. Avoid progestins in pump-dependent mothers of premature infants to avoid affecting milk supply.[295] Unknown long-term risk for cancer—no evidence in past 30 years.[245]
Medroxyprogesterone (Depo-Provera)	Increased prolactin levels before/after sucking.	No adverse effects—3-month injection (increased protein and quantity of milk); 6-month injection (increased quantity but decrease in protein, fat, calcium).[245]
Birth control implant (IMPLANON)	Small amount of hormone passes into breast milk. Best to delay implant until 4 weeks postpartum.	Small number of children studied for 3 years after breastfeeding—no effects on growth and development.
Barrier methods (diaphragm, condoms, foams, cervical cap)	No chemicals to be excreted into breast milk.	No effects on infant.
DIAGNOSTIC RADIOACTIVE COMPOUNDS		
^{66}Ga, ^{124}I, and ^{63}Cu	Appear for 24–48 hr.	Check half-life of specific compound. Pump and discard; then resume breastfeeding.
DIURETICS		
Hydrochlorothiazide	May suppress lactation.	Inadequate milk; no significant risks are present; compatible with breastfeeding.

Continued

TABLE 18.7 DRUGS EXCRETED IN BREAST MILK—CONT'D

IMMUNOSUPPRESSANT		
Azathioprine	One small study ($n = 10$ mothers; 31 breast milk samples) found small levels (1.2 and 7.6 ng/mL) of 6-mercaptopurine (6-MP) in breast milk samples at 3 and 6 hr, respectively, after azathioprine ingestion.	Potential risks of bone marrow suppression, increased risk for infections and pancreatitis. No signs of clinical immunosuppression in the small study.
PSYCHOTHERAPEUTIC AGENTS		
Lithium	Appears in breast milk; infant serum level is 10%–50% of mother's level.	Contraindicated in pregnancy because of the risk of congenital heart defects[336]; use controversial during lactation. Cyanosis, hypotonia, electrocardiogram changes. Evaluate lithium levels. Inhibits cyclic 3′,5′-AMP, a substance significant to brain growth.
	A small study ($n = 10$ mother/baby pairs) found the average breast milk concentration of lithium to be 0.35 mEq/L with an infant trough concentration of 0.16 mEq/L.[451]	Carefully selected mothers may breastfeed a healthy infant while taking lithium: (1) maternal mood stable, (2) simple medication regimen and/or monotherapy with lithium, and (3) a pediatrician collaborating to monitor the infant.[451]
Olanzapine	Small amount (1.02%). Avoid breastfeeding during peak levels within 5 hr after dose.[137]	No adverse effects. Monitor for drowsiness and sedation; developmental milestones, especially if combination antipsychotics used.
Haloperidol	Low levels in breast milk.	Monitor for drowsiness and sedation; developmental milestones, especially if combination antipsychotics used.
Risperidone	Low levels in breast milk.	Little data; another antipsychotic agent preferred during breastfeeding.
Phenothiazines	Appear in small amounts.	Evaluate each drug separately; observe for sedation.
Diazepam (Valium)	Appears in breast milk and may accumulate in infant because it is detoxified in liver.	Poor feeding, weight loss, hypoventilation, and drowsiness may be seen. Low incidence of toxicity and adverse events.
Tricyclic antidepressants (amitriptyline, nortriptyline, desipramine)	Appear in minimal amounts (<1%)	Careful considerations to select the safest for the infant. Nortriptyline may be the preferred choice.
Selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, sertraline, paroxetine, citalopram, escitalopram)	Appear in varying amounts. Fluoxetine—high levels, highly lipid bound. Produces the highest proportion (22%) of infant levels that are elevated above 10% of the average maternal level.[34] Citalopram produces elevated levels in 17% of infants.[34]	SSRI intake does not alter milk supply, and untreated psychiatric illness does lower milk supply.[166] Sertraline and paroxetine have a better neonatal safety profile than other SSRIs.[322] Sertraline is the drug of choice after birth because plasma levels are low (<2 ng/mL),[460] and there are few side effects.[322] May alter short-term and/or long-term central nervous system development and function. Slower growth curve or weight gain with fluoxetine.[71] Most infants may continue breastfeeding when mother is treated with 20–40 mg daily.[118] Citalopram—minimize maternal dose to decrease elevated infant levels.[460] Paroxetine levels are also low.[460] Adverse effects include insomnia, restlessness, and constant crying that ceases when sertraline is used.[438] Escitalopram—somnolence and sedation in young infants.

TABLE 18.7 DRUGS EXCRETED IN BREAST MILK—CONT'D

PSYCHOTHERAPEUTIC AGENTS		
Serotonin-norepinephrine reuptake inhibitors (SNRIs) (duloxetine, venlafaxine, desvenlafaxine)	Appears in breast milk in low levels	Monitor for drowsiness, sedation, adequate weight gain, and developmental milestones, especially if combination antipsychotics used.
STIMULANTS		
Amphetamines (methamphetamine* MA)	Amphetamine concentration 3–7 times higher in breast milk than in maternal plasma on the 10th and 42nd days of life.[417] Half-life of smoked MA in breast milk is 11.3 and 40.3 hr.[78] MA disappears from breast milk approximately 24 hr after maternal urine MA is negative.[78]	Stimulation of the infant—poor sleeping patterns and irritability. Infant death and SIDS-like syndrome reported with methamphetamine intake of mother.[14] Small amounts of amphetamine in infant's urine.[417]
Caffeine	Appears in small amounts (<1%) but may accumulate in infant.	Symptoms include jitteriness, wakefulness, and irritability. May alter iron concentration in milk and iron deficiency anemia at 1 month of age.
Theophylline	Appears in moderate amounts.	Irritability, jitteriness, and wakefulness may be seen in infant.
Cocaine*	Appears in breast milk.	Cocaine intoxication: neurotoxicity (e.g., irritability, hyperactive reflexes, tremulousness, and mood lability), tachycardia and seizures have been reported (see Chapter 11).[72,75] Infant urine may be positive for cocaine for 60 hr after maternal use; delay breastfeeding to allow cocaine elimination (24–48 hr).[92]
OTHER SUBSTANCES		
Buprenorphine†	Appears in low concentrations; poor oral bioavailability of drug in infants.	Safe during breastfeeding.[80,362] Monitor for drowsiness, adequate weight gain, and developmental milestones. Observe for sedation and withdrawal symptoms.
Methadone†	Appears in breast milk, concentration low (range 21.0–46.2 ng/mL).[204] Peak methadone levels occur in 4 hr after oral administration; the maximum amount secreted into breast milk is approximately 2.2% of the mother's dose.[246]	Management depends on maternal dosing for methadone maintenance.[7] Observe for sedation and withdrawal. Studies have found that breast milk intake is associated with less neonatal abstinence syndrome (NAS) and less use of pharmacologic treatment, regardless of type of drugs and gestation.[79,80,204,362]
Naltrexone†	Minimally excreted into breast milk	Monitor for drowsiness, adequate weight gain, and developmental milestones. Observe for sedation and withdrawal symptoms.

Continued

TABLE 18.7 DRUGS EXCRETED IN BREAST MILK—CONT'D

OTHER SUBSTANCES		
Ethanol (alcohol)	Quick equilibration between serum and breast milk levels.	Large quantities associated with lethargy, drowsiness, and affected motor development. The deficit in motor development was not replicated in a study of 18-month-olds exposed to moderate alcohol use during breastfeeding.[251] May inhibit milk letdown reflex and suppress lactation. Avoid nursing within 2–3 hr of alcohol intake. Low levels of postpartum maternal alcohol use not associated with shorter duration of breastfeeding or adverse outcomes up to 12 months of age.[467]
Marijuana*	THC, the active ingredient in marijuana, appears in median concentration of 9.47 ng/mL; concentrations influenced by time of last use and for up to 6 hr after use.[32] Recommended to discontinue use while breastfeeding.[11]	THC, the active ingredient in marijuana, is absorbed and metabolized by the infant.[362] May decrease prolactin levels, milk supply, and motor development. Exposure to secondary smoke. Avoid breastfeeding for several hours after use.[245] Decreases motor development at 1 year of age;[19] other long-term effects on development are unknown.[11,58,362]
Nicotine	Appears in breast milk in proportion to number of cigarettes smoked and/or time from last cigarette.	Irritability; failure to thrive may result because of suppression of lactation. Effects of secondary smoke: increased incidence of upper respiratory infections, otitis media, bronchitis, pneumonia, and SIDS. Avoid smoking in the same room with the infant.
	Smoking reduces the transport of iodine into breast milk. Mothers should receive iodine supplement.[243]	Infants whose mothers smoke are at increased risk for iodine deficiency–induced brain damage if the mother does not receive iodine supplementation.[243]
Herbal tea mixtures (containing anise, fennel, licorice, galega) used to stimulate lactation (i.e., mother's milk tea)	Essential oils found in anise and fennel appear in breast milk.	Recent RCT found no adverse effects for 30 days of study or first year of life.[457]
Fenugreek	Appears in breast milk; milk has a maple syrup smell.	Urine may have a maple syrup smell.
Ginseng	No data on amount in breast milk.	May cause neonatal androgen effect and hirsutism.
Comfrey	No data on amount in breast milk; caution use in any form.	Associated with veno-occlusive disease and hepatotoxicity and is carcinogenic. Contraindicated in breastfeeding.

TABLE 18.7 DRUGS EXCRETED IN BREAST MILK—CONT'D

OTHER SUBSTANCES		
Silicone breast implants	Silicon in cow's milk has been shown to be 10 times higher and even higher in commercial infant formulas than in mothers with silicone implants.[391] Breastfeeding mothers with silicone implants are similar to mothers without implants with respect to levels of silicon in their blood and breast milk.[391]	No adverse effects.
RESPIRATORY DRUGS		
Inhalants (steroids—budesonide)	Lower levels of budesonide (mean ratio of 0.46) in milk than in maternal plasma.[124]	Negligible systemic exposure to inhaled corticosteroids[124]: Mean infant dose 0.3% of daily maternal dose; average infant plasma concentration 1/600th of maternal plasma concentration.

*Drug of abuse; contraindicated during breastfeeding—hazardous to both the mother and infant.
†Food and Drug Administration–approved drug for opiate withdrawal.
3′,5′-AMP, 3′,5′-Adenosine monophosphate; *FDA,* Food and Drug Administration; *G6PD,* glucose-6-phosphate dehydrogenase; *SIDS,* sudden infant death syndrome; T_3, triiodothyronine; T_4, thyroxine; *TSH,* thyroid-stimulating hormone.
Modified from Sachs HC; the Committee on Drugs. Transfer of drugs and therapeutics into human milk: an update on selected topics. *Pediatrics.* 2013;132:e796; Lawrence RA, Lawrence RM. *Breast Feeding: A Guide for the Medical Profession.* 8th ed, Philadelphia, PA: Elsevier; 2016; LactMed. Available at: www.toxnet.nlm.nih.gov.

BOX 18.5 PARENT/CAREGIVER TEACHING KEY POINTS FOR SUCCESSFUL BREASTFEEDING

- Breast milk is the best milk for preterm or sick neonates. Teach parents the benefits and advantages of breast milk for their infant(s).
- Teach parents how to interpret their infant's cues/behaviors of self-regulation and stress (see Chapter 13), hunger, and satiety.
- Teach parents proper collection/storage/transport of pumped breast milk; teach proper care and cleaning of breast pump supplies to prevent infection.
- Teach mothers self-care: need for rest, diet, and fluid intake for lactation.
- Provide anticipatory guidance about pumping and a dwindling milk supply (see Fig. 18.12). Teach parents realistic expectations for the first feeding at the breast and that breastfeeding is a learned behavior for both mother and the preterm or sick infant.
- Provide positive feedback, support, and encouragement to the mother for pumping and with feeding at the breast.
- Teach parents the importance of their involvement in their infant's care, especially in skin-to-skin (kangaroo) care and its benefits for both the mother and preterm infant.

pump,[42] new guidelines for cleaning pumps have been released by the CDC.[67] A written handout of pumping, storing, and thawing practices is helpful. Often the mother pumps and collects the milk, and the father transports it to the NICU (see Chapter 29). In addition, fathers assist with pumping, assume more daily domestic duties, and provide moral support to pumping mothers.[406] **Methods of treatment and storage are listed in Box 18.6.**

Rewarming techniques include (1) placing frozen milk in a room-temperature water bath, in a hot-water bath, in a microwave oven, or under cold running water and then tepid water or (2) using commercially available devices. Slow room-temperature rewarming is a concern because of bacterial overgrowth, especially if thawing is prolonged. Most nurseries use room-temperature water bath rewarming to avoid exposure to the high temperatures of the hot-water bath and the microwave. Microwaving is contraindicated—*never* use microwave heating of breast milk because of the destruction of anti-infective properties (e.g., lysozyme and secretory IgA), resulting in an overgrowth of

BOX 18.6 TREATMENT AND STORAGE OF BREAST MILK

Treatment

1. Heat: Significant loss of lysozyme, lactoferrin, immunoglobulins, lactoperoxidase, lymphocyte function, complement, phagocytosis, and macromolecules may occur. Fat content altered (approximately 13%) by milk sterilization.[10] Pasteurization (Holder method: 62.5° C for 30 minutes)[140] does not alter fatty acid composition, but fat absorption by small preterm infants may be reduced from inactivation of bile salt lipase.[237]
2. Lyophilization: Effects are similar to those of heat treatment.
3. Freezing: Limited information; cells are not viable, but there is no effect on IgA content. Fat content is altered by freezing and thawing.

Storage

1. Use sterile glass or hard food-grade plastic containers (to ensure minimal loss of immunologic properties and fat-soluble vitamins)[5,15,338] with an airtight lid (to maintain closed system).[5,15,338] Milk stored in plastic bags may lose immune components and/or become contaminated.[325] Use a new container for each expression. Place amount for one feeding/container.
2. Label with name, date, and time of collection, so that oldest milk is used first and colostrum is fed in the order in which it was pumped.[5]
3. Store in refrigerator for 24 hours (at 0° to 4° C [32° to 39.2° F]) or for longer periods (at –18° C [0° F]).

bacteria, and possible "hot spots" in the liquid.[10,353] The Human Milk Banking Association of North America recommends warming feedings to body temperature for preterm infants.[193] However, research shows a range of temperatures at which feedings are actually delivered, from a low of 21.8° C[115] to a high of 46.4° C.[244] Commercial warming devices are either waterless or heat milk with water (below the level of the container lid).

Fresh breast milk is preferable for feedings because it has the greatest amount of immunologic properties. If the mother visits the infant at feeding time, she may pump her breasts, and the breast milk can be immediately fed to the infant, if the infant cannot be put to the breast.

Maternal Care

A mother may be so concerned about the welfare of her infant that she spends most of her time at the hospital and receives inadequate rest, which is a common cause of milk production problems. The care plan includes encouraging, educating, and suggesting to the mother that she go home and rest, which may require someone to assist with the care of the newborn's siblings. The stress of having a sick infant and the time spent at the hospital may mean that the mother does not receive adequate nutrition.

It is necessary to add about 600 kcal to the nonpregnant diet and to replace elements, such as calcium, minerals, and fat-soluble vitamins, used in producing milk. The recommended dietary increases are even greater than those during pregnancy.[468] Adequate fluid intake (six to eight glasses of water, skim milk, or other noncaffeinated liquids) should be consumed every day. Certain components of breast milk (e.g., quantity, protein and calcium content) do not vary with the mother's diet, whereas others (e.g., fatty and amino acids, lysine, methionine, water-soluble vitamins) vary with maternal intake.

A mother's diet does not have much effect on the quality of the breast milk (unless malnutrition intervenes) but affects the mother's overall health. She should be reminded to eat a balanced diet. Vegetarian diets should be supplemented with about 4 mg/day of cyanocobalamin (vitamin B12) to prevent neurologic impairment in the breastfed infant.[68,245]

Anticipatory Guidance and Realistic Expectations

Anticipatory guidance is essential for mothers who are breastfeeding preterm infants. Mothers must be informed in the beginning that their milk supply may dwindle, even though they closely adhere to the pumping schedule. This is normal, because most pumps do not stimulate the breast as efficiently and physiologically as the suckling infant. Use of breast pumps that mimic the sucking pattern of the human infant result in greater amounts of pumped milk and are more efficient, comfortable, and convenient.[293,347,358] **When the pumping regimen begins, explaining and drawing the mother a picture (Fig. 18.12) of what is commonly experienced helps alleviate guilt caused by a dwindling milk supply. A rather sparse supply of milk does not mean she cannot nurse the infant, because the milk supply builds in response to the infant's nutritive suckle. The parent should be taught that**

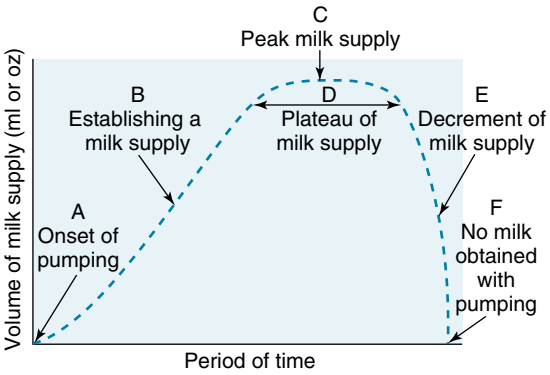

FIGURE 18.12 Establishing and maintaining milk supply by pumping. **A**, Pumping begins. **B**, Milk supply is established and increases. **C**, Peak or maximum volume of milk is established and plateaus. **D**, Gradually, supply begins to dwindle and may totally cease. **E** and **F**, The volume of milk and the period for decline in supply to begin and end in no milk production is an individual process. Some women begin and end this cycle in days or weeks; others are able to pump for months. Even if the supply dwindles to no milk, nutritive *suckling* of the infant with a Lact-Aid Nursing Trainer in place (see Fig. 18.10) will reestablish the supply.

there is no correlation between the amount of breast milk expressed and the amount of milk a mother actually lets down when the infant is at the breast.

Breastfeeding problems may be particularly detrimental to the mother's perception of breastfeeding success. **Disappointment with the breastfeeding experience may result from unrealistic expectations about breastfeeding the preterm infant. Establishing realistic parental expectations for the first time the infant breastfeeds decreases disappointment from unattainable goals.** Breastfeeding, like parenting, is not instinctual but, rather, is a learned behavior for both the mother and the infant. No one, including the health care provider, should expect immediate latch-on and vigorous sucking. **The first several attempts at breastfeeding may consist only of direct skin contact, nuzzling, and licking behaviors by the infant and cuddling and positioning by the mother.[412] Any actual sucking is an "extra" reward but should not be anticipated.**

Facilitating Breastfeeding Success

Emotional support during breastfeeding of a normal or sick infant facilitates a successful experience for both the mother and the infant.[325] Mothers are more successful with breastfeeding when they have a positive attitude toward breastfeeding, have breastfeeding goals that change during the NICU stay,[187] are confident in their ability, and have support from significant others (both professionals and laypeople).[325,410] Breastfeeding support programs in the NICU result in improved breastfeeding rates at discharge. Use of peer counselors and lactation consultants has been shown to positively influence the provision of breast milk to infants in the NICU.[297,325]

The incidence and duration of breastfeeding preterm or sick newborns vary among NICUs and among countries. There is an inverse relationship between gestational age and duration of breastfeeding, with most mothers (more than 50%) abandoning breastfeeding before their infants are discharged from the hospital.[226,287] In a German cohort study, the average duration of breast milk feedings in VLBW infants was one-third of that of a matched group of term infants.[226] A recent population-based French study in a socioeconomically deprived area found an increase in breastfeeding initiation rates among preterm infants from 52.9% to 61%, especially among the very preterm infants whose rates rose at 2.2% per year.[74]

In the United States, older studies found that between 30% and 54% of premature infants were exclusively receiving human milk at discharge,[99,183] but at 4 weeks only 51% were still receiving human milk,[183] and even fewer (10%) were exclusively feeding at the breast.[99] The Breast Milk Early Saves Trouble (BEST) program (initiated to improve use of breast milk in the first week of life in preterm infants <2000 g) resulted in 50% (vs. 33%) of preterm infants receiving EBM, 82% (vs. 74%) receiving some breast milk, and 33% (vs. 2%) receiving banked breast milk; trends of more mothers breastfeeding and more discharged home breastfeeding also occurred.[306] Using quality improvement methods and a 10-step process for promoting and protecting breastfeeding in vulnerable infants,[410] over a 3-year period there was a 3.1-fold increase in the odds of VLBW infants receiving mother's own milk at discharge.[134]

Establishing an adequate milk supply is a key factor in successful transition from primarily bottle feeding at discharge (e.g., 60% of the infants were discharged when direct breastfeeding was less than 50% of the time) to

primarily breastfeeding at home.[471] The most common reason cited by mothers for discontinuation of breastfeeding (both in the hospital and after discharge) is inadequate milk supply (or "not getting enough").[57,215,287,471] Early initiation and establishment of adequate feeding at the breast before discharge encourages both mothers and professionals that exclusive breastfeeding is successful. **However, the early postdischarge period may be significantly stressful for mothers, because the breastfeeding pattern of a preterm infant may predispose to underconsumption (i.e., inability to compensate for inadequate intake in one feeding by increasing the number or intake of subsequent feedings), result in behaviors indicative of inadequate intake, and require nutritional supplementation.[215,296]**

Education and training about the many facets of breastfeeding are essential for medical and nursing staff.* Education about human milk use in the NICU has been shown to change NICU nursing staff's knowledge and attitudes.[30,151,248] Staff attitudes and behaviors are important to breastfeeding families and affect the breastfeeding experience,[35,341] as well as increasing human milk feeding rates.[151,248,302] A multidimensional approach to such education includes providing the staff with manuals, guides, and other educational materials, as well as scheduling routine classes, in-service training, and continuing education workshops. Moreover, professionals with clinical expertise should be identified; these resource personnel can increase the staff's competency in counseling and assisting breastfeeding families. A multidisciplinary quality improvement approach of parent and professional education, a resource team of nurses, and lactation consultation time focused on the VLBW infant resulted in a change of breast milk availability at discharge from 36% to 80%.[35]

Evidence-based protocols addressing breastfeeding can outline a consistent approach for staff and provide resource material that addresses successful strategies for handling common problems. Protocols can also reduce the amount of incorrect information that is disseminated.[295] A number of protocols, including a model hospital policy[341] for managing breastfeeding issues, have been developed by the ABM and are available from their website (www.bfmed.org).

Providing a breastfeeding program for preterm infants that is grounded in evidence-based practices demonstrates strong success.[296,297] The Rush Mother's Milk Club is an evidence-based NICU lactation program in which 98% of mothers provide milk for their infants, even though 50% of these mothers initially intended to breastfeed.[297] Seventy-three percent of mothers of VLBW infants initiated breastfeeding, and breastfeeding outcomes of low-income black mothers were 63%.[297] This program provides assistance to low-income mothers who are a group known to have low breastfeeding rates. Among these mothers, the average amount of human milk provided to VLBW infants exceeded 60 mL/kg/day, and total human milk intake was 71% of total enteral feeding volume.[297] Support groups with mothers who have had similar experiences are helpful in supplementing support obtained from significant others and professionals. Table 18.8 shows evidence-based barriers and facilitators of human milk feedings at and after discharge for VLBW infants.

A study of lactation counseling for mothers of VLBW preterm infants showed that more mothers decided to pump breast milk, mainly because of the health benefits for their infant.[405] In mothers who intended to formula feed, there was an 85% milk expression rate; in mothers intending to breastfeed, the rate was 100%. Black and Hispanic mothers pumped at 95% and 93% rates, respectively. All mothers believed that pumping was worth the effort and appreciated the help they received; none felt more stress or anxiety.

Breast milk is the best milk, especially for a sick or premature infant. By understanding normal lactation, the health care provider can support the breastfeeding dyad when breastfeeding is delayed or disrupted.

*References 10, 73, 120, 130, 134, 151, 248, 295, 345

TABLE 18.8 BARRIERS AND FACILITATORS OF HUMAN MILK FEEDINGS FOR (VLBW) PREMATURE INFANTS AT AND AFTER DISCHARGE FROM NICU: RESEARCH BASIS

BARRIERS	FACILITATORS
Social and Neighborhood Structural Factors: • Black race[366,454] (with limited role models and exposure to breastfeeding)[128] • Perception of breastfeeding support by black mothers from their mothers (i.e., infant's maternal grandmother)[128] • WIC eligibility[128,366] • Previous experience with formula feeding[128] • Presence of additional children in household[128] • Longer LOS[366] • Living in a neighborhood with lower education levels[56,*] and poverty[403] • Travel/distance to NICU[403] • Return to work/school[403,405]	**Social and Neighborhood Structural Factors:** • Older maternal age[128] • Hispanic/Caucasian/Asian ethnicity[128,366] • Married[128] • Higher level of maternal education[182] • Near time of discharge: maternal goal to provide any human milk[128,187] • Female infant[128] • Lack of WIC eligibility[128,366] • Shorter LOS[366] • Living in a highly educated neighborhood[56,*] • Family support[24,403]

Maternal Factors:
Initiating milk expression:
• Pregnancy complications[196,224,296,297,403]
• Anxiety regarding infant's health[403]
• Lack of privacy[403]
• Breast pump dependency: lack of infant nutritive sucking stimuli to breast; dislike and inconvenience[296]
After NICU discharge:
• Difficulty with time management[403]
• Low milk supply[187,296,405]
• Inability to pump as frequently as needed[405]
• Perception that human milk has "done its job" in preventing NICU complications[187]
• Breast pump dependency: dislike and inconvenience[296]
	Maternal Factors:
	• Obstetric factors[466]:
	  • Primiparous
	  • Received ANS
	  • Vaginal, singleton birth
	• Positive attitudes toward pumping[403]
	• Anticipation of breastfeeding[403]
	• Establishing full human milk volume with pumping by 14 days postpartum[297,299]: Three times more likely to provide human milk at discharge[188]

Breastfeeding Programmatic Factors:
• Inconsistent/lack of information about the science of human milk, lactation, and breastfeeding
• Lack of peer counselors who have provided human milk for their VLBW infants in and after the NICU
• Delayed breast pump use,[196,329] long intervals between pumping,[299] fewer pumping episodes (<6 times/day)[196]
• Prolonged hand expression, lack of access to breast pump[257]
• Using manual or small electric breast pumps after NICU discharge[403]
• Lack of evidence-based decisions about the use of donor human milk.[298] Fewer black mothers providing any human milk at discharge when donor milk program introduced[214]
• Lack of developmentally based transitioning to feeding at the breast.
  • Failure to encourage and facilitate early skin-to-skin contact at/shortly after birth
  • Failure to provide taste and smell of mother's own breast milk by oral care with colostrum (see Box 18.3)
• Determining readiness for initiation of oral feedings based on gestational age, postconceptual age, and/or birth weight rather than individual assessment and research evidence in Table 18.5
• Initiating oral enteral feeding by bottle feeding, even if maternal goal is breastfeeding[45]
	Breastfeeding Programmatic Factors:
	• Consistent, information about the science of human milk, lactation, and breastfeeding[24,297]
	• Timely information about the health benefits for the infant so that an informed decision can be made[187,296,303,405]
	• Supportive NICU environment with multidisciplinary lactation teams and rounds[24,35]
	• NICU staff education that increases knowledge of evidence-based practices and influences staff attitudes[35,248]
	• Use of breastfeeding peer counselors[295,374–376]
	• Early (within first hour after birth) breast pump use[329]
	• Use of more physiologic breast pumps[35,292,293,347,358] with pumping intervals of every 2–4 hr (8–12 pumping episodes/day)
	• Use of evidence-based milk expression protocols[222,466]
	• Protection, storage, and safe handling of expressed milk[224,296]; use of donor human milk[466]
	• Use of developmentally based transitioning to feeding at the breast[224]:
	  • Encourage and facilitate skin-to-skin contact with mother at/shortly after birth, if possible[242] (see Table 5.1)
	  • Providing taste and smell of mother's own breast milk by oral care with colostrum (see Box 18.3)
	• Determining readiness to initiate oral feedings by individual assessment based on evidence from research in Table 18.5
	• First enteral feeding is mother's own colostrum/directly suckled from breast, if possible[63,466]

*Not a VLBW premature infant population.

ANS, Antenatal steroids*; LOS,* length of stay; *NICU,* neonatal intensive care unit; *VLBW,* very low birth weight; *WIC,* Women Infants and Children Supplemental Food Program

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19 SKIN AND SKIN CARE

CAROLYN LUND AND DAVID J. DURAND

The skin is a large organ in premature and term infants, comprising at least 13% of body weight in contrast to 3% of the body weight in adults.[77] Skin functions include thermoregulation, barrier against toxins and infections, water and electrolyte excretion, fat storage and insulation, and tactile sensation.

Like many other organs, the skin of a premature infant is immature. The combination of immaturity with the need for intensive care monitoring and procedures places **premature infants at risk for skin trauma and loss of skin integrity. Skin trauma and skin immaturity have serious consequences for infants in the neonatal intensive care unit (NICU), including problems in thermoregulation, fluid and electrolyte balance, diversion of calories for tissue repair, discomfort, potential toxicity from absorbed substances, and increased risk for infection.**

This chapter reviews the physiology of term and premature infants' skin, the differences in structure and function related to skin immaturity, and prevention and treatment strategies to promote optimal skin integrity for infants in the NICU.

PHYSIOLOGY

There are three layers to the skin: the epidermis, the dermis, and the subcutaneous layer (Fig. 19.1). The *epidermis* is comprised of the stratum corneum, a nonliving layer, and the basal layer. The *stratum corneum* is formed of lipids and protein in "brick and mortar" configuration. **The basal layer of the epidermis replaces the stratum corneum with cells called *keratinocytes.*** Approximately every 26 days, keratinocytes migrate from the basal layer to the exfoliated layers of the stratum corneum. In addition to keratinocytes, *melanocytes* are also found in the basal layer.

The *dermis,* a woven layer of collagen and elastin fibers, is 2 to 4 mm thick at birth. It contains nerves, blood vessels, and hair follicles. **Sensations of heat, touch, pressure, and pain originate in the dermal layer. Sebaceous glands and sweat glands are located in the dermis and in the subcutaneous layer of the skin.** Sweat glands become mature in term infants during the first week of life, whereas maturation in premature infants occurs between 21 and 33 days and perhaps even longer in extremely premature infants.

The *subcutaneous layer* is composed of fatty connective tissue, with fat deposition occurring primarily during the last trimester of pregnancy. This layer provides heat insulation and functions as a calorie reservoir.

The skin of a normal term infant is covered with *vernix caseosa,* a "cheesy" substance composed of water (80%), lipids and proteins,[127] sebum from sebaceous glands, broken-off lanugo, and desquamated cells from the amnion. **Vernix production begins at the end of the second trimester, accumulates on fetal skin in a cephalocaudal manner,**[65] and protects the fetus against maceration from the amniotic fluid and chafing caused by crowding in utero. Vernix detaches from fetal skin as the levels of pulmonary surfactant rise, resulting in a progressive increase in the turbidity of the amniotic fluid.[65,100] **Leaving residual vernix intact may be beneficial after delivery, because the presence of vernix produces earlier acidification of the skin, facilitates colonization by normal bacterial flora, and serves as a natural moisturizer for the skin.**[126,127]

BLUE type highlights content that is particularly applicable to clinical settings.

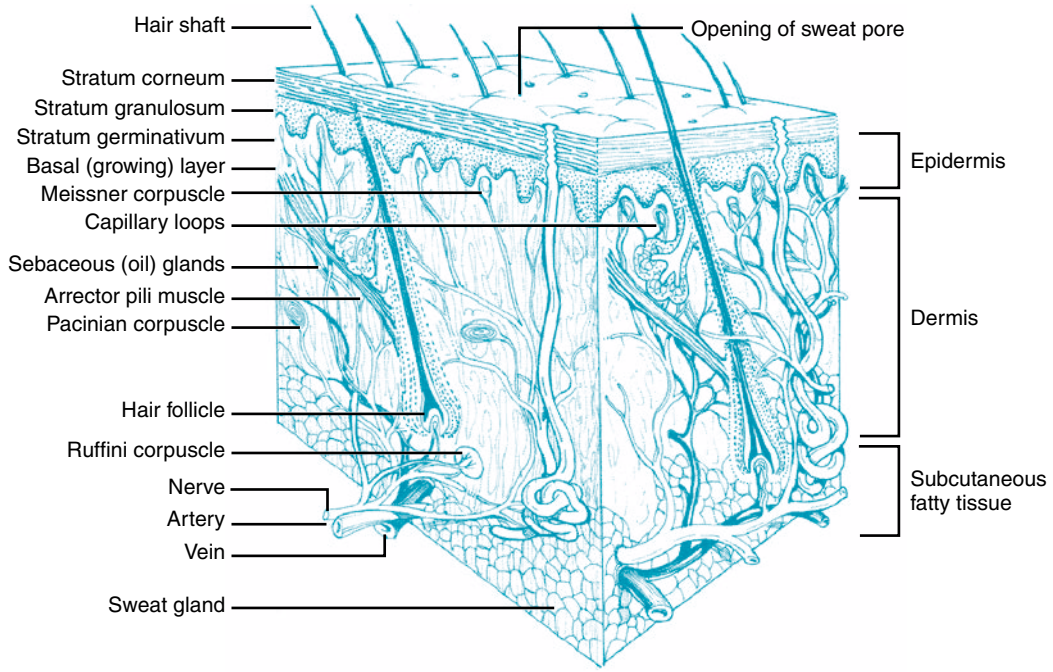

FIGURE 19.1 Cross section of skin layers and anatomic structures. (From Skillman NJ. *Principles of Infant Skin Care.* Skillman, NJ: Johnson & Johnson; 1994.)

The skin of premature infants is thinner than that of term infants and may appear transparent or even gelatinous in extremely immature infants. There is usually a ruddy, red appearance caused by the underdeveloped stratum corneum, making **skin color a poor tool for assessing the oxygenation status of very immature infants.** There are fewer wrinkles on skin surfaces than in term infants, and the skin is covered by lanugo to varying degrees, depending on maturity; these fine hairs cover the upper back, arms, and forehead. The amount of *vernix caseosa* depends on the gestational age at birth. **The subcutaneous layer in premature infants is often edematous because of an excess of cutaneous water and sodium (see Chapter 14).**

ETIOLOGY

Term Newborn Skin Variations

Although the basic skin structures are the same in all term newborns without dermatologic disease, there may be **cutaneous variations seen on physical examination.** These variations (Table 19.1) are not considered pathologic, but it is useful for clinicians to know them, because many parents ask the significance of physical variations as they examine their newborn.

Physiologic and Anatomic Differences in Premature Skin

There are developmental differences in skin physiology and anatomy between skin of full-term and premature infants compared with skin of older children and adults. This section discusses these differences and identifies the implications for care.

UNDERDEVELOPMENT OF THE STRATUM CORNEUM

The *stratum corneum*, the nonliving layer of the epidermis that is responsible for controlling evaporative heat loss and transepidermal water loss (TEWL), contains 10 to 20 layers in adults and term infants. Term infants have been shown to have lower transepidermal water loss than adults,

TABLE 19.1 NORMAL VARIATIONS OF TERM NEWBORN SKIN

VARIATION	DESCRIPTION
Linea nigra	Line of increased pigmentation from umbilicus to genitalia
Mongolian spots	Irregular, blue-gray, bruise-like spots Usually seen over sacrum and buttocks, may extend over back and shoulders Caused by pigmented cells in dermis Most common in infants with darker pigmentation
Lanugo	Fine, downy hair over back, shoulders, and face Shed at 32–36 weeks' gestation
Milia	White, pinhead-size bumps over chin, cheeks, nose, and forehead Tiny epidermal cysts If on palate, called *Epstein pearls*
Miliaria	Caused by retention of sweat from edema in stratum corneum that blocks sweat glands Most common is rubra (prickly pear), but there are also clear versions
Harlequin sign	Color of half of body turns deep red, whereas the other half is pale Caused by immature autoregulation of blood flow
Vernix caseosa	Gray-white, cheesy substance that protects fetal skin in utero Gradually diminishes near term
Cutis marmorata	Mottling caused by vasomotor immaturity
Erythema toxicum neonatorum	Small, firm white or yellow pustules with erythematous margin Most often seen on trunk, arms, and perineal area Benign condition seen in 30%–70% of newborns
Acne neonatorum	Acne-like rash seen in newborns at several weeks of age Caused by stimulation of sebaceous glands by maternal hormones More common in males Instruct caregivers not to use creams, lotions, or ointments because they can worsen the rash
Transient neonatal pustular melanosis	Resembles miliaria but present at birth Most frequently found on face, palms of hands, soles of feet Not infectious or contagious
Café-au-lait spots	Irregularly shaped oval lesions If large size (>4 × >6 cm), or if >6 in number, associated with neurofibromatosis

with the lowest levels seen on the first day of life.[136] Despite reports of normal barrier function at birth, other studies indicate that infant **skin is prone to higher percutaneous absorption and prone to irritant and contact dermatitis,** which has prompted others to maintain that barrier function is not fully developed in the term neonate and young infant.[63,66] **The infant stratum corneum is 30% thinner than adult,** with the overall epidermis 20% to 30% smaller. ***Keratinocyte*** **cells are small, with a higher cell turnover rate that may explain some observations of faster wound healing in infant skin.**[119]

Premature infants have fewer layers of *stratum corneum* depending on their gestational age; at less than 30 weeks' gestation, it may contain only two or three layers (Fig. 19.2), and extremely premature infants of less than 24 weeks' gestation are just beginning to develop the stratum corneum.[62,66] **Another function of the stratum corneum—protection against toxins and infectious agents such as bacteria and viruses—is minimal in premature infants, leaving them vulnerable to percutaneously transmitted infections and toxicity from topically applied substances.**

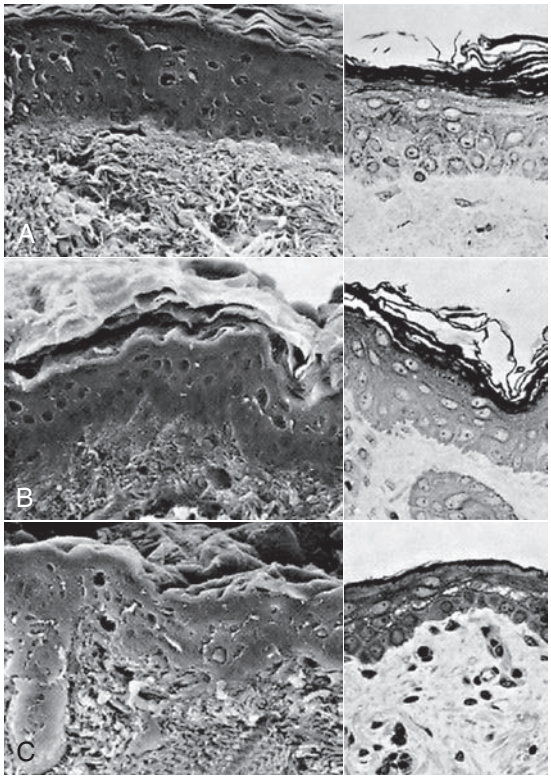

FIGURE 19.2 Photomicrograph of the stratum corneum in an adult **(A)**, a term newborn **(B)**, and a premature infant of 28 weeks' gestation **(C)**. Note fewer layers of stratum corneum in the premature infant. (From Holbrook KA. A histological comparison of infant and adult skin. In: Maibach HI, Boisits EK, eds. *Neonatal Skin: Structure and Function*. New York, NY: Marcel Dekker; 1982.)

The transition from the aquatic, intrauterine environment to the atmospheric, external environment has been thought to result in accelerated maturation of the stratum corneum and more mature function after the first 10 to 14 days of life.[49,63] However, other authors cite **a slower process in premature infants less than 27 weeks' gestation, with rates of TEWL nearly double adult levels even at 28 days of life.[117] Premature infants of 23 to 25 weeks' gestation have losses 10 times higher than term infants initially, and they continue to have elevated heat and water loss resulting from immature barrier function for a longer period.[2]** The maturation process can take as long as 8 weeks in an infant of 23 weeks' gestation.[73]

DERMAL INSTABILITY

The dermis is made of collagen and elastin fibers in a gel matrix, providing mechanical strength, protection, and elasticity to the skin. **The dermis of the term newborn is thinner than the adult dermis and has a higher water content.[67,85]**

Collagen deposition in the dermis increases with advancing gestational age, preventing fluid from accumulating in this layer. **Premature infants have a tendency to become edematous, because they have less collagen and fewer elastin fibers in the dermis.**

Both term and premature infants may be prone to necrotic injury from excessive edema because of alteration in blood flow and perfusion to the epidermis. Edematous infants need protection from pressure and ischemic injury, including routine turning and the use of surfaces to minimize pressure points such as gelled mattresses or pads.[10]

DIMINISHED COHESION BETWEEN EPIDERMIS AND DERMIS

Numerous fibrils connect the epidermis to the dermis at the *dermo-epidermal junction*. These fibrils are more widely spaced and fewer in number in the premature infant[67] (Fig. 19.3) **but become stronger with advancing gestational and postnatal age.** Genetically abnormal fibrils at this junction are found in certain types of the genetic disorder *epidermolysis bullosa,* a blistering skin condition that occurs with even minimal trauma. **Premature infants also are prone to blistering from injury, although this decreases as they mature. Diminished cohesion also places premature infants at risk for injury from adhesive removal. Particularly if extremely aggressive adhesives are used, there may be a stronger bond of the adhesive to the epidermis than of the epidermis to the dermis, and epidermal stripping may result during adhesive removal.[88]**

SKIN pH

The ability of the skin surface to form and maintain an acid surface is a function of various chemical and biologic processes. An acid skin surface with a pH less than 5 has been documented extensively in adults and children.[17] **This *acid mantle* contributes to the stratum corneum's innate immune function by inhibiting the growth of pathogenic microorganisms.[128]**

Term newborns are born with a relatively alkaline skin surface, measuring a mean pH

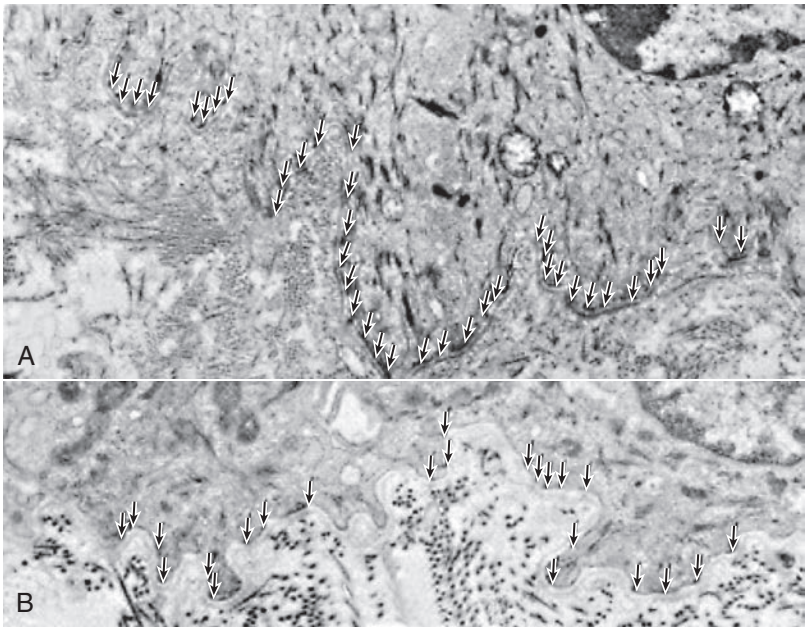

FIGURE 19.3 **A** and **B**, *Arrows* indicate fibrils called *hemidesmosomes,* which anchor the epidermis to the dermis. **B**, They are fewer in number and more widely spaced in the premature infant. (From Holbrook KA. A histological comparison of infant and adult skin. In: Maibach HI, Boisits EK, eds. *Neonatal Skin: Structure and Function.* New York, NY: Marcel Dekker; 1982.)

of 6.34. Within 4 days the pH declines to a mean of 4.95.[17] Skin pH measurements have been reported in **premature infants of varying gestational ages, and the pH was above 6 on the first day, decreasing to 5.5 during the first week, and gradually declining to 5 during the first month.**[51] **Bathing and other skin care practices alter skin pH; it may take an hour or longer to regenerate the acid mantle after bathing with an alkaline soap.** Skin that is occluded by wearing diapers has been shown to have a pH of 6, which is known to be a risk factor in the development of diaper dermatitis.[130] This may occur because an alkaline skin surface may reduce stratum corneum integrity and enhance susceptibility to mechanical damage.[130]

PREVENTION

During daily skin care practices such as bathing, emollient use, antimicrobial skin disinfection, and adhesive removal, the skin of newborns is at risk for trauma or disruption of normal barrier function. This is particularly true of newborns in the NICU, who may have been born prematurely or may be critically ill or require surgery.

This section reviews basic skin care practices in terms of impact on skin integrity, preventing potential toxicity, and reducing exposure to potentially sensitizing chemicals. **Recommendations for preventing trauma, protecting immature barrier function, and promoting skin integrity supported by scientific evidence are presented. These recommendations also are integrated into an evidence-based skin care guideline for health professionals.**[10]

Bathing

Bathing the newborn provides overall hygiene, aesthetics, and protection of health care workers by removing blood and body fluids. However, **bathing during the immediate post-birth period can result in hypothermia, increased oxygen consumption, and respiratory distress.** There remains a debate about when the first bath should be given, and even whether to bathe the newborn at all.[34] The Neonatal Skin Care Evidence-Based Clinical Practice Guideline recommends **giving the**

first bath when thermal and cardiorespiratory stability has been achieved, between 6 and 24 hours of age.[10] The World Health Organization (WHO) recommends delaying the bath for 24 hours, or if this is not possible due to cultural reasons, waiting at least 6 hours in an effort to prevent hypothermia especially in developing countries.[135] However, infants born to a mother who is HIV positive should be bathed as soon as possible after delivery once their temperatures have stabilized.[7]

The first bath may be given by sponge bathing, sitting in a small basin, or an immersion bath in a larger tub. Immersion bathing places the infant's entire body, except the head and neck, into warm water (37.8° to 38.8° C) deep enough to cover the shoulders. Studies including over 1000 full term newborns report that tub or immersion bathing, compared to sponge bathing, maintains temperature better, causes less crying and distress for the infant, and does not result in increased infection, even with the umbilical cord in place.[25,33] A study of 100 late preterm infants (35 to 36⅘ weeks gestation) randomized to immersion tub bathing or sponge bathing after 24 hours of life reported higher temperatures and less variability in body temperature when immersion bathed.[86]

The term "swaddled bath" describes using a cloth wrapped around the baby while lowering them into the tub to provide comfort. A randomized controlled study of providing this support for full term newborns during their first bath found swaddled bathing was more effective in maintaining temperature and other physiologic parameters such as heart rate and oxygen saturation.[26] An additional benefit is that this technique reduces parental stress during bathing.[50]

The Neonatal Skin Care Guideline recommends using warm tap water with or without a mild cleansing bar or liquid cleanser that has a neutral or slightly acidic pH to assist in the removal of blood and meconium, as water alone may not easily remove some lipid-soluble substances such as meconium. For premature infants <32 weeks, warm water only during the first week of life is the recommendation.[10]

Leaving residual vernix caseosa on the skin is important, as vernix facilitates skin adaptation including skin hydration and the formation of the acid mantle of the skin surface.[127] WHO guidelines for newborn care recommends leaving vernix intact for at least 6 hours.[126,135]

Once the acid mantle is established, bathing can alter the skin pH for a period of time, even with water alone, in older infants.[57] Bathing two to three times per week with cleansing products compared to water alone has been shown to have little or no difference on skin pH, TEWL, and stratum corneum hydration (SCH) in the neonatal period in full-term healthy infants.[45,55,82] Similar studies involving measuring skin parameters have not been performed in hospitalized neonates or in premature infants. The recommendation is to select cleansers that have neutral or mildly acidic pH (5.5 to 7.0) and to bathe the infant no more than every other day.[10]

The effects of bathing on skin parameters in small premature infants have not been studied to date. In an effort to reduce alterations in skin pH, dryness, and irritation in premature infants less than 32 weeks, cleanse with warm water baths during the first week using soft cotton cloths, cotton balls, or the caregiver's hands.[10] Skin colonization with bacteria does not increase with bathing as infrequently as every 4 days.[109] Less frequent bathing may offer other advantages for premature infants, who have demonstrated physiologic and behavioral disruptions during sponge baths.[106] Immersion bathing, even of stable infants on ventilators or nasal continuous positive airway pressure (CPAP), may be soothing and less stressful.[4]

Emollients

The skin surface of term newborns is drier than that of adults but becomes gradually better hydrated as the eccrine sweat glands mature during the first year of life.[113] Maintaining the hydration of the ***stratum corneum*** is necessary for an intact skin surface and normal barrier function. Skin that is dry, scaly, or cracking not only is uncomfortable but can also be a portal of entry for microorganisms. Products used to counteract dryness are called moisturizers, emollients, or lubricants. Common emollients include mineral oil, petrolatum, and lanolin and its derivatives. Emollients are sometimes divided into oil-in-water or water-in-oil emulsions. Emollient use to prevent dermatitis and improve skin integrity has been studied in several randomized, controlled trials in premature infants.

In one report, premature infants of 29 to 36 weeks' gestation were treated with Eucerin cream daily and had less dermatitis as measured by a visual grading scale but no differences in direct measurements of TEWL with an evaporimeter.[80] In a later study, **premature infants of both lower gestational and younger postnatal age were treated with Aquaphor ointment, a water-miscible oil-in-water preparation that contains neither dyes nor perfumes.** In this study there was improvement in both TEWL and visual scale dermatitis. **No increases in skin surface temperatures or thermal burns were seen, even when the emollient was applied to infants under radiant heaters or phototherapy lights.** In addition, **cutaneous cultures revealed no increase in bacterial or fungal colonization on skin treated with emollients.** It was noted that a smaller number of treated infants had positive blood or cerebrospinal fluid culture results compared with control subjects, although the study was not large enough to prove this effect.[102]

A large, randomized controlled trial of 1191 infants with birth weights of 501 to 1000 g was conducted to determine whether **twice-daily application of Aquaphor ointment would reduce combined outcome measures of mortality and sepsis. Although skin integrity appeared improved with routine emollient use, no effect was seen in the outcomes of sepsis plus mortality.** Of note, an **increase in coagulase-negative *Staphylococcus epidermidis* bloodstream infections was seen in infants with birth weights below 750 g, although the mechanism and relationship to emollient use are not clearly understood.**[47] **Several other studies have not reported higher infection rates when comparing emollient therapy with no treatment**[16,75] **and report benefits in fluid and electrolyte balance, as well as less dermatitis.**

A *Cochrane* review evaluated randomized controlled trials of emollient use in the NICU and concluded that the prophylactic application of topical ointment increases the risk of coagulase-negative *Staphylococcus* infection and other nosocomial infections. **The routine use of emollients in preterm infants is not recommended.**[35]

The benefits of emollient use in premature infants must be carefully weighed against the risk of infection. In general, emollients can be safely used in this population to treat skin with excessive drying, skin cracking, and fissures. They may also be beneficial in reducing TEWL and evaporative heat loss, although methods such as using a high-humidity environment are also available for this purpose. **Small tubes or jars for single patient use are recommended to prevent contamination with microorganisms.**

There is little consensus to date about the routine use of emollients for full-term newborns.[71] One study reports improved skin parameters in healthy full term infants when the skin care regime included a "baby cream" emollient after bathing and did not adversely affect bacterial skin colonization.[55] Some studies report a **decreased risk of developing atopic dermatitis in infants with a strong family history of this disorder with daily use of emollients in infancy**, so the routine use of emollients may be indicated in this population.[68]

Skin Disinfectants

Use of skin disinfectants prior to invasive procedures such as inserting intravenous lines, venipuncture, arterial puncture, umbilical catheter placement, and chest tube placement is common practice in neonatal nurseries. **Concerns with disinfection practices include the effects of absorption of disinfectants and skin injury resulting from topical skin preparation with these agents, which must be weighed against their effectiveness in preventing infection.**

Disinfectants that are used in newborns include 70% isopropyl alcohol (IA), 10% povidone-iodine (PI), and chlorhexidine gluconate (CHG), in varying concentrations as both an aqueous solution and one combined with 70% isopropyl alcohol (CHG/IA). It is widely accepted that **CHG-containing formulations are the most effective for skin disinfection in children and adults for central venous catheter insertion and dressing changes, and their use is recommended as best practice in several guidelines.**[30,95] However, there are **no studies in neonates that have confirmed the superior efficacy of CHG preparations over other disinfectants, such as PI, in the prevention of bloodstream infection.**[107,115] Therefore, **Centers for Disease Control and Prevention (CDC) guidelines have maintained that there is insufficient evidence to make a recommendation about the safety or efficacy of CHG products in infants younger than 2 months of age.**[29]

Use of 0.5% CHG in isopropyl alcohol reduces peripheral IV catheter colonization in premature and term newborns compared with use of povidone-iodine.[53] A randomized controlled trial (RCT) of 344 infants admitted to the NICU and special care nursery (SCN) settings showed significantly fewer blood-culture contaminants in infants having skin disinfection with 1% aqueous CHG compared with those using 10% PI.[103]

A sequential study reported that the rate of positive blood cultures (the number of true infections) or contaminated cultures during the time when 10% PI was used in this NICU was not statistically different from a subsequent period when 0.5% CHG/IA was used.[83] A pilot trial of 47 infants who weighed more than 1500 g and were older than 7 days of age evaluated cutaneous tolerance of 2% CHG/IA compared with 10% PI for peripherally inserted central venous catheter (PICC) placement. There were no differences in the number of bloodstream infections or sepsis evaluations between the two groups, but this pilot study was not powered to look at bloodstream infection rates.[54] An RCT of 304 preterm infants compared 2% CHG/IA to 10% PI for insertion of 815 central venous catheters and reported no difference between the proportion of catheter-related bloodstream infections between the two disinfectants, although more infants in the PI group had thyroid dysfunction. The authors acknowledged that the study was not adequately powered to detect differences in actual numbers of catheter-related bloodstream infections and that a larger study is needed.[76]

TOXICITY FROM SKIN DISINFECTANTS

If absorbed through the skin, PI has been shown to alter thyroid function in premature newborns. A systematic review of 15 articles reported evidence of thyroid dysfunction in premature infants exposed to iodine-containing disinfectants, with incidence ranging from 12 to 33 cases per 100 infants. The review also found no long-term neurodevelopmental studies that cited harm from exposure to iodine-containing solutions, and although the researchers recommended restricting iodine-containing solutions in premature infants, more research is needed.[3]

Systemic toxicity from percutaneous absorption of CHG in neonates has been raised as a concern. A small study of CHG antisepsis for PICC placement and subsequent dressing changes in premature infants who weighed more than 1500 g found measurable concentrations of CHG, ranging from 13 to 100 mcg/mL, in 7 of the 10 infants who had levels drawn. However, there were no reported systemic side effects. **The role of IA in combination with CHG may be a possible contributing factor to cutaneous absorption of CHG.**[54] Another study involving 20 premature infants with a median gestational age of 28 weeks had an extremity disinfected with 2% aqueous CHG prior to insertion of a PICC. Ten infants had detectable serum CHG levels ranging from 1.6 to 206 mcg/mL, with the highest levels occurring 2 to 3 days after initial exposure.[32]

Past reports of neurotoxicity from exposure to hexachlorophene bathing[9,28] have **prompted research on the potential neurotoxicity from systemic absorption of CHG.** An in vitro model of neurite cells was exposed to CHG levels comparable to the highest levels reported in premature infants. CHG inhibited L1-mediated neurite growth, and researchers concluded that it is important to determine whether the blood–brain barrier is permeable to CHG in premature infants.[97]

There is interest in using CHG to decrease infection in adult and pediatric ICU patients and patients with central venous catheters with daily wiping of skin surfaces with CHG.[97] A study was undertaken in a NICU population using 2% CHG-impregnated wipes in a quasi-experimental design, comparing the treated infants to a historical cohort.The algorithm for wiping the skin with CHG determined the frequency based on postnatal age and weight. A decrease in central line–associated bloodstream infections was reported, but infants weighing less than 1000 g and younger than 28 days were excluded from CHG bathing. Serum CHG levels were not obtained.[108]

Numerous case reports document chemical burns in premature infants from disinfectants containing CHG; these include various concentrations of CHG, both aqueous and alcohol preparations.* There have also been reports of chemical burns from IA and PI solutions in extremely-low-birthweight (ELBW) infants.[114] Fig. 19.4 shows skin injury resulting from skin disinfectant.

The United Kingdom Medicines and Healthcare Products Regulatory Agency published a review of 44 case reports of chemical burns after the

*References 23, 79, 81, 93, 101, 110.

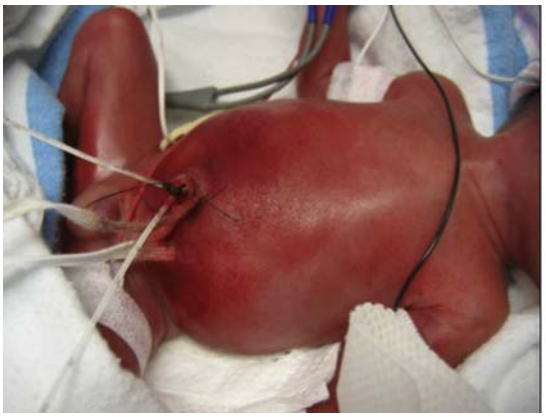

FIGURE 19.4 Skin injury resulting from skin disinfectant.

application of aqueous or alcohol-based CHG solutions. **Most burns occurred in premature infants younger than 26 weeks of gestation or those who weighed less than 1000 g with long-term sequelae in some infants, to include scarring, discoloration, and keloid formation.**[19] Because of these concerns, **safety labeling in the United States and Europe continues to state the potential for chemical burns from CHG solutions used for skin disinfection in premature infants.**[105,124]

Several studies have been undertaken to determine how CHG affects skin integrity. A prospective study of 40 infants with a mean gestational age of 32 weeks (range of 23 to 39 weeks) found that the use of 2% CHG/IA for PICC insertion and weekly dressing changes compromised skin-barrier function, which was measured by elevated TEWL, an increase in erythema, and dryness.[125] A pilot trial comparing **2% CHG/IA in 47 premature infants weighing more than 1500 g and older than 7 days of age found no increase in skin redness or breakdown when CHG was used for PICC insertion and weekly dressing changes and only one incidence of erythema in a newborn treated with PI.**[54]

The selection of appropriate disinfectants in neonates remains a dilemma, particularly for extremely premature infants during the first weeks of life. CHG products in the United States are limited to a 2% aqueous surgical scrub solution available only in 4 ounce bottles, and a 2% and 3.15% chlorhexidine solution in 70% isopropyl alcohol available in single-use packaging. **The U.S. Food and Drug Administration states that chlorhexidine-containing disinfectants should be used with care in premature infants or infants less than 2 months of age, as these may cause skin irritation and chemical burns.**[124] **PI continues to be used in many nurseries to avoid the above complications, although the issues of thyroid toxicity remain a concern.**

Although removal of disinfectants with sterile water or saline after a completed procedure is advocated,[10] **the manufacturer of the 2% CHG/IA product advises that removal not be attempted, as the residual effect of the disinfectant on the skin may be beneficial.** However, it is not known whether this feature may contribute to skin irritancy and absorption of CHG in newborns and premature infants.

CHG should not be used as preoperative skin disinfection on the face or head because misuse has been reported to result in injury if it remains in contact with either the eye or ear during surgical procedures. However, **careful use before scalp intravenous or central-line insertion is acceptable, providing that splashing or using excessive amounts of chlorhexidine is avoided.** In addition, there is no clinical data to discourage the use of chlorhexidine gluconate products prior to lumbar puncture or epidural catheter placement, as this is considered skin antisepsis.[98]

UMBILICAL CORD CARE

The use of antibiotic ointments and skin antiseptics to the umbilical cord can prolong the time to cord separation and has no beneficial effect on the frequency of infection.[138] Although the umbilicus is a possible route for infection by invasive pathogenic microorganisms until healed, **the evidence suggests that dry cord care, defined as keeping the cord clean and leaving it exposed to air or loosely covered by a clean cloth, is effective for infants born in high-resource countries.**[120]

For newborns born in health facilities, dry cord care is recommended as evidence-based practice. A cluster RCT in France, involving over 8000 near-term and term newborns found dry cord care was not inferior to antiseptic cord care in preventing omphalitis.[60] A group of 150 consecutively born, healthy, late-preterm and term infants born in a hospital setting in Taiwan (high humidity, subtropical country) were randomized to alcohol or dry cord care. **Cord separation time was significantly**

decreased for those infants having dry cord care compared with those cleansed with 95% isopropyl alcohol, and the incidence of cord infection was not increased.[69] A meta-analysis showed the use of topical isopropyl alcohol was not superior to dry cord care in reducing the incidence of omphalitits.[70]

Recommendations for umbilical cord care include washing hands before handling the cord, and, if the cord becomes soiled with urine or stool, cleansing with water, drying with absorbent gauze, and keeping the diaper folded down and away from the umbilical stump to prevent contamination.[10] The development of omphalitis is not necessarily related to cord disinfection, because it also occurs in infants who have received topical disinfectants. **Vigilant attention to the signs and symptoms of omphalitis is necessary by health professionals. Parents need guidance about how to manage the umbilical cord and when to consult their health care provider.[46]**

Medical Adhesives

Hospitalized newborns often require medical adhesives to secure life support and monitoring equipment such as endotracheal tubes, intravenous devices, oxygen saturation sensors, and electrodes. Categories of medical adhesives include acrylates, hydrocolloids, hydrogels, and silicone-based adhesives.[88]

Acrylate-based adhesives include products such as paper, plastic, and soft cloth tape. Adherence of these tapes increases over time, and they may leave a residue on the skin after removal.[96] **These acrylate adhesive tapes adhere well to both skin and medical devices and are often selected for use in intensive care settings.** Acrylate adhesives are also found on polyurethane films, such as transparent adhesive dressings. These allow visualization of catheter insertions sites and are permeable to water vapor, oxygen, and carbon dioxide, allowing the skin to breathe.[41]

Hydrocolloid adhesives are used to protect peristomal skin for ostomy patients and are also a wound dressing. Because **hydrocolloids absorb moisture and mold well to skin surfaces, they are used as a platform between skin and acrylate tapes and transparent dressings.[20,104]** In some cases hydrocolloids are integrated into products such as endotracheal tube securement devices. Hydrocolloids cause skin trauma that is equal to acrylate tape when removed at 24 hours.[89] Decreased skin-barrier function and erythema under hydrocolloid adhesives has also been found.[137] A comparison of transparent dressing placed directly on the skin versus a transparent dressing place over a hydrocolloid base found no statistically significant quantitative difference.[20] However nurses participating in the study preferred transparent dressings placed over a hydrocolloid base as a more effective adhesive and a belief that it was gentle for the skin.

Hydrogel adhesives are found in some products such as EKG electrodes, temperature probe covers, and in dressings for wounds where they may have a cooling or analgesic effect on damaged skin. Hydrogel adhesives have been shown to reduce the trauma associated with electrode removal.[41,89] However, adherence is not adequate to secure critical lines and tubes, nor do they adhere well in humidified incubators.

Silicone-based adhesive products adhere well to skin with minimal discomfort when removed. These adhesives hold promise for developing products that adhere and cause minimal skin trauma such as erythema, skin stripping, and keratin loss, compared with acrylate-based paper tapes when removed from the skin of pediatric patients.[61] However, silicone adhesives do not adhere well to plastic devices, such as nasogastric tubes and cannulas, which limits their use. **Dressings with silicone adhesive borders can be lifted up and replaced for wound assessment.** Silicone tapes can be used to secure brain-monitoring electrodes because they adhere well to hair and can be removed with minimal discomfort.

Newborns are at high risk for medical adhesive related skin injury (MARSI), a term first used in a consensus paper involving a number of different health providers.[96] **Types of MARSI include skin stripping, skin tears, and contact and allergic dermatitis.** In an evidence-based practice project for the Neonatal Skin Care Guideline that included skin assessments for 2820 premature and full-term newborns, **adhesives were the primary cause of skin breakdown.[90] Functional changes in premature skin, including altered skin barrier function (measured as increases in TEWL), are seen after one application/removal of adhesive tape in premature infants,[63,89]** compared to similar results

after 10 consecutive applications and removals in adults.[84]

Topical skin protectants, wiped on prior to attaching adhesives, protect the skin from adhesives as well as fecal and ostomy output and urine. Silicone-based skin barrier films do not sting when applied, rapidly evaporate, do not leave a residue, reduce TEWL, and provide skin protection.[22] Additional research on skin protectants is warranted in a larger ELBW population.

Removal of medical adhesives can result in skin stripping and pain. A technique involving slowly pulling adhesives at a very low angle parallel to the skin surface while holding the surrounding skin in place may reduce epidermal stripping.[91,96] **Adhesive removers aid in the removal of medical adhesives. Three categories of adhesive removers: include alcohol–organic-based solvents, oil-based solvents, and silicone-based removers.**[36] **Removers containing solvents such as hydrocarbon derivatives, petrolatum distillates, or isopropyl alcohol carry the potential of systemic and topical toxicities.** A case report of a premature infant developing a severe dermatologic reaction (i.e., blistering and hemorrhage) to an adhesive remover led to concerns about safety with these products in the NICU population.[72] **Oil-based solvents based on paraffin or citrus oil extracts release the bond between skin and adhesive. However, they leave a residue that prevents adherence during reapplication of adhesives to the site where they were previously applied.**

Silicone-based removers effectively assist in removal of adhesives. These evaporate readily after application without drying of the skin and are less likely to leave a residue. Silicone-based removers are available in spray, liquid, lotion, or wipe formulations.[36] The safety and effectiveness of silicone-based removers in the neonatal population has been described, including infants with epidermolysis bullosa.[37,43]

DATA COLLECTION

History

The gestational age and postnatal age of neonates in the NICU are both important considerations for determining appropriate skin care practices. Premature infants of lower gestational ages have underdeveloped skin layers and function. With advancing postnatal age and maturation there is improved skin integrity and skin barrier function.

Reviewing the maternal history for any dermatologic diseases is also important. **Many of the most severe skin diseases, such as forms of *congenital ichthyosis* or *epidermolysis bullosa,* are inherited disorders.** A positive family history alerts the clinician to the potential for developing these rare disorders.

Signs and Symptoms

A thorough daily examination of all skin surfaces reveals the state of skin integrity for neonates in the NICU. Early signs such as skin abrasions or small excoriations may call for either diagnostic or treatment procedures. **A scoring tool such as the *Neonatal Skin Condition Score* (NSCS)** (Box 19.1), used in the Association of Women's Health, Obstetric, and Neonatal Nurses (AWHONN)/National Association of Neonatal Nurses (NANN) research-based practice project,[90] **has been extensively used in both premature and full-term infants, with validity and reliability established.**[92] **This scoring system can be integrated into skin care protocols to identify neonates with excessive dryness, erythema, or skin breakdown.**[10] Risk factors for skin injury in individual patients are listed in Box 19.2. **In the first week of life in ELBW infants (<30 weeks, <1000 g), there may be problems with thermoregulation (see Chapter 6) and dehydration (see Chapter 14) because of the large evaporative heat losses and transepidermal water losses through the immature stratum corneum.**

The Braden Q and Starkid Scales assess risk for pressure sores.[39] However, in these studies the number of neonates is unknown, so the applicability of these tools to a NICU population is undetermined. The Braden QD was developed to predict hospital-acquired pressure injuries (HAPI) in pediatric patients, including those caused by both immobility and medical devices.[40] The Braden QD evaluates for intensity and duration of pressure based on the patient's mobility and sensory perception. However, there is no scoring for prematurity or gestational age, both important aspects of skin tolerance in NICU patients, so how helpful it is to use the Braden QD in NICU patients is questionable. It is also important to recognize that risk assessment is

BOX 19.1 THE NEONATAL SKIN CONDITION SCORE

Dryness
1 = Normal, no sign of dry skin
2 = Dry skin, visible scaling
3 = Very dry skin, cracking/fissures

Erythema
1 = No evidence of erythema
2 = Visible erythema <50% body surface
3 = Visible erythema >50% body surface

Breakdown
1 = None evident
2 = Small localized areas
3 = Extensive

Note: Perfect score = 3; worst score = 9.
From Lund C, Osborne J, Kuller J, et al. Neonatal skin care: clinical outcomes of the AWHONN/NANN evidence-based clinical practice guideline. *J Obstet Gynecol Neonatal Nurs.* 2001;30:41.

BOX 19.2 RISK FACTORS FOR SKIN INJURY

- Gestational age <32 weeks
- Edema
- Use of paralytic agents and vasopressors
- Multiple tubes and lines
- Numerous monitors
- Surgical wounds
- Ostomies
- Technologies that limit movement: high ventilation, extracorporeal membrane oxygenator
- Respiratory device interfaces, such as nasal continuous positive airway pressure

not the same as skin assessment, and careful observation and documentation of the skin condition is an essential component of skin care in NICU patients.

Laboratory Data

With the many skin excoriations in both small and large neonates that result from traumatic events such as adhesive removal or pressure necrosis, there is the potential for infection through this portal of entry in the skin. In VLBW infants it may be useful to obtain a skin culture, Gram stain, or potassium hydroxide preparation[14] for early detection of microorganisms that can lead to systemic illness in these immunocompromised patients. **A skin surface culture is helpful if the skin breakdown cannot be traced to a traumatic injury, because the origin of the breakdown often is linked to infection, especially with fungal infections**[112] or *staphylococcal scalded skin syndrome.* **A more comprehensive workup for infection may be indicated if there is evidence of clinical deterioration in infants with extensive skin breakdown (see Chapter 22).** If the culture is positive for a candidiasis species, antifungal ointment and systemic treatment with fluconazole or amphotericin may prevent devastating disseminated disease.[18,74] Although fungal causes are sometimes suspected, other microorganisms such as *Staphylococcus aureus* species, *E. coli,* and other gram-negative bacteria have been cultured in extremely premature infants. The knowledge of their skin colonization may be very useful in guiding systemic treatment should their clinical condition worsen, suggesting systemic disease including sepsis.

TREATMENT

Skin Injuries

Although little clinical research is available to guide selection of topical agents and products to treat skin injuries in neonates, there are several principles to help inform practitioners. **These include the concept of moist wound healing, gentle cleansing, and understanding the proper application of appropriate dressings.**[38]

Ointments are sometimes used on skin injuries because of their antibacterial or antifungal properties. Petrolatum-based emollients and ointments are used to cover wounds and provide a semi-occlusive layer that facilitates the migration of epithelial cells across the surface and may actually become part of the stratum corneum layer during the healing process. Antibacterial ointments such as Polysporin, Bacitracin, or Bactroban are useful to treat gram-positive colonized surfaces but can actually promote the growth of gram-negative organisms.[118] Many dermatologists recommend against the use of Neosporin because of the potential for developing later sensitization to

this ointment, although sensitization to Bacitracin is also being reported with increasing frequency.[94] **If fungal infection is suspected, nystatin ointment is used and can also be applied to surrounding intact skin to prevent extension of the infection.** In general, ointments are preferable to creams in this application because of better adherence and healing properties.

Gentle cleansing of the skin injury or wound removes debris and exudate, thus promoting a clean wound bed. The presence of debris, exudate, or necrotic tissue impedes wound healing, while their removal reduces the level of bacterial contamination.[38] **Wound cleansing is best accomplished by gentle irrigation with normal saline, either diluted or undiluted, using a 20 to 60 mL syringe and a blunt intravenous catheter.**[10] **The use of antiseptic solutions and cleansers are to be avoided, as these can cause further injury to delicate healing tissue and may delay healing.**[111,134]

Dressings for wound care and for skin injury should be occlusive and nonadherent to promote moist healing and facilitate the migration of epithelial cells. These include silicone dressings, hydrocolloid dressings, hydrogel dressings, transparent dressings, and dressings made of foam or other composite materials. In addition, some dressings may be impregnated with silver ions that may bestow potential benefit due to their anti-infective properties.[52] Although use of silver-containing creams and dressings were initially avoided because of concerns about toxicity, **recent research demonstrates safe uses of silver-containing agents in neonates.**[12,121]

Medical grade honey, both as an ointment or in a dressing, has also been used in neonatal skin injuries. Benefits of medical grade honey include that it (1) facilitates debridement,[6] (2) has anti-infective properties, and (3) facilitates the moist healing cascade.[5] Several case studies report positive results using medical grade honey in premature infants.[21,48,99]

Surgical wounds that open or dehisce are infrequent but require expert wound management. Nutrition is often a part of the process in promoting wound healing, as is the prevention of infection.[56] Often the surgeon or a wound/ostomy specialist designs an appropriate wound management program for individual situations.

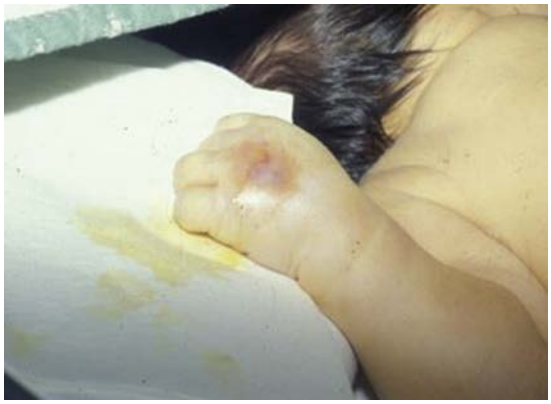

FIGURE 19.5 IV extravasation injury with swelling, discoloration, and leaking of fluid.

Intravenous Extravasations

The extravasation of intravenous fluids and medications can result in skin injury and in some cases deep-tissue injury to muscle and nerves (Fig. 19.5). Newborns are more susceptible to extravasation injuries because of their immature skin, lack of subcutaneous tissue, and the small size of their blood vessels.[8] Extravasation injuries are iatrogenic complications that can lead to pain, prolonged hospitalization, and increased morbidity, such as infection. Extravasation injuries can also result in increased hospital costs and the potential for legal action.

Prevention includes meticulous monitoring of intravenous sites, low threshold for removing IV catheters when suspicious, and immediate interventions that reduce the extent of tissue injury. Some of the risk factors for tissue injury from intravenous extravasations in NICU patients are listed in Box 19.3.

Hourly assessment of the IV insertion site is recommended with more frequent assessments during administration of certain medications. Although an infusion pump can indicate increasing pressure, these are not sensitive enough to detect infiltration of fluid into the tissue and should not be relied on as an infiltration detection device.[8,123] Quality-improvement efforts involving standardizing assessment strategies are beneficial, such as "Touch, Look, Compare" and "Assess, Compare, Touch."[123,133] In one NICU standardizing IV site assessment, along with review

BOX 19.3 RISKS FOR TISSUE INJURY FROM IV EXTRAVASATION

- Length of exposure to extravasation fluid, medication
- Nature of extravasation fluid(s), medication(s):
  - Hypertonic solutions containing high concentrations of calcium, potassium, glucose or amino acids, such as total parenteral nutrition, glucose concentrations of >10%
  - Medications with vesicant properties such vancomycin, nafcillin, calcium chloride/gluconate, acyclovir, phenobarbital, potassium, phenytoin, digoxin, dopamine, dobutamine, epinephrine, etc.
- Mechanical compression caused by electronic infusion pumps

of factors such as catheter type, securement method, and daily review of catheter necessity, resulted in a reduction in infiltrations rates over a 6-month period.[131] **"When in Doubt, Pull the Catheter Out" using an evidence-based protocol to prevent infiltration, which includes standardized IV assessments, staging of infiltration, and an algorithm for evaluation and treatment which contains wound care recommendations has been published.**[44]

Prevention of more extensive tissue injury after infiltration is an important consideration. The insertion site should be clearly visible with appropriate documentation *every* hour. Medical adhesive tape should be carefully placed on the extremity to avoid obstruction of venous return. Tape placed loosely over a bony prominence, such as the knee or elbow, allows extravasated fluids and medications to disperse over a larger surface area and thus reduce the risk of injury, compared with extravasation that is limited to a small surface area. In some NICUs, taping strategies are used that do not involve securing the limb to an IV board, which avoids this problem. Avoiding extremities with poor perfusion in favor of better-perfused scalp veins (except, of course, those on the forehead) may also be prudent. **Using central venous lines such as peripherally inserted central catheters to infuse highly irritating solutions and medications is also recommended.**

Risk factors for extravasation include the type of fluid that is being infused, its chemical properties, osmolality, and pH.[59] Normal serum osmolality is 280 to 295 mOsm/kg, and solutions that exceed this are considered hypertonic. Solutions that are infusing through a peripheral vein in a neonate should stay within this range.[44] Glucose concentrations higher than 12.5% are at risk for extravasation injury.[132] Some medications can be both hyperosmolar and irritating due to pH extremes. **Vesicants are very irritating medications and solutions and should be either avoided or carefully watched during infusion. Posting a chart listing vesicant solutions and medications is helpful for caregivers who prescribe and administer neonatal medications, as well as identifying neonates who would benefit from central venous access.**[59]

Once an IV extravasation occurs, immediate measures to reduce injury are instituted.[44] **The device should be carefully removed, and the extremity elevated (if it is an arm or leg). Treatment with heat or moisture is not recommended because the compromised tissue could be further injured by a burn or the effects of maceration. Making multiple puncture holes over the area of greatest swelling and squeezing to allow the fluid to leak out of the tissue releases the infiltrated fluid and can potentially prevent skin injury.**[31,116] **Saline washout has also been described,**[78] **although no randomized trial has been published to compare efficacy.**[58]

Hyaluronidase is an enzyme that facilitates diffusion of the extravasated fluids by temporarily dissolving the normal interstitial barriers decreasing tissue damage and injury following extravasation.[15,44] **A dose of 15 to 20 units is administered in five subcutaneous injections around the periphery of the extravasation**[44] and may be repeated (Figs. 19.6 and 19.7). Keeping the site moist for several hours using a hydrogel product or moist compresses may also be beneficial.

If tissue damage results despite the immediate care measures, the use of topical wound care treatments are necessary. In the most severe cases of deep-tissue necrosis after extravasation injury, a surgical or plastic surgery consultation may be necessary.

Diaper Dermatitis

A common skin disruption that occurs in neonates and infants is *diaper dermatitis* (diaper rash). This term encompasses a range of processes that affect the perineum, groin, thighs, buttocks, and anal area of infants who are incontinent and wear some covering to collect urine and feces. **Diaper dermatitis**

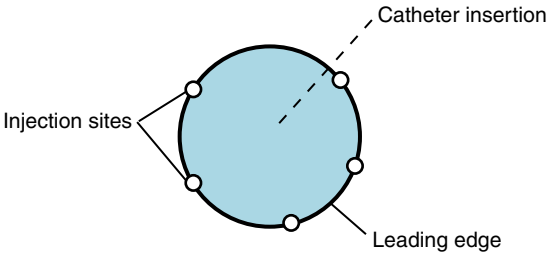

FIGURE 19.6 Technique for administration of hyaluronidase and/or phentolamine. A total volume of 1 mL is administered at five sites subcutaneously (0.2 mL each) around the periphery of the intravenous extravasation.

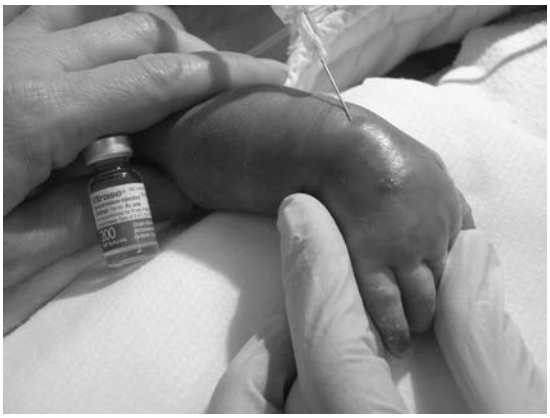

FIGURE 19.7 Hyaluronidase (Vitrase) being administered to extravasation in hand using 27-gauge needle.

can be caused by many different mechanisms, but the condition of the skin has a direct role in the progression of skin injury. Review articles provide an excellent background for current evidence-based care in the prevention of and treatment for diaper dermatitis.[1,64]

The pathogenesis of diaper dermatitis is partly related to the degree of wetness of the skin. **Skin that is moist and macerated becomes more permeable and susceptible to injury because wetness increases friction. In addition, moisture-laden skin is more likely to contain microorganisms than dry skin.**

Another component in the process of skin injury from diaper dermatitis is the effect of an alkaline pH. **Normal skin pH is acidic—ranging between 4.0 and 5.5—but can become alkaline when it is diapered.[130] The increased pH of the skin increases its vulnerability to injury and penetration by microorganisms and stimulates fecal enzyme activity.** Specifically, both protease and lipase in stool can injure the skin, which is made up of protein and fat components. These enzymes can quickly cause significant injury to the epidermis and are responsible for the contact irritant diaper dermatitis that is commonly seen.

Strategies for preventing diaper dermatitis include maintaining a skin surface that is dry and has a normal (acidic) skin pH. Frequent diaper changes are recommended, especially in the newborn period. Insufficient evidence exists to support any specific type of diaper for preventing diaper dermatitis.[13] **However, superabsorbent gelled diapers with breathable covers have been shown to keep skin surfaces dryer by "wicking" the moisture away from the skin and separating urine from feces.[27,42] Use of powders is discouraged because of the risk of inhalation of particles into the respiratory tract.**

After skin injury from diaper dermatitis has occurred, protecting injured skin to prevent reinjury is the primary goal of treatment. Topical treatment for diaper dermatitis involves ointments and creams containing a variety of ingredients. Most contain zinc oxide and petrolatum and are generally similar in composition.[64,129] **Generous application of protective skin barriers that contain zinc oxide can prevent further injury while allowing skin to heal. Once skin excoriations occur, keeping skin open to air may not be effective, because the already impaired tissue may be reinjured with fecal contact, and dryness is counterproductive to healing. It is not necessary or desirable to completely remove skin barrier products with diaper changes, because this may disrupt healing tissue. Instead, remove as much waste material as possible and reapply the barrier generously to the affected areas with each diaper change.** Another class of barrier products are *semipermeable barrier films,* **designed to repel moisture and protect the skin from irritants.[64,129]** Although these products are FDA approved for use in infants older than 30 days of age, they can be used "off label" and have been beneficial for neonatal ostomy care.[122]

If *Candida albicans* is involved in the diaper dermatitis, it is necessary to use an antifungal ointment or cream (Fig. 19.8). Antifungal preparations include Mycostatin, miconazole, clotrimazole, and ketoconazole in ointment or cream forms; ointments are preferable to coat the skin and repel moisture. If the dermatitis is

both fungal and a contact irritant dermatitis, it may be necessary to layer the ointment with the antifungal preparation: (1) Mycostatin powder is used, (2) followed by an application of alcohol-free skin protectant to seal the powder onto the skin surface, and (3) a generous application of a skin barrier cream is then done, such as zinc oxide or pectin paste.

Occasionally infants may experience extremely severe diaper dermatitis from intestinal malabsorption syndromes or if there is constant dribbling of stool (i.e., decreased or lack of rectal innervation [myelomeningocele, bladder exstrophy, or following a "pull-through" procedure for Hirschsprung disease]). With malabsorption, stool not only is more frequent but also may have a high pH because of rapid transit through the small intestine resulting in significant amounts of undigested carbohydrates and stool enzymes. Severe diaper dermatitis in this case can be a symptom of a more severe nutritional deficiency, or even dehydration, and needs thorough medical evaluation.

While optimal nutritional therapy is being addressed with special diets or parenteral nutrition, skin protection from injury should be initiated. Products that contain pectin without alcohol (such as Ilex, a nonalcohol pectin paste) may provide a sturdier barrier for these infants than zinc oxide preparations. The skin should be thoroughly cleansed before a very thick application of the pectin paste. Then it is necessary to apply a greasy ointment because the pectin-based paste may adhere to the diaper. When the infant has a stool, it is not necessary to completely remove the barrier paste; the stool can be wiped away as much as possible before the thick paste barrier is reapplied. The skin will heal under this protective covering as long as it is protected from reinjury.[87] If fungal infection is a component of the dermatitis, antifungal therapy must be instituted in addition to the protective barriers. In this case, Mycostatin powder attached with alcohol-free skin protectant is the first layer; then the barrier cream is applied as described previously.

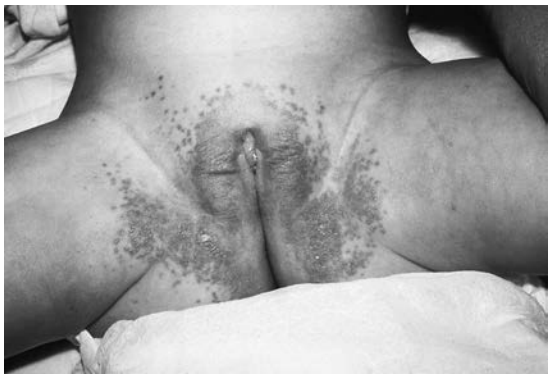

FIGURE 19.8 Diaper dermatitis caused by a *Candida albicans* infection. Red pustular satellite lesions extend into the periphery.

COMPLICATIONS

Improper handling of newborn skin (and injudicious use of products) can cause damage, prevent healing, and interfere with normal maturation processes. Other compromised skin integrity can lead to infection, pain and discomfort, and diversion of calories for tissue repair. Other dangers include toxicity from topically applied substances that are readily absorbed by small infants with a large surface area to body weight ratio and immature renal and hepatic function that cannot detoxify chemicals readily.

Injury from infiltrated IV solutions can cause skin injury and occasionally deep tissue necrosis with both muscle and nerve damage (Fig. 19.9). Factors that increase the risk of injury from IV extravasations include length of time between extravasation and treatment; hypertonic solutions, such as those with high calcium, potassium, amino acid, or glucose solutions; medications such as nafcillin that are irritating to veins; and the use of mechanical pumps for infusions. There

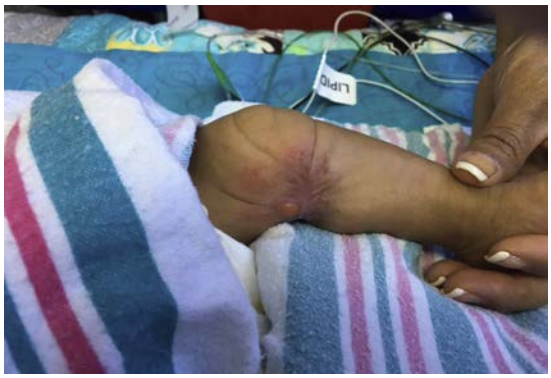

FIGURE 19.9 IV extravasation injury that requires plastic surgery.

may be an added risk for injury in patients with **poor perfusion to extremities and in limbs that have been secured with restricting adhesives that obstruct venous return.**

If the **epidermis has been injured, it can easily become a portal of entry for infection.** Thus a contact irritant diaper dermatitis can progress to a fungal or staphylococcal infection. *Staphylococcus aureus* can **cause pustule formation at hair follicles and is a rare complication of diaper dermatitis.** The mechanism for fungal diaper dermatitis is still debated. Some researchers believe that *Candida albicans* infection is a secondary invasion to skin that has been previously injured, whereas others see this organism as a primary cause of skin disruption.

***Candida albicans* diaper dermatitis causes an intense inflammation that is bright red and sharply demarginated** in the inguinal folds, buttocks, thighs, abdomen, and genitalia, often with satellite lesions that extend the rash over the trunk (Fig. 19.8). ***Candida albicans* can be harbored in the gastrointestinal tract, necessitating oral therapy if lesions are found in the mouth.**

PARENT TEACHING

It is the responsibility of professionals to teach parents informally during caregiving about procedures such as bathing, cord care, and diaper changes and to prepare written materials about appropriate skin care practices for their infant after discharge from the NICU (see Box 19.4). **Parents will need education about the normal mechanisms of cord healing,** including the range of appearance in umbilical cords, because some cords can appear very moist and soggy. **The cord can be cleansed with water if it becomes soiled with urine or stool.**[10] **Inform parents that minimal use of skin care products is optimal and may reduce the incidence of contact sensitization to chemicals.**[24] It is also extremely useful to **educate parents about the mechanisms that are involved in diaper dermatitis so that prevention is stressed** and appropriate interventions are selected depending on the underlying cause. A parent education handout in PDF form, based on the AWHONN *Evidence-Based Neonatal Skin Care Guideline* (Newborn Skin Parent Brochure 2014),[11] is now available online at www.health4mom.org/zones/newborn-skin-care-basics.

BOX 19.4 PARENT/CAREGIVER TEACHING
APPROPRIATE SKIN CARE PRACTICES

- Baby needs to be bathed only two or three times per week: sponge bath with water between tub bathings.
- Use on the skin only products that have as few additives and as little fragrance as possible; minimal skin care products reduce the incidence of contact sensitization of the skin by added chemicals.
- Do not use powder because of inhalation into baby's lungs.
- Prevent diaper rash by frequently changing wet and soiled diapers, cleansing diaper area, and using diapers that "wick" moisture away from the skin. If baby's skin becomes red and irritated with one brand of disposable diaper, try another brand.
- Treat diaper rash by using protective skin barriers (e.g., zinc oxide) with each diaper change to prevent further injury and allow skin to heal. Clean waste from skin barrier but do not clean off the skin barrier because this may disrupt skin healing.
- Diaper rash caused by a yeast infection requires antifungal medication.
- Umbilical cord dries and falls off within 7 to 10 days. Turn diaper back away from the cord until it falls off; as the cord separates, a small amount of blood stain may be on the diaper. Keep cord area clean, and rinse with water if it becomes soiled with urine or stool. Call the health care provider immediately if the cord develops an area of red, warm-to-touch skin at the base, a foul odor, or drainage from the base of the cord.

Developmental differences in the anatomy and physiology of neonatal skin affect skin integrity for term and premature infants in the NICU. Prevention is the primary focus of care, and decisions about the best way to provide basic skin care and hygiene based on current research are essential for care providers, both professionals and parents.

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20 NEWBORN HEMATOLOGY

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RED BLOOD CELLS

Physiology

Red blood cells (RBCs) are primarily responsible for the transportation and delivery of oxygen to tissues in the body. Red blood corpuscles are simple cells composed of a membrane encasing hemoglobin with an energy system to fuel the cells and an enzyme system to maintain an adequate redox environment to protect against oxidative damage. **Hemoglobin is the protein in RBCs that carries oxygen, binding and releasing it based on concentration differences.** Ex utero, RBCs absorb oxygen by diffusion in the lungs, where the oxygen tension of the alveolar air is higher than that of the capillary blood, and release it from the systemic capillaries, where the oxygen tension is higher than that of surrounding tissues. In utero, oxygen diffuses to the fetus from the placental venous circulation.

Fetal red blood cells contain a unique hemoglobin (fetal hemoglobin, *hemoglobin F*) in which the two beta chains of adult hemoglobin *(hemoglobin A_1)* are replaced by two gamma chains. *Fetal hemoglobin* has a higher affinity for oxygen than does adult hemoglobin, allowing fetal RBCs to compete successfully for available oxygen. Normal fetal RBCs have an increased mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), hemoglobin, and hematocrit compared with adult RBCs. After birth, with the transition to air breathing and a higher blood oxygen tension, the hypoxic stimulus driving fetal red cell production in the bone marrow ceases. **The plasma concentration of *erythropoietin,* a hormone that stimulates bone marrow production of RBCs, falls.** The number of circulating *reticulocytes,* which are young RBCs in the circulation, decreases. Subsequently, the hemoglobin and hematocrit diminish until they reach a new equilibrium. **Postnatal changes in RBC production include an increase in the ratio of hemoglobin A to hemoglobin F and an increase in levels of the red cell enzyme *2,3-diphosphoglycerate* (2,3-DPG). 2,3-DPG promotes the release of oxygen to tissues by decreasing the affinity of hemoglobin to oxygen.** Oxygen delivery in the neonate is enhanced by increases in the concentrations of hemoglobin A and RBC concentration of 2,3-DPG.

The production of hematopoietic cells first appears within the yolk sac in the 14-day embryo and disappears by the eleventh week of gestation.[60] *Hematopoiesis* in other tissues results from colonization by stem cells derived from the yolk sac.[15] By the fifth to sixth week, embryonic erythropoietic activity is present in the liver and is the primary source of RBC production by 8 to 9 weeks.[174]

Between the eighth and twelfth weeks, the spleen and lymph nodes are involved in erythropoiesis.[38] Other tissues and organs involved in erythropoiesis include the kidney, thymus, and connective tissue. **Erythropoiesis shifts to the bone marrow at 10 to 11 weeks.** This activity increases rapidly until the 24th week, when bone marrow erythropoiesis replaces liver erythropoiesis. **There is no evidence of erythropoietin production before the**

BLUE type highlights content that is particularly applicable to clinical settings.

tenth week.[196] After the 10th week of gestation, erythropoietin production rises and appears to stimulate RBC production in the bone marrow during the third trimester.[55] Initially, erythropoietin is produced in the fetal liver, and by the last trimester, production relocates to the kidneys. The level of erythropoietin gradually rises to significant levels after the 34th week of gestation.[38] Elevated erythropoietin levels occur when the fetus is hypoxic.

In more than 90% of healthy term infants, the hematocrit range is 48% to 60%, and the hemoglobin range is 16 to 20 g/dL.[74] Changes in erythropoiesis around the time of birth are shown in Table 20.1.[38] Normally after a term birth, hemoglobin concentrations fall from a mean of 17 g/dL to approximately 11 g/dL by 2 to 3 months of age. This nadir in RBC values is called ***physiologic anemia of the newborn*** and is a normal process in the adaptation to extrauterine life.

Several factors influence the interpretation of hematocrit values in the newborn, including age of the infant (both in hours and days), site of blood collection, and method of analysis. Hematocrit changes significantly during the first 24 hours of life; it peaks at 2 hours of age and then progressively drops, with decreases at 6 and 24 hours of age.[164] The method used to determine hematocrit can significantly affect the value. ***Capillary hematocrit*** measurements are highly subject to variations in blood flow; hematocrit results generally are highest in capillary samples, intermediate in venous samples, and lowest in arterial samples.[86,121,180] Prewarming the site minimizes the artifactual increase in the hematocrit. In both term and preterm infants, there can be as much as a 20% difference between the hematocrit obtained from a capillary puncture (commonly termed ***heel stick***) and the hematocrit drawn from a central vein.

Interpretation of blood count parameters requires an understanding of the source of the reference values. Normal ranges are generally derived from large populations of healthy subjects for whom major confounding medical conditions, including personal and familial disorders, can be excluded. The newborn infant, particularly the preterm baby, is at risk for many complicating conditions, such as infection, hypoxia, and inflammation, and it is difficult to determine if a preterm infant is healthy at birth. In settings such as this, reference ranges are often used. Reference ranges determine values of a parameter of interest in a population that has no known confounding illness. Reference ranges for most blood tests in term and preterm infants are derived from relatively small sample sizes. From the Intermountain Healthcare System, a large primary care–based health network, reference ranges of various blood indices from a very large population of infants (>20,000 infants) have been derived.[66] For otherwise healthy extremely preterm infants (<28 weeks), the lower 5% of hemoglobin was slightly less than 10 g/dL, and the hematocrit was slightly less than 30%. In comparison, the lower limits for infants 32 weeks of gestation and greater were 13 g/dL and 40% (Fig. 20.1).[74]

TABLE 20.1 CHANGES IN ERYTHROPOIESIS AROUND THE TIME OF TERM BIRTH

	IN UTERO	POSTDELIVERY
Oxygen saturation (%)	45*	95
Erythropoietin levels	High	Undetectable
Red cell production	Rapid	<10% (by day 7)
Reticulocyte count (%)	3–7	0–1 (by day 7)
Hemoglobin (g/dL)	16.8	18.4
Hematocrit (%)	53	58
MCV (fL)	107	98 (by day 7)
MCHC (g/dL) [5,8]	31.7	33 (by day 7)

*Mean values represented.
MCHC, Mean corpuscular hemoglobin concentration; *MCV,* mean corpuscular volume.

Pathophysiology of Anemia

Anemia is defined as a decrease in RBC mass usually reflected by a hemoglobin concentration or hematocrit less than the 2.5th percentile for age, gender, and ethnicity. Anemia results in an impairment in tissue oxygen delivery resulting in hypoxia and acidosis. For a normal full-term infant in the first week of life, hemoglobin values less than 13 g/dL signify anemia.

Determination of the cause of anemia is important to direct treatment. Anemia in the newborn results from one or more of the following basic mechanisms:

- Blood loss (acute or chronic)
- Decreased RBC production
- Decreased RBC survival (hemolysis)

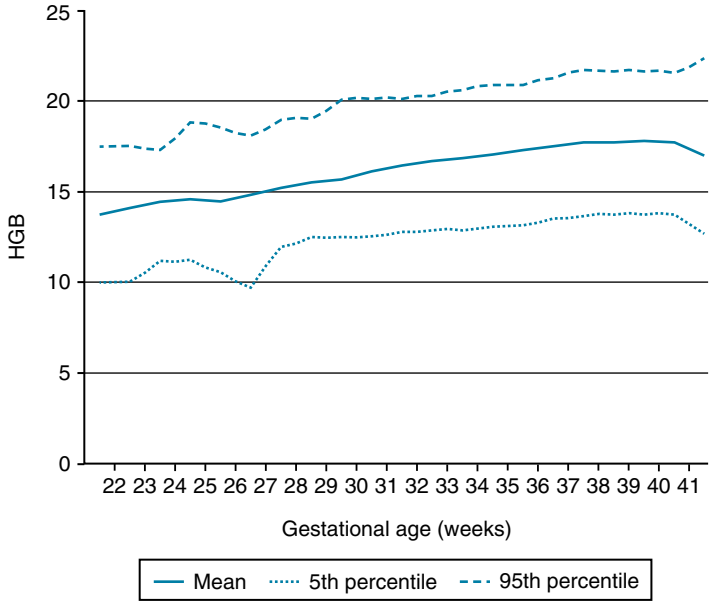

FIGURE 20.1 Reference ranges (5th percentile, mean, and 95th percentile) are shown for blood hemoglobin concentrations obtained during the first 6 hours after birth among patients 22 to 42 weeks' gestational age. Values were excluded if the diagnosis included abruption, placenta previa, or known fetal anemia, or if a blood transfusion was given before the first hemoglobin was measured. (From Joplin J, Henry E, Wiedmeier SE, Christensen RD. Reference ranges for hematocrit and blood hemoglobin concentration during the neonatal period. *Pediatrics.* 2009;123:e333.)

BLOOD LOSS

Acute and chronic blood losses are the most common causes of anemia in the neonate. Blood loss can occur in utero, perinatally, or postnatally. **The total blood volume of the fetus is approximately 90 mL/kg. Large blood loss can cause profound asphyxia and death; determination of a profound drop in hemoglobin and hematocrit may lag by hours as blood volume equilibrates. Anemia caused by chronic blood loss is better tolerated because the neonate is able to compensate for the gradual loss in RBC mass by increasing production of 2,3-DPG.** There is a large differential for blood loss in the neonate (Box 20.1).

Fetomaternal transfusion is a common cause of occult blood loss in the fetus. **Some degree of fetomaternal blood mixing occurs in almost 50% of all pregnancies.**[31] **Massive fetomaternal hemorrhage defined as greater than 30 mL occurs in only 3 of 1000 pregnancies.**[156] The *Kleihauer-Betke* acid elution test is used to confirm the presence of fetal blood cells in the maternal circulation.[198] This test depends on the increased acid resistance of fetal hemoglobin. Fetal cells retain red staining of hemoglobin after acid exposure, whereas adult cells (also called *ghost cells*) are very pale because hemoglobin has been eluted. **The volume of fetal blood in the maternal circulation is estimated by counting fetal RBCs on the maternal blood smear under light microscopy. Ten fetal cells per 30 fields viewed under high power are equal to 1 mL of fetal blood.**

***Twin-to-twin transfusion* is another cause of occult blood loss and is seen in 15% to 30% of all monochorionic twins with abnormalities of placental blood vessels.**[49,179] The anemic twin is on the arterial side of the placental vascular malformation. The clinical significance of twin-to-twin transfusion depends on the duration of blood transfer. **With chronic transfusion, a 20% weight discordance similar to that observed with placental insufficiency can be found; the recipient twin (i.e. the plethoric or polycythemic one) usually suffers greater morbidity.**[129,179]

Intracranial bleeding associated with prematurity, later birth order of a multiple-gestation delivery, rapid or breech delivery, or massive cephalohematoma can cause anemia. Other forms of neonatal

BOX 20.1 CAUSES OF BLOOD LOSS IN THE NEONATE

1. Hemorrhage before birth
   a. Fetomaternal
      Traumatic amniocentesis or periumbilical blood sampling
      Spontaneous
      Chronic gastrointestinal bleeding
      Blunt trauma to the maternal abdomen
      Post–external version
   b. Twin-to-twin
   c. External
      Abruptio placentae
      Placenta previa
2. Hemorrhage during birth
   a. Placental malformation
      Chorangioma
      Chorangiocarcinoma
   b. Hematoma of the cord or placenta
   c. Rupture of a normal umbilical cord
      Precipitous delivery
      Entanglement
   d. Rupture of an abnormal umbilical cord
      Varices
      Aneurysm
   e. Rupture of anomalous vessels
      Aberrant vessel
      Velamentous insertion of the cord
      Communicating vessels in the multilobular placenta
   f. Incision of placenta during cesarean delivery
3. Internal fetal or neonatal hemorrhage
   a. Intracranial
   b. Giant cephalohematoma, caput succedaneum
   c. Pulmonary
   d. Retroperitoneum
   e. Subcapsular liver or spleen
   f. Renal or adrenal
4. External neonatal hemorrhage
   a. Delayed clamping of the umbilical cord
   b. Gastrointestinal
   c. Iatrogenic from blood sampling

Modified from Luchtman-Jones L, Schwartz A, Wilson D. Hematologic problems in the fetus and neonate. In: Fanaroff A, ed. *Neonatal-Perinatal Medicine: Diseases of the Fetus and Infant.* Vol 2. St Louis, MO: Mosby; 1997.

hemorrhage predisposing to anemia include umbilical, retroperitoneal, adrenal, renal, and gastrointestinal (GI) bleeding, as well as ruptured liver or spleen.

Swallowed maternal blood **may be confused with GI bleeding. The Apt test is used to distinguish swallowed maternal blood from neonatal blood and is based on alkali resistance of fetal hemoglobin.**[9] A 1% solution of sodium hydroxide is added to 5 mL of diluted blood. Fetal hemoglobin remains pink, but adult hemoglobin becomes yellow.

Iatrogenic blood loss **results from blood sampling with inadequate replacement.** Premature infants can have a blood volume that is as little as 50 mL, so even a small amount of phlebotomized blood may result in anemia. **Strategies for preventing iatrogenic blood loss include sampling of umbilical cord blood for initial laboratory evaluation, using pediatric microcontainers and specialized equipment that can perform assays using smaller blood volumes, and avoiding excessive testing.**[72]

DECREASED RED BLOOD CELL PRODUCTION

Anemia caused by decreased production of RBCs tends to develop slowly, allowing time for physiologic compensation. Affected infants may have few signs of anemia other than pallor. The reticulocyte count will be low and inappropriate for the degree of anemia.

Worldwide, iron deficiency is the leading cause of anemia in infancy and childhood. Iron-deficiency anemia can occur at any time when growth exceeds the ability of the stores and dietary intake to supply sufficient iron for erythropoiesis. **Newborn iron stores are proportional to gestational age and weight at time of delivery. More than 80% of newborn iron stores are transferred from the mother to the fetus in the last trimester.**[101] **Typically term infants are born with iron stores sufficient to support new RBC production until they double their birth weight.**[126] Infants who are exclusively fed breast milk or iron-enriched formula and cereal are less likely to develop iron-deficiency anemia. At birth, delayed cord clamping reduces the incidence of anemia at 8 to 12 months of age.[76] **Premature infants have iron stores adequate for less than 3 months postnatally because of low birth weight, faster rate of growth, and iatrogenic blood losses. Iron supplementation is necessary**

TABLE 20.2 RECOMMENDED IRON SUPPLEMENTATION FOR THE NEONATE

GROUP	DOSE (mg/kg/DAY)	INITIATION, DURATION
Full term	1	4 mo to 3 yr
Preterm, low birth weight	2	2 mo to 1 yr, then
	1	1–3 yr
Very low birth weight	4	2 mo to 1 yr, then
	1	1–3 yr

mo, Month; *yr*, year.

early in preterm infants to prevent anemia (Table 20.2).

Iron deficiency causes a hypochromic, microcytic anemia. The peripheral smear shows small, pale RBCs with a large variety of shapes and sizes, resulting in an increased relative distribution of width (RDW). The platelet count is increased and may be greater than 1,000,000/μL. **Mild forms of iron deficiency may be confused with other causes of anemia, including infection and thalassemia. A therapeutic trial of iron can be used to diagnose iron deficiency. Although the American Academy of Pediatrics recommends 2 to 4 mg/kg/day of elemental iron for preterm infants and 4 to 6 mg/kg/day for preterm infants receiving concomitant erythropoietin, higher doses for prevention of iron deficiency may be associated with improved outcomes.**[79]

Iron deficiency with or without accompanying anemia has been associated with cognitive and behavioral deficits.[100] One longitudinal study followed patients diagnosed with iron deficiency in early infancy for 10 years and found higher rates of psychomotor impairment and specific cognitive deficits, including spatial memory, selective recall, and attention.[88] More recent studies of iron-deficiency anemia in infancy also found lower gross motor development and locomotion at 9 months of age[154] and an increase in adolescent behavioral problems.[45] Possible biologic mechanisms for this effect of iron deficiency include impairment of iron-dependent cytochromes, decreased myelination, and alterations in neurotransmitter systems, which have been demonstrated in iron-restricted animal models.

Anemia of prematurity is common in infants born at less than 35 weeks of gestation. This appears as a normocytic, normochromic anemia between 2 and 6 weeks characterized by a low reticulocyte count and an inadequate response to erythropoietin.[160] **If hemoglobin levels drop below 10 g/dL, the infant may display decreased activity, poor growth, tachypnea, and tachycardia.** Randomized placebo-controlled trials demonstrate that preterm infants can respond to erythropoietin with decreased amount of blood transfused if they are also supplemented with iron.[107] However, the decrease in volume of transfused blood does not result in a decrease in donor exposures.[123] **Delayed umbilical cord clamping/milking can reduce both the number and exposure to transfusions among premature infants and the incidence of late anemia in infancy among term infants.**[56,76,102,137,163]Another recent RCT found that milking the umbilical cord in preterm infants resulted in a significantly higher initial hemoglobin and hematocrit with a reduction in the need for transfusions but a higher need for phototherapy.[85]

***Hypothyroidism*, deficiency of transcobalamin II, and inborn errors of cobalamin utilization cause macrocytic anemia** because of decreased and ineffective bone marrow production. **Metabolic causes of anemia are important to diagnose and treat because deficiencies can cause permanent neurologic and cognitive deficits.**

***Diamond-Blackfan anemia* is an inherited pure red cell aplasia** that may be caused by a mutation in one of numerous ribosomal protein genes.[50] This normocytic or macrocytic anemia manifests at birth in 10% and by one month in 25% of affected infants. **Signs and symptoms include pallor, anemia, and reticulocytopenia.** In red cell aplasia, the platelet count may be moderately elevated and the leukocyte count may be slightly decreased. Bone marrow examination is normocellular with a paucity of erythroid precursors. **Thirty percent of affected infants demonstrate congenital anomalies, primarily of the head, face, eyes, and thumb.** The syndrome can have autosomal dominant or autosomal recessive inheritance. As infants grow older, characteristics of fetal erythropoiesis persist, including elevations in fetal hemoglobin, *i* antigen, and red cell adenosine deaminase, as well as fetal patterns of red cell enzymes. **Seventy percent of affected infants respond to corticosteroid therapy.** Because of the toxicity of chronic corticosteroid exposure (e.g., growth impairment, decreased bone density, cataract

formation), a trial of this therapy is usually deferred until the patient is 1 year of age, and until then the infant is chronically transfused with packed red blood cells (PRBCs). Infants who do not respond to steroids require long-term RBC transfusion therapy and are at risk for subsequent iron overload.[50]

Fanconi's anemia **is a congenital syndrome of progressive bone marrow failure with autosomal recessive inheritance** that is caused by increased chromosomal breakage and a defect in the ability to repair damaged DNA.[87] At birth, infants with this type of anemia may be recognized by one or more of the associated congenital defects, which include microcephaly, short stature, absent or abnormal thumb, and other abnormalities of the integumentary, musculoskeletal, or urogenital systems. Thrombocytopenia and an elevated MCV usually are the first hematologic abnormalities, but they are seldom recognized in the neonatal period. Chromosomal breakage analyses and specific molecular diagnosis have been used for prenatal diagnosis. **Diamond-Blackfan and Fanconi's anemias have been successfully treated with bone marrow transplantation.**

B19 parvovirus **preferentially infects erythroid precursors in the bone marrow and exerts an inhibitory effect on the production of RBCs.**[125,187] Infection with B19 parvovirus during pregnancy can cause hydrops *fetalis*, the clinical syndrome caused by severe intrauterine anemia of any cause and consisting of congestive heart failure, massive skin edema, and possible intrauterine demise, especially during the first two trimesters.[125,187] Early detection of parvovirus infection in pregnant women and serial examinations with ultrasonography are important to diagnose and monitor the condition. Affected fetuses have been supported successfully with intrauterine transfusions of RBCs. Postnatal infection with parvovirus does not cause anemia in most infants unless they have preexisting shortened RBC survival. Infants with congenital or acquired immunodeficiency may become anemic because of an inability to clear parvovirus.

SHORTENED RED BLOOD CELL SURVIVAL

Adult RBCs circulate for an average of 120 days. Normal neonatal RBCs have a circulating half-life reduction of 20% to 25% compared with the RBCs of older children or adults. Survival of RBCs of premature infants is reduced by approximately 50%. Senescent RBCs are removed from the circulation by the reticuloendothelial system. Bilirubin is produced by degradation of the heme moiety of hemoglobin, and RBC iron is recycled. Many conditions accelerate the removal of RBCs from the circulation.

Hemolysis **is a term for RBC destruction that is premature in terms of the expected life span of the RBCs relative to postconceptual age.** *Hyperbilirubinemia* is evident in most cases of hemolysis. Compensatory reticulocytosis is usually present. However, in the presence of chronic illness, nutritional deficiency, or congenital infection, the reticulocyte count may be lower than expected for the degree of anemia. **In the most severe cases of intrauterine hemolysis, the outcome is *hydrops fetalis* (Box 20.2).**

Isoimmune hemolytic anemia occurs when fetal cells, bearing antigens of paternal origin that are not shared by the mother, **enter the maternal circulation and stimulate production of immunoglobulin G (IgG) antibodies.** The IgG antibodies are transferred across the placenta, coat fetal RBCs, and mediate their removal from the circulation through the reticuloendothelial system.

The major fetal RBC antigens responsible for isoimmune hemolytic anemia include the Rh (also called D) antigen in an Rh-negative mother and the blood group A and B antigens in a group O mother. *Kell, Duffy,* and *Kidd antigens* can also cause isoimmune hemolytic anemia. Sources of maternal sensitization to fetal RBC antigens include chorionic villus sampling, amniocentesis, abortion, rupture of an ectopic pregnancy, maternal blood transfusion, and fetomaternal transfusion. **To prevent sensitization, anti-Rh antibodies derived from plasma of previously sensitized donors are given to Rh-negative mothers at 28 weeks of gestation, at delivery, and at the time of any of the previously mentioned events.** These antibodies coat any fetal RBCs present in the maternal circulation and prevent them from initiating the maternal immune response. Thus they provide a form of passive immunization. **With widespread use of Rh immunoglobulin (Ig) in Rh-negative mothers, the rate of Rh isoimmunization has dropped by over 90% to about 3 per 1000 pregnancies.**[4,99] The rate of Rh hemolytic disease in the United States is 1 case per 1000 live births.[24] The persistence of Rh isoimmunization may be attributed to failures

BOX 20.2 CAUSES OF SHORTENED RED CELL SURVIVAL IN THE NEONATE

1. Isoimmune-mediated hemolysis
   a. Rh incompatibility
   b. ABO incompatibility
   c. Minor blood cell antigen incompatibility
2. Infection
   a. Bacterial sepsis
   b. *Campylobacter jejuni*
   c. *Clostridium welchii*
   d. Rubella
   e. Cytomegalovirus
   f. Epstein-Barr virus
   g. Disseminated herpes
   h. Malaria
   i. Toxoplasmosis
   j. Syphilis
3. Microangiopathic and macroangiopathic
   a. Cavernous hemangioma (Kasabach-Merritt)
   b. Renal vein thrombosis
   c. Disseminated intravascular coagulation
   d. Severe coarctation of the aorta
   e. Renal artery stenosis
4. Vitamin E deficiency
5. Congenital red cell membrane disorders
   a. Hereditary spherocytosis
   b. Hereditary elliptocytosis
      i. Hereditary poikilocytosis
      ii. Hereditary pyropoikilocytosis
      iii. Hereditary stomatocytosis
   c. Infantile pyknocytosis
6. Congenital red cell enzyme disorders
   a. Glucose-6-phosphate dehydrogenase deficiency
   b. Pyruvate kinase deficiency
7. Congenital hemoglobinopathies
   a. Alpha and gamma chain defects including thalassemias; structural abnormalities; unstable hemoglobin
8. Metabolic disorders
   a. Galactosemia
   b. Organic aciduria; orotic aciduria
   c. Prolonged or recurrent acidosis
9. Liver disease

in administering Rh Ig to all women at risk and incorrect dosing. Women who receive no prenatal care and women who develop silent antenatal sensitization compose two populations that are difficult to reach with prevention strategies.[4]

***ABO hemolytic anemia* is more common than Rh hemolytic disease but less severe. Unlike Rh disease, hemolysis secondary to ABO incompatibility can occur during the first pregnancy** because A and B antigens are ubiquitous in foods and bacteria, causing sensitization. Most isoimmune hemolytic diseases that are not related to ABO or Rh incompatibility are caused by sensitization to minor blood group antigens Kell, Duffy, Lewis, Kidd, M, or S. Mothers should be screened at 34 weeks for antibodies to these minor blood group antigens.

***Congenital bacterial* and *viral infections* may cause hemolytic anemia and bone marrow suppression with reticulocytopenia.** Microspherocytes may be very prominent.

***Microangiopathies* and *macroangiopathies* are characterized by red cell fragmentation, shortened red cell survival, and thrombocytopenia.** Coagulation proteins are also consumed in cavernous hemangiomas and disseminated intravascular coagulation (DIC).

***Vitamin E* is a fat-soluble vitamin that functions as an antioxidant. Deficiency of vitamin E manifests with hemolytic anemia, reticulocytosis, thrombocytosis, and edema of the lower extremities.**[21] Diets high in polyunsaturated fatty acids and iron increase requirements for vitamin E. With current supplementation of infant formulas and parenteral nutrition with vitamin E, prevention of vitamin E deficiency using a water-soluble form of tocopherol is not currently necessary.

Intrinsic red cell defects are a rare but important cause of shortened red cell survival in the neonate. Because even normal neonates have shortened red cell survival and hyperbilirubinemia, the presentation of these syndromes with anemia and hyperbilirubinemia in the neonate often is more severe than in older affected family members. Splenomegaly develops later in infancy or early childhood. A preliminary diagnosis of constitutional red cell defect is made by family history and careful inspection of the peripheral smear. Abnormally shaped RBCs, including spherocytes, elliptocytes,

pyknocytes, "bite cells," target cells, and other bizarre morphologic structures, are often characteristic of the specific red cell defect.

Constitutional defects in red cell membranes cause lifelong hemolytic anemia. ***Hereditary spherocytosis* is the most common red cell membrane defect and is usually inherited as an autosomal dominant trait** primarily affecting infants of Northern European descent. This is a common cause of exaggerated jaundice in the neonate. ***Pyropoikilocytosis,* an infantile form of the mild membrane defect *hereditary elliptocytosis,*** is characterized by striking red cell pyknocytes and fragments on peripheral smear with evidence of mild hemolysis. Typical elliptocytes may not become apparent until a few months of life. **Patients usually do not have long-term issues outside of the neonatal period.**

Glucose-6-phosphate dehydrogenase (G6PD) is the first rate-limiting enzyme in the pentose phosphate pathway. This enzyme is important in the production of nicotinamide adenine dinucleotide phosphate (NADPH), which is responsible for maintaining an adequate supply of reduced glutathione and preventing oxidative damage to the RBC from reactive oxygen species. **G6PD deficiency is the most common inherited disorder of red blood cells and is transmitted as an X-linked recessive trait; therefore affected infants are overwhelmingly male.** Females may also be affected through excessive lyonization of the unaffected X chromosome or coinheritance of biallelic mutations. There are many isoforms of abnormal G6PD enzymes. The Mediterranean type produces severe hemolysis, whereas the form found in African Americans is usually mild.[4,90] **Infants are asymptomatic until challenged with oxidant stresses from infections or drugs but may present with prolonged neonatal hyperbilirubinemia.** Agents associated with hemolysis in G6PD-deficient infants are shown in Box 20.3. ***Pyruvate kinase deficiency* is the second most common RBC enzyme defect.** Pyruvate kinase is a glycolytic enzyme involved in the production of ATP that is used as an energy source by RBCs for ATP-dependent cation pumps. Deficiency of this enzyme results in a chronic hemolytic anemia with varying degrees of severity. Some patients may develop splenomegaly or gallstones, or they may require chronic blood transfusions. Pyruvate kinase deficiency may be inherited in either an autosomal dominant or autosomal recessive fashion and thus may be seen in female or male infants.

***Hemoglobinopathies* are inherited disorders resulting from gene mutations that affect the quantity or quality of globin chains.** Thalassemias are quantitative disorders resulting in decreased or absent production of specific globin chains. Thalassemias are categorized according to the affected globin chain (e.g., alpha, beta, or gamma) and the severity of the clinical phenotype (thalassemia trait, thalassemia intermedia, or thalassemia major). **Hemoglobinopathies presenting at birth affect either the alpha or gamma chain of hemoglobin.**[41] Hemoglobin beta chains are not the predominant globin chain until 3 months of postnatal age; therefore defects of beta chains, such as *sickle cell anemia* and *beta-thalassemia,* do not present in the neonate. Because there are four genes controlling alpha globin synthesis (two on each allele of chromosome 16), clinical presentations may range from asymptomatic (one alpha hemoglobin gene deletion) to abnormalities incompatible with life (absence of production from all four alpha globin genes), resulting in hydrops fetalis.[175] Most infants with moderate to severe anemia related to alpha-thalassemia have a three-gene deletion, termed *hemoglobin H disease.* Alpha globin is an essential component of both hemoglobin F and hemoglobin A. Alpha thalassemia may be detected on universal newborn screening by the presence of hemoglobin Barts, which is composed of a tetramer of gamma chains. Hemoglobin Barts is replaced later by the compensatory hemoglobin, hemoglobin H, which is a beta-chain tetramer. In Western populations, there has been a dramatic decline in the incidence of new births with severe thalassemia syndromes because of the widespread use of molecular diagnostic techniques by couples at risk.

***Methemoglobin* contains an oxidized form of heme iron, Fe^{3+}, which renders it incapable of reversible binding to oxygen.** Constitutional methemoglobinemia presenting in the neonatal period is caused either by deficiency of the red cell enzyme *methemoglobin reductase* or by an *M hemoglobinopathy* of the gamma chain of hemoglobin. **Infants with either of these disorders present with cyanosis of the skin and mucous membranes** but are otherwise usually asymptomatic. ***Acquired methemoglobinemia* can be life-threatening because of severe hypoxemia.** Normal newborn infants are at

BOX 20.3 SOME AGENTS REPORTED TO PRODUCE HEMOLYSIS IN PATIENTS WITH G6PD DEFICIENCY

Drugs and Chemicals Clearly Shown to Cause Clinically Significant Hemolytic Anemia in G6PD Deficiency

Acetanilide
Methylene blue
Nalidixic acid (NegGram)
Naphthalene
Niridazole (Ambilhar)
Phenylhydrazine
Primaquine
Pamaquine
Pentaquine
Sulfanilamide
Sulfacetamide
Sulfapyridine
Sulfamethoxazole (Gantanol)
Thiazolsulfone
Toluidine blue
Trinitrotoluene

Drugs Probably Safe in Normal Therapeutic Doses for G6PD-Deficient Individuals (without Nonspherocytic Hemolytic Anemia)

Acetaminophen (Paracetamol, Tylenol, Traralgon, Hydroxyacetanilide)
Acetophenetidine (Phenacetin)
Acetylsalicylic acid (aspirin)
Aminopyrine (Pyramidon, Amidopyrine)
Antazoline (Antistine)
Antipyrine
Ascorbic acid (vitamin C)
Benzhexol (Artane)
Chloramphenicol
Chlorguanidine (Proguanil, Paludrine)
Chloroquine
Colchicine
Diphenhydramine (Benadryl)
L-dopa
Menadione sodium bisulfite (Hykinone)
Menaphthone
p-Aminobenzoic acid
Phenylbutazone
Phenytoin
Probenecid (Benemid)
Procaine amide hydrochloride (Pronestyl)
Pyrimethamine (Daraprim)
Quinidine
Quinine
Streptomycin
Sulfacytine
Sulfadiazine
Sulfaguanidine
Sulfamerazine
Sulfamethoxypyridazine (Kynex)
Sulfisoxazole (Gantrisin)
Trimethoprim
Tripelennamine (Pyribenzamine)
Vitamin K

G6PD, Glucose-6-phosphate dehydrogenase.
From Beutler E. Hemolytic anemia in disorders of red cell metabolism. New York, NY: Plenum; 1978.

risk for developing toxic/acquired methemoglobinemia from environmental toxins and pharmacologic agents because neonatal RBCs contain lower levels of the enzyme *NADH-methemoglobin reductase.* In addition to the ingestion of nitrates, lidocaine and its derivatives, aniline dyes, and dapsone are the most common drugs precipitating methemoglobinemia.

Data Collection

HISTORY

A careful history should solicit a maternal history of illness and dietary intake during pregnancy, delivery type, hemorrhage, transfusion or iron therapy, and any abnormal occurrences during birth. A family history should include specific questioning about anemia, iron or transfusion therapy, pallor, jaundice, splenomegaly, splenectomy, gallstones, cholecystectomy, or congenital malformations in the parents, grandparents, siblings, aunts, uncles, and cousins of the infant.

SIGNS AND SYMPTOMS

In performing a physical examination of a newborn with anemia, attention should be paid to the infant's cardiovascular function, general vigor, and signs of pallor, jaundice, skin lesions, hepatosplenomegaly, lymphadenopathy, and congenital malformation (Box 20.4).

BOX 20.4 CRITICAL FINDINGS
SIGNS AND SYMPTOMS OF ANEMIA IN THE NEONATE

1. Acute anemia (with hemorrhage, anemia may not be present initially; hemodilution develops over 3 to 4 hours)
   a. Hypovolemia, hypotension
   b. Hypoxemia, tachypnea
   c. Tachycardia
2. Chronic anemia (may be well compensated)
   a. Pallor, metabolic acidosis, poor growth
   b. High-output congestive heart failure
   c. Persistent or increased oxygen requirement
   d. Iron deficiency with hypochromia, microcytosis

LABORATORY DATA

The diagnosis of anemia is based on the hemoglobin and hematocrit in comparison with normal values established for postconceptional and postnatal age. Initial laboratory evaluation of anemia should include a complete blood count (CBC) with careful attention to the RBC indices, reticulocyte count, and a review of the peripheral blood smear. Additional laboratory testing depends on the characterization of the anemia (Table 20.3). **The mean cell hemoglobin concentration (MCHC) is usually greater than 36 g/dL, and the MCHC/mean cell volume ratio may be elevated greater than 0.36 in patients with hereditary spherocytosis.**[29] If the peripheral smear suggests a constitutional RBC abnormality by severe anisocytosis, poikilocytosis, spherocytes, blister cells, bite cells, or elevated RDW, an ACD tube (yellow) for assay of G6PD, pyruvate kinase, and other red cell enzymes and an EDTA tube (lavender) for assay of red cell membrane proteins and hemoglobin electrophoresis should be obtained before transfusing the baby. **A clinical decision tree in the evaluation of anemia is shown in** Fig. 20.2.

TABLE 20.3 CHARACTERIZATION OF ANEMIA

CHARACTERIZATION	TEST
Blood loss	Kleihauer-Betke on maternal sample
	Apt test on gastric blood from infant as indicated
Bone marrow production	Reticulocyte count
	Platelet and white blood cell count
	Erythropoietin level
	T_3, T_4, TSH
	Bone marrow aspirate and biopsy
	Fetal hemoglobin iAg, MCV
Iron deficiency	Ferritin, iron, and iron-binding capacity
Antibody mediated	Maternal and infant blood type
	Direct and indirect Coombs' tests
Hemolysis	Bilirubin
	Coagulation tests (if sepsis or liver disease is suspected)
	Osmotic fragility, specific determinations of red cell membrane proteins, enzymes, hemoglobin, and ceruloplasmin as indicated
Infection	Culture and serologies as appropriate
Microangiopathy, macroangiopathy	DIC screen
Vitamin E deficiency	Vitamin E level
Metabolic disorder	pH, lactate, pyruvate
	Galactosemia screen

DIC, Disseminated intravascular coagulation; *MCV,* mean corpuscular volume; *TSH,* thyroid-stimulating hormone.

Treatment of Anemia

If acute blood loss is suspected and the infant is pale and limp at birth, blood pressure should be monitored, perfusion should be assessed, a bolus of intravenous (IV) fluids started at 20 mL/kg, and oxygen administered. A catheter should be inserted into the umbilical artery to measure blood gases. Blood should be obtained for CBC, reticulocyte count, Coombs' test, blood type, fractionated bilirubin, and serum screen for blood group antibodies. Because infants less than 4 months of age rarely produce antibodies against blood group antigens, maternal serum can be used in the antibody screen.

Once the infant's condition stabilizes, a decision can be made about transfusion based on clinical status. If the infant is anemic with signs of hypoxemia or has underlying pulmonary or cardiac disease, transfusion of 10 mL/kg of RBCs

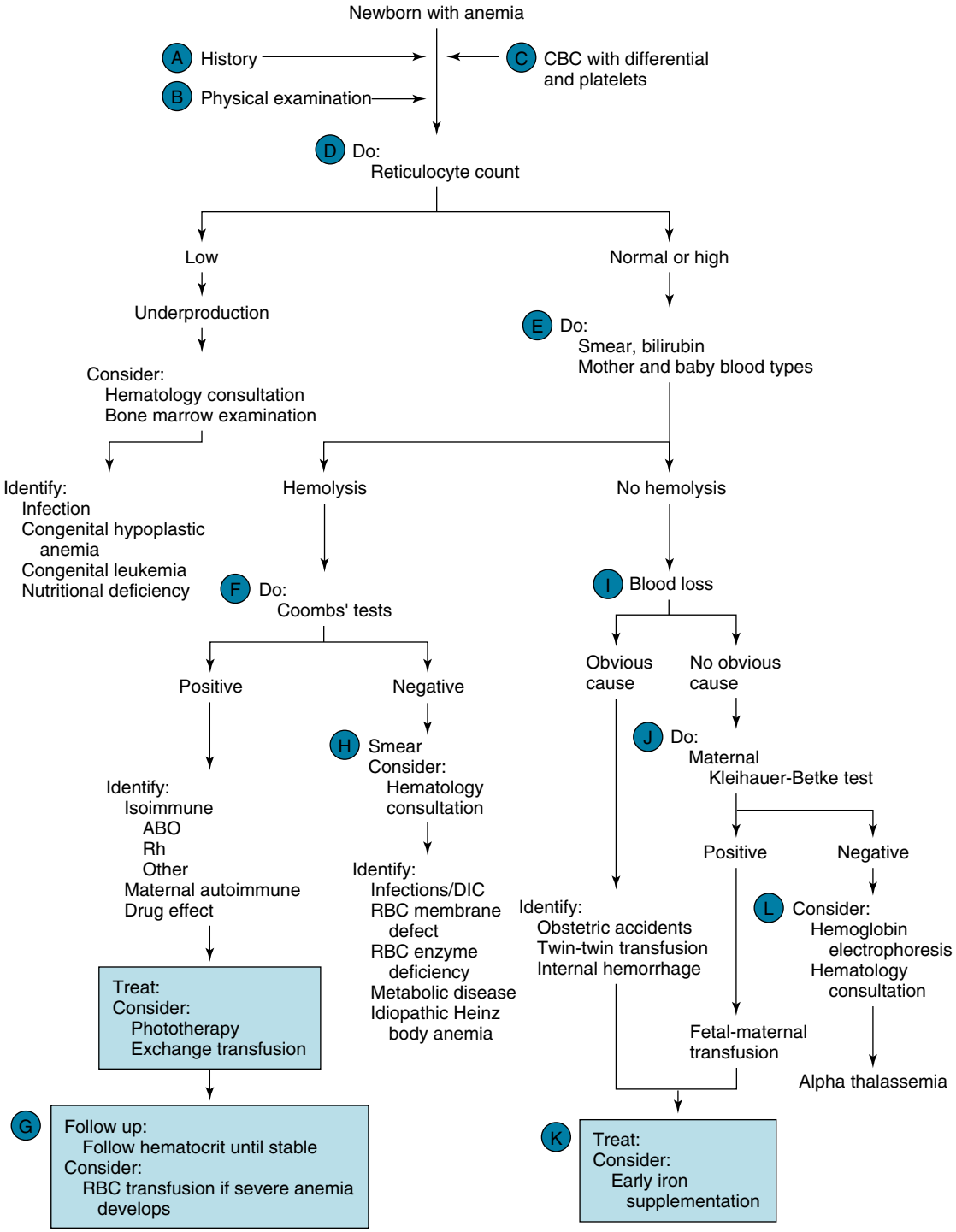

FIGURE 20.2 Clinical decision tree in the evaluation of anemia. *CBC,* Complete blood count; *DIC,* disseminated intravascular coagulation; *RBC,* red blood cell. (From Lane PA, Nuss R. Anemia in the newborn. In Berman S, ed: *Pediatric Decision Making.* 3rd ed. St Louis, MO: Mosby; 1996.)

Continued

A. In the history, document any prenatal infections or drug use. Also note any history of maternal vaginal bleeding, placenta previa, abruptio placentae, or umbilical cord rupture, constriction or velamentous insertion, as well as cesarean, breech, or traumatic delivery. Obtain a family history of neonatal jaundice, anemia, splenomegaly, and unexplained gallstones.
B. In the physical examination, note tachypnea, tachycardia, peripheral vasoconstriction (acute blood loss), and hepatosplenomegaly (chronic anemia, intrauterine infection, congenital malignancy). Jaundice appearing before 24 hours of age suggests significant hemolysis.
C. A hematocrit less than 45% during the first 3 days of life is abnormal and requires explanation. The mean corpuscular volume (MCV) at birth is normally above 95. An MCV below 95 suggests alpha-thalassemia or chronic intrauterine blood loss (as with fetal maternal transfusion). Rarely, a low MCV may be seen with hemolytic disease caused by hereditary elliptocytosis or pyropoikilocytosis. The presence of neutropenia or thrombocytopenia suggests the possibility of infection. Except in an emergency, no anemic newborn should receive a blood transfusion before adequate diagnostic studies.
D. Normal reticulocyte values are 3% to 7% during the first day of life and 1% to 3% during the second and third days. A low reticulocyte count in the presence of significant anemia suggests bone marrow failure.
E. An indirect hyperbilirubinemia, abnormal peripheral blood smear, or ABO or Rh incompatibility between the mother and infant suggests hemolysis.
F. Perform direct and indirect Coombs' tests. ABO isoimmunization is usually associated with a negative direct and a positive indirect Coombs' test.
G. Infants with immune hemolysis have varying degrees of hemolysis, which may continue for 3 months. Severe, life-threatening anemia may develop in infants with Rh sensitization; such infants require close follow-up with serial hematocrit measurements until the hemolysis resolves.
H. Examine the peripheral blood smear. Spherocytes suggest ABO isoimmunization, hereditary spherocytosis, or infection (e.g., cytomegalovirus). Red cell fragmentation suggests intravascular hemolysis (infection, disseminated intravascular coagulation [DIC]). Consider infection or DIC in any ill newborn with hemolysis, particularly if thrombocytopenia is also present.
I. Review the obstetric history and examine the placenta for clues to the cause of fetal blood loss.
J. Perform a Kleihauer-Betke test to detect fetal red cells in the maternal circulation. False-negative results occur when an ABO incompatibility results in the rapid clearance of the infant's red cells from the maternal circulation.
K. Newborns with significant prenatal or perinatal blood loss are at risk for iron deficiency during the first 6 months of life.
L. Anemic infants without evidence of hemolysis or blood loss whose mothers have a negative Kleihauer-Betke test may have alpha-thalassemia, especially if the MCV is below 95. Ethnic groups affected most often include South and Southeast Asians, Mediterraneans, and Africans. The diagnosis of alpha-thalassemia may be confirmed with a hemoglobin electrophoresis that shows hemoglobin Barts.

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FIGURE 20.2, cont'd.

over 2 to 3 hours will serve to increase oxygen-carrying capacity (see discussion on diagnosis of congenital red cell defects in the Laboratory Data section earlier in this chapter). **Normally, larger quantities of blood should not be given in one transfusion.** Most blood banks at institutions with neonatal intensive care units have protocols for neonatal blood transfusion and will give leukodepleted, either type-specific or O-negative non-crossmatched RBCs if the antibody screen is negative. **Blood used for transfusion should be less than 7 days old and negative or reduced for cytomegalovirus (CMV).** Irradiation of RBCs and other blood cell products to prevent graft-versus-host disease is recommended for intrauterine transfusions or neonatal exchange transfusion and for infants with congenital or acquired immune deficiency. **For infants with continuing hemorrhage requiring massive transfusion exceeding one blood volume, transfusions of fresh frozen plasma (FFP) are necessary to replace clotting factors and prevent the consumptive coagulopathy that results from massive transfusion of stored blood. Platelet transfusions may also be needed.**

An order from a physician or nurse practitioner is necessary for any blood transfusion. Parental consent should be obtained by the physician before transfusion. **In the neonatal intensive care nursery, a policy of "double-checking" blood is essential to ensure that the proper blood is being administered to the infant. Blood should be warmed and administered through a blood filter of 40 μm or finer. Fresh blood can be administered through a 25-gauge needle without significant hemolysis.**

Directed donor programs may be used in hospitals for nonemergent blood transfusions, especially

in small preterm infants. In most cases, **biologic parents are able to serve as directed donors for their neonates.** Preparation of directed donations is more costly than standard blood units and requires the same time for testing; however, **there are no scientific data that suggest directed donor programs increase blood safety**. Some immunologic incompatibilities may exist between maternal and paternal donors; therefore the **following guidelines should be considered for parental donors:**[128]

- Mothers should not provide blood components containing plasma. If maternal RBCs are transfused, they should be washed.
- Fathers are not recommended as blood cell (red, white, or platelet) donors for their newborns unless maternal serum is shown to lack cytotoxic antibodies.
- All parental blood components should be irradiated before transfusion to the infant to prevent transfusion-associated graft-versus-host disease.

A recent study compared parental-directed versus non–parental-directed blood donation in a pediatric tertiary center in the United States. Both first-time parental and community donors were found to have a higher rate of infectious disease risk when compared with repeat blood donors. The highest rates of positive infectious disease testing occurred among the first-time parental donors. These researchers **recommend use of repeat donors and first-time nonparental donors and discourage first-time parental donation.**[70]

The equipment necessary for blood transfusion includes a filter, extension tubing, and a pump. Except in extreme emergencies, blood should be administered through a peripheral catheter rather than through an umbilical artery catheter (UAC). It is essential to confirm that the unit of blood infused matches the typed blood bank form and assigned number, patient name, and patient hospital number. The expiration date and time must be respected. IV tubing used for blood transfusion should be flushed with 0.45% normal saline solution before use.

Blood bags should not be used for more than 4 hours after opening. Vital signs are obtained and recorded every 15 minutes during blood transfusion. Careful observations should be made for reactions, including increased temperature, diaphoresis, irregular respiration, bradycardia, restlessness, and pallor. Transfusions should be stopped promptly if any of these signs are present. All materials used for blood transfusion should be disposed of properly.

Infants who are anemic as a result of acute or chronic external blood loss who do not require transfusion therapy should be treated with iron replacement 6 mg/kg/day until the blood count is normal and then for 2 additional months to replace stores.

Infants who are born with *isoimmune hemolytic anemia* are often treated with exchange transfusion. In this procedure, catheters placed in central and peripheral veins (or a central vein and artery) are used to remove the infant's blood in small aliquots and replace it with packed RBCs usually reconstituted with FFP. General guidelines for aliquot volumes are as follows:

- 3 kg : 20 mL per aliquot
- 2 kg : 15 mL per aliquot
- 1 kg : 5 mL per aliquot

Infants who are treated for isoimmune hemolytic anemia with intrauterine transfusions may be born with normal or near-normal hematocrit and bilirubin levels. **Exchange transfusion is often used early after delivery to remove antibodies and decrease postnatal hemolysis.** Hyperbilirubinemia can be managed subsequently using phototherapy (see Chapter 21).

Data regarding the use of intravenous immunoglobulin (IVIG) for treatment of hemolytic disease of the newborn are conflicting. Although a recent systematic review demonstrated a decrease in the need for exchange transfusions in patients treated with IVIG, several high-quality prospective, randomized clinical trials have not shown a benefit.[155,167,198,199] Additionally, there is **some evidence that high-dose IVIG administration may be associated with increased rates of necrotizing enterocolitis.**[54,189] Therefore, there is no consensus for the routine use of IVIG in severe hemolytic disease of the newborn at this time.

Prevention of Anemia

Many forms of neonatal anemia are preventable. Improved fetal monitoring and obstetric care may prevent anemia caused by blood loss during delivery.

Administering RhIg to unsensitized Rh-negative mothers within 72 hours of delivery of an Rh-positive infant prevents most cases of hydrops fetalis in subsequent pregnancies. For previously sensitized Rh-negative mothers

carrying Rh-positive fetuses, amniocentesis performed between 20 and 22 weeks of gestation may allow for intrauterine transfusion of Rh-negative RBCs and possible early delivery of a nonhydropic infant. **Prenatal diagnosis of severe thalassemia syndromes and sickle cell anemia is possible.** Intrauterine transfusions are also indicated for infants with alpha-thalassemia major.

Hemolysis may be prevented in infants with significant G6PD deficiency by avoiding administration of drugs known to present an oxidative stress to the RBCs. Supportive care consisting of phototherapy and IV hydration may be required in the setting of hyperbilirubinemia.

Low-birth-weight (LBW) premature infants are at high risk for late-onset anemia because of low endogenous production of erythropoietin, exacerbated by phlebotomy losses for laboratory surveillance. Inadequate nutrition and other factors also may play a significant role. Strategies for minimizing blood donor exposure related to anemia of prematurity include delayed umbilical cord clamping, using placental blood for initial laboratory studies, decreasing the number of blood draws, using the absolute minimum quantity of blood possible for testing, and using satellite packs (aliquots of a larger unit from a single donor) for transfusion.

LBW premature infants often undergo transfusion because they are critically ill and have the highest blood sampling loss in relation to their weight. In an attempt to reduce the number of transfusions and donor exposure, most centers have implemented more restrictive transfusion guidelines, with very encouraging results. **Recombinant human erythropoietin (r-HuEPO) has been successfully used to decrease the severity of anemia and lessen the use of blood transfusion in small premature infants.** The clinical benefits of erythropoietin administration may be trivial because it has not been shown to decrease the total number of donor exposures when using a conservative transfusion protocol employing satellite packs.[2,123] **In addition, there is also evidence suggesting an association between r-HuEPO and retinopathy of prematurity (ROP).**[75,97,188] **More recent studies show that anemia in the first week of life in preterm infants less than 28 weeks' gestational age is a significant risk factor for severe ROP,**[89] **but erythropoietin promotor variant is not associated with severe ROP with or without r-HuEPO administration,**[39] **and early r-HuEPO administration is not associated with increased risk for ROP.**[26] The benefits of therapy other than decreased exposure to blood transfusion are also unknown at present. Potential improvements in organ maturation or infant growth because of higher sustained levels of hemoglobin and improved neural development are speculative at present.

Treatment with EPO is most frequently considered in infants of birth weight 800 to 1300 g. Infants with a birth weight less than 800 g may receive so many transfusions early in their hospital course that treating with r-HuEPO may confer no substantial additional benefit. Infants with a birth weight of more than 1300 g rarely require blood transfusion.

If the decision is made to treat with r-HuEPO, therapy can begin when infants are stable and able to tolerate iron supplementation, usually when tolerating approximately 60% of caloric requirements by enteral feedings. The recommended dose of r-HuEPO is 400 U/kg given IV or subcutaneously three times weekly. Oral iron supplementation should be initiated at the time of therapy. A baseline hematocrit measurement and reticulocyte count should be obtained and followed weekly. **Dosing should be adjusted to maintain a reticulocyte count above 6%.** Once treatment is discontinued, hematocrit levels should be monitored every other week until stable.[122]

The *treatment of methemoglobinemia* is methylene blue, 1 to 2 mg/kg given intravenously over 5 to 10 minutes or orally; this therapy is ineffective in infants with deficient NADPH or G6PD, as well as M-hemoglobinopathies. **Treatment of methemoglobinemia in G6PD-deficient infants consists of ascorbic acid, 200 to 500 mg/kg/day.**[71,149]

POLYCYTHEMIA AND HYPERVISCOSITY

Physiology

Neonatal polycythemia **in a term infant is defined by a peripheral venous hemoglobin and hematocrit more than 2 standard deviations (SDs) above the mean; this translates to a hemoglobin greater than 22 g/dL and a hematocrit greater than 65%.**[63] Viscosity is related to but not identical to hematocrit. **The viscosity of blood increases**

linearly with hematocrit up to a hematocrit of 60% and then increases exponentially, but inconsistently thereafter.[91] Although viscosity may be measured directly, required instrumentation is not widely available in clinical laboratories, and hematocrit is often used as a surrogate for viscosity. Blood sampling at 12 hours postnatal age seems ideal to determine hematocrit and viscosity for diagnosis of polycythemic hyperviscosity.[164] Capillary hematocrit can be used as a screening test, but a central venous sample should be analyzed to confirm an abnormally high capillary hematocrit because these values may differ by as much as 20%.[86]

Pathophysiology

The pathophysiology of polycythemia can be attributed to either hyperviscosity or increased RBC mass. ***Hyperviscosity*** is a syndrome of circulatory impairment resulting from increased resistance to blood flow. Complications of polycythemia and hyperviscosity include respiratory distress, congestive heart failure, neurologic signs, and sequelae, such as significant motor and mental retardation and cerebral palsy. Thromboemboli, arterial ischemic stroke, necrotizing enterocolitis, and acute tubular necrosis are additional complications. Complications related to increased RBC mass include hypoglycemia and hyperbilirubinemia.

Polycythemia can result from a large number of perinatal complications, as shown in Box 20.5. Polycythemia and hyperviscosity result from chronic hypoxia, such as that associated with intrauterine growth restriction. However, the cause of polycythemia and hyperviscosity in otherwise normally developed term infants may be unknown. Although delayed cord clamping and umbilical cord milking have been cited as the most frequent causes of polycythemia in term infants, randomized clinical trials in term and near-term infants refute this assertion.[5,106,177] Infants in these trials demonstrated higher hemoglobin and increased ferritin levels with less anemia than infants undergoing early cord clamping, without cord milking. There was also no difference in the incidence of polycythemia or jaundice.[5,106,177]

In up to one-third of ***monochorionic twins***, there is a significant transfusion of blood from one twin into the other, defined as a discrepancy in the infants' blood counts of greater than 5 g/dL of hemoglobin. The recipient twin is usually larger and prone to cardiorespiratory symptoms, hyperviscosity, and hyperbilirubinemia, whereas the donor twin is smaller, anemic, and at risk for congestive heart failure.[173,179] Blood viscosity correlates better with symptoms than does hematocrit.[129] In addition, clinical signs and symptoms may be related to an underlying condition instead of polycythemia per se.

BOX 20.5 CAUSES OF NEONATAL POLYCYTHEMIA

1. Placental transfusion
   a. Excessive transfusion with umbilical cord milking
   b. Twin-to-twin transfusion
2. Intrauterine hypoxia/placental vascular insufficiency
   a. Intrauterine growth restriction syndrome
   b. Maternal diabetes
   c. Maternal smoking
   d. Maternal hypertension syndromes
   e. Maternal cyanotic heart disease
3. Fetal factors
   a. Trisomy 13, 18, 21
   b. Hyperthyroidism
   c. Neonatal thyrotoxicosis
   d. Congenital adrenal hyperplasia
   e. Beckwith-Wiedemann syndrome
4. High altitude
5. Idiopathic

Data Collection

HISTORY

In addition to a complete history of the pregnancy and delivery, questions should be directed to pertinent maternal medical conditions, including insulin-dependent diabetes mellitus, hypertension, and heart disease. Additional maternal risk factors include cigarette smoking and living at high altitude. Fetal risk factors include documented intrauterine growth restriction and umbilical cord milking.

SIGNS AND SYMPTOMS

Newborn infants with hematocrit values greater than 65% to 70% may manifest symptoms because of increased viscosity.[157] Physical

examination may be normal except for plethora and, occasionally, cyanosis. Neurologic findings may include lethargy, irritability, hypotonia, tremor, seizures, and poor suck. Tachypnea, tachycardia, and respiratory distress may be present. Poor GI function is common with abdominal distention, decreased bowel sounds, and poor feeding.

LABORATORY DATA

The diagnosis of polycythemia is based on hemoglobin and hematocrit in comparison with 2 SD normal values for postconceptual and postnatal age. The diagnosis of hyperviscosity may be based on direct viscosity measurement, but usually is assigned based on polycythemia in the presence of consistent clinical signs and symptoms. Affected infants often have thrombocytopenia, hyperbilirubinemia, and hypoglycemia. Tests to rule out hyperthyroidism and adrenal hyperplasia should be performed when indicated. Chromosome analysis should be considered for babies with dysmorphic features.

Treatment

Therapy for polycythemia should be based on the presence of clinical signs and symptoms consistent with hyperviscosity and not laboratory values alone. Traditionally, treatment of polycythemia aims to decrease blood viscosity through phlebotomy or partial exchange transfusion with replacement of removed RBC volume with volume expanders. Supportive care measures should also include IV fluids to treat hypoglycemia and phototherapy to treat hyperbilirubinemia. Although partial exchange transfusion may increase short-term cerebral blood flow,[51] the long-term benefits (follow-up at >2 years) appear to be negligible, with no difference in neurodevelopmental outcomes in patients who were managed conservatively with observation and fluids.[113,109]

Neurologic sequelae in babies with hyperviscosity appear to be related to prenatal risk factors for fetal asphyxia as much as or more so than hematocrit at birth.[150] Additionally, there may be a relationship between partial exchange transfusion and increased GI morbidity related to necrotizing enterocolitis.[127] In general, all peripheral hematocrits greater than 65% need to be checked and confirmed in a central venous sample. Asymptomatic infants with a hematocrit 60% to 70% may be managed conservatively with adequate hydration and glucose monitoring. Some centers recommend that partial exchange transfusion in asymptomatic patients be limited to patients with repeated venous hematocrit measurements greater than 70%.[12,158] For symptomatic patients, conservative treatment aimed at plasma expansion using early feeding or IV fluids may be attempted. However, partial exchange transfusion should be strongly considered in patients with significant cardiopulmonary or neurologic symptoms and those with a central venous hematocrit greater than 70%.

FFP has not shown greater efficacy than saline in an initial correction in hematocrit or viscosity or in improvement in outcome. In a randomized controlled trial, partial exchange transfusion using crystalloid solution (lactated Ringer's solution) was as effective as partial exchange transfusion using a colloid (plasma) in decreasing the hematocrit of polycythemic neonates.[147] Crystalloid solutions are preferable to colloids because they are less expensive and are free from the risk for transmitted infection. Exchange transfusion often requires placement of an umbilical venous catheter (UVC). Risks of umbilical catheterization in polycythemic infants include portal vein thrombosis, phlebitis of the portal vein, and decreased plasma volume (with phlebotomy alone). In addition, infants with polycythemia and hyperviscosity are at increased risk of spontaneous large vessel thrombosis, especially renal vein thrombosis and stroke.

COAGULATION

Physiology

When a blood vessel is torn, blood clots form at the site of vessel injury through a series of carefully controlled cellular and enzymatic reactions. First, *platelets,* which are small, platelike blood cells without nuclei, adhere to the damaged vessel wall by binding to *von Willebrand Factor (VWF)* from Weibel-Palade bodies of the endothelial cells and binding to collagen in the subendothelial matrix. *Glycoprotein (GP)1bα* in nonactivated platelets binds VWF transiently, causing platelet rolling. As contact time between platelets and the subendothelium

increases, platelets adhere to collagen through *GPIa/IIa* (or α2β1) and *GPVI* receptors. As platelets become activated by collagen binding, *GP1bα* joins *GP1bβ*, *GPIX*, and *GPV* (*GP1b-IX-V*) to bind VWF more tightly.[16] The platelets release *adenosine diphosphate (ADP),* which recruits more platelets to the activation process. Activated platelets express a receptor for the blood protein fibrinogen, *GPIIb/IIIa,* which binds to adjoining platelets, leading to platelet aggregation.[96]

Fibrinogen is a contractile protein that pulls platelets together, forming a tightly woven net over the vessel tear. *VWF, fibronectin, and thrombospondin* similarly link activated platelets through the *GPIIb/IIIa receptor.* This is known as a *platelet plug* and is responsible for the initial cessation of bleeding, especially in mucous membranes of the nose, mouth, throat, and GI and genitourinary tracts. At the same time, *thromboxanes* produced by the platelet prostaglandin pathway stimulate platelet aggregation, vasoconstriction, and decreased local blood flow.

Fig. 20.3 **shows the sequential reactions in activation of coagulation known as the *clotting cascade,* which leads to activation of *thrombin,* an important coagulation regulator, and *fibrin,* which stabilizes clot formation.**[96] Procoagulant factors II, VII, IX, and X and regulatory proteins protein C and protein S are all produced in the liver and require vitamin K to become functional. Vitamin K catalyzes the transfer of carboxyl groups to the gamma carbons of glutamic acid residues in vitamin K–dependent proteins; only after carboxylation can these unique proteins bind to phospholipid surfaces via calcium.[59]

The coagulation proteins in blood are inert proenzymes called *zymogens* until they are activated. The primary activation process involves exposure of a potent membrane protein for clotting activation called *tissue factor,* for which the tissue factor pathway of coagulation activation is named (see Fig. 20.3, *panel 2*). Tissue factor is normally hidden in the subendothelium and becomes exposed by vascular injury, or it is presented on the intact surface of monocytes and endothelial cells through the inflammatory process. Small amounts of circulating *activated factor VII (FVIIa)* in the plasma bind to exposed tissue factor and form a complex that results in the sequential activation first of factor X to factor Xa and then of factor II (also called *prothrombin*) to factor IIa (also called *thrombin*). These biochemical reactions are similar in that they take place preferentially on procoagulant phospholipid surfaces of activated endothelial cells and platelets at the site of injury, involve calcium-dependent binding to the phospholipid surface, and can be accelerated by cofactors *(activated factors VIII [FVIIIa] and V [FVa]).*

The contact activation pathway is an alternative route to factor X activation. In this pathway, factor XII is activated by contact with negatively charged subendothelial collagen or by acidosis, cold, or heat injury. Activated factor XII subsequently activates factors XI and IX. *Prekallikrein* and high-molecular-weight *kininogen* serve as cofactors for activation. Contact activation initiates clot lysis and also many inflammatory pathways, including the complement system, which is important for host defense. There is cross-activation between the tissue factor and contact pathways, and they do not function completely independently.

***Thrombin* is the terminal coagulation enzyme and functions as an important regulator of coagulation.** It is a potent platelet activator, and it provides positive feedback activation of factors VIII and V. Thrombin cleaves fibrinogen to form a sticky fibrin strand. Factor XIII is activated by thrombin and cross-links the fibrin strand, greatly increasing its strength and stability. Fibrin then contracts and forms a tight dense clot. A fibrin clot holds apposed surfaces together for about 1 week as thrombin and other growth factors stimulate fibroblasts to grow. Ultimately, scar tissue bridges the original injury.

Thrombin also inhibits coagulation; when complexed to the cell receptor, *thrombomodulin,* it initiates the inactivation of factors VIIIa and Va through activation of protein C (APC). The endothelial protein C receptor (EPCR) enhances the activation of protein C and complements the important protein C system.[36]

Blood clots are dissolved by enzymes in the *fibrinolytic system,* and components of the fibrinolytic system are activated by tissue damage and procoagulant proteins. The blood zymogen plasminogen is activated by tissue plasminogen activator (tPA) or urokinase-type plasminogen activator (uPA), which is released from vascular endothelial cells or renal epithelial cells, respectively. Thrombin also activates a protein called the *thrombin activatable fibrinolytic inhibitor (TAFI),* which removes lysine residues from fibrin resulting in inhibited binding of plasminogen and tPA to fibrin, decreasing fibrinolysis. The activated enzyme plasmin cleaves the fibrin clot into fragments of various sizes, called *fibrin split*

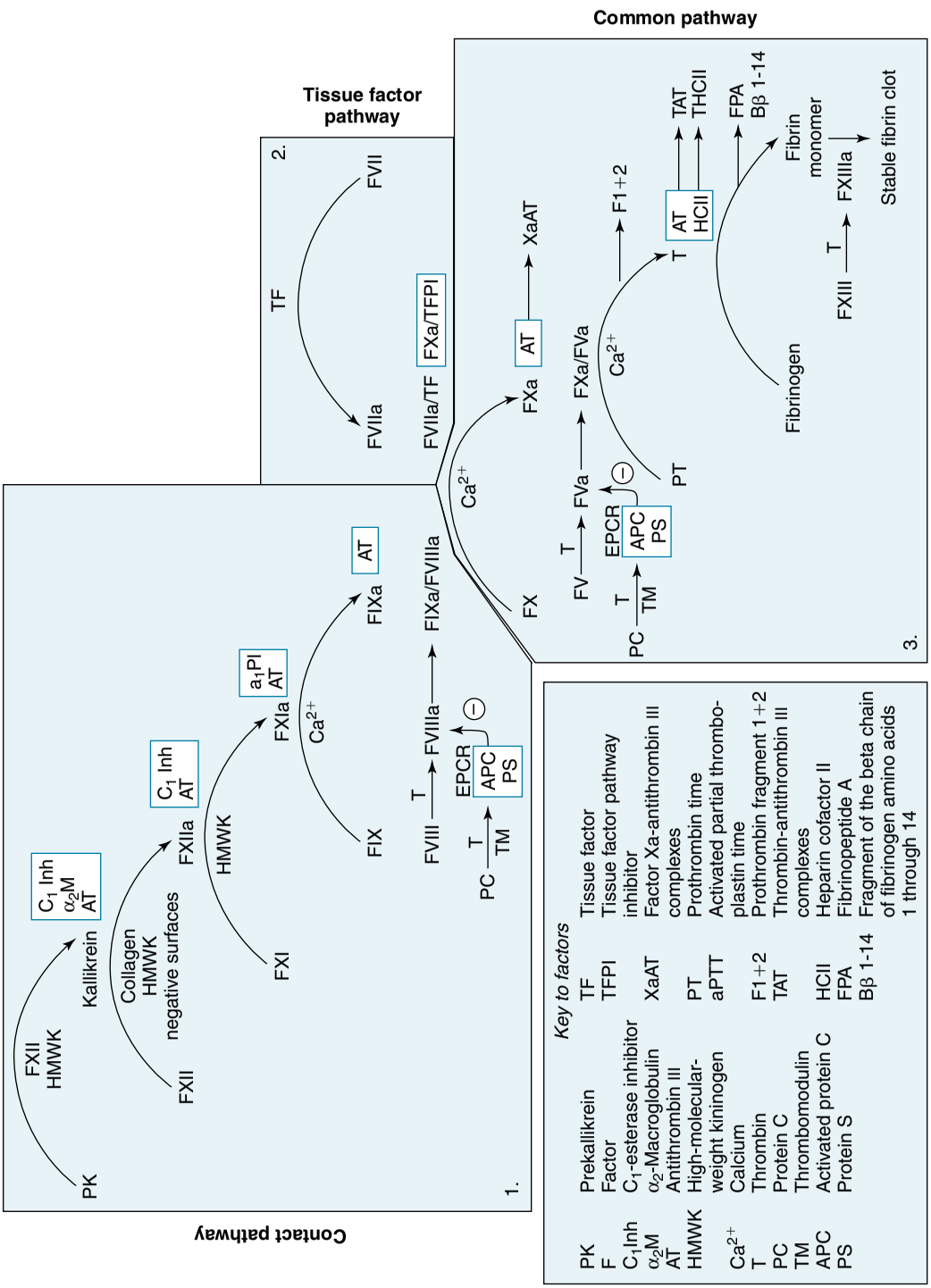

FIGURE 20.3 The clotting cascade. The aPTT screening test and coagulation test factors are included in *panels 1 and 3*. The PT test factors are shown in *panels 2 and 3*. Proteins encased in *boxes* inhibit the procoagulant reactions. *EPCR*, Endothelial protein C receptor.

products (FSPs). Split products that contain factor XIII–mediated cross-linked fibrin are called *D-dimer* fragments.

Several proteins are responsible for regulating the coagulation process and ensuring that these powerful enzymes are not activated in the systemic circulation, causing uncontrolled blood clotting. The most important of these regulatory proteins are antithrombin (AT), protein C, and the protein C cofactor, protein S. Heparin cofactor II, alpha$_2$-macroglobulin, and alpha$_1$-antitrypsin also function as coagulation regulatory proteins. Plasminogen activator inhibitor (PAI) and fibrin binding of plasminogen regulate the activation of fibrinolysis.

NORMAL VALUES

In general, healthy term and preterm infants have platelet counts within the normal adult range. A study of cord blood from more than 34,000 deliveries between 22 and 42 weeks of gestation determined **mean platelet counts ranging from 200,000 to 250,000/μL that increased slightly with gestational age.** The lowest fifth percentile was slightly above or below 100,000/μL in otherwise well infants less than 33 weeks of gestation[28](Fig. 20.4). **In addition, platelet counts increased rapidly after birth, and the fifth percentile was 150,000/μL by 7 days regardless of gestational age.**[28] Certain tests of specific platelet function, including platelet aggregation to physiologic agonists and flow cytometry evaluation of platelet activation, suggest **platelet hyporeactivity at birth and for the first 10 to 14 days of life, with more pronounced effects in premature infants less than 30 weeks' gestational age.**[168] Studies on the duration of platelet hyporeactivity have had mixed results, with some studies reporting normalization to adult levels within a few weeks[166,170] and others reporting a longer period of hyporeactivity.[67,170] Classical aggregometry is difficult to perform in the neonatal period because of a large required blood volume.[170] The platelet function analyzer (PFA-100) is a whole blood test that estimates platelet function by occlusion of a membrane coated with either collagen and epinephrine or collagen and ADP. In contrast with the suggestion of hyporeactivity in aggregation and flow cytometry studies, neonatal platelets have shorter

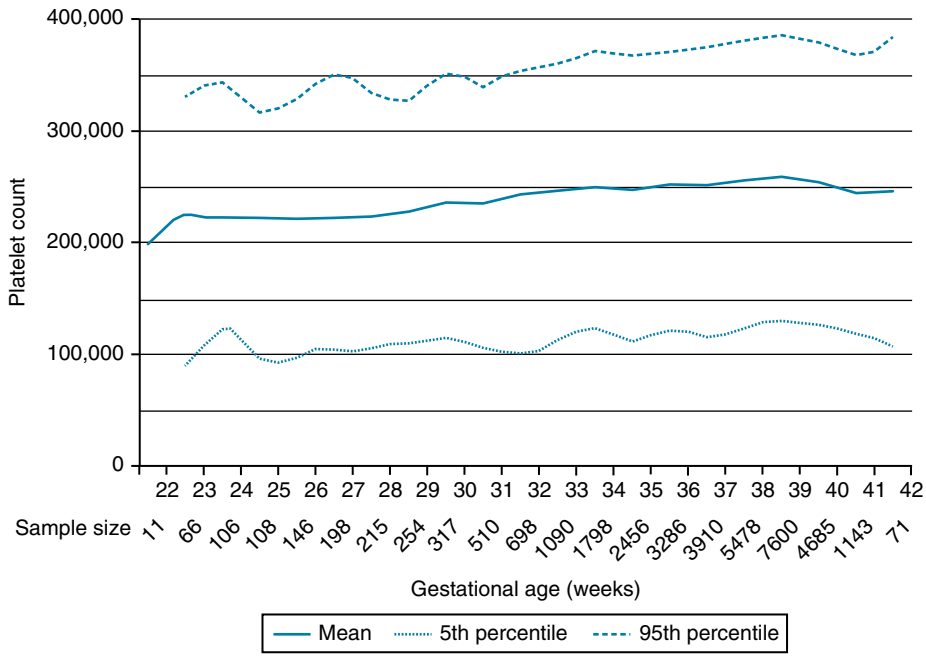

FIGURE 20.4 Reference ranges for platelet counts on the day of birth according to gestational age 22 to 42 weeks. Values were excluded from infants diagnosed with bacterial or fungal sepsis, necrotizing enterocolitis (NEC), or extracorporeal membrane oxygenation (ECMO). (From Christensen RD, Henry E, Del Vecchio A. Thrombocytosis and thrombocytopenia in the NICU. *J Matern Fetal Neonatal Med.* 2012;25:15.)

closure times in the PFA-100 than adult platelets do.[168] Of note, the PFA-100 is primarily used for severe platelet dysfunction such as Glanzmann's thrombasthenia or severe von Willebrand disease and is not sensitive to milder platelet function defects.[19] In addition, the PFA-100 can be falsely abnormal if hematocrit or platelet count is too low. Overall, **newborn platelet hyporeactivity is felt to be balanced by enhancement of other aspects of the coagulation system, and it likely does not increase bleeding risk.**[168]

The *coagulation system* of the newborn infant is unique in that blood clotting proteins mature at different rates (Table 20.4).[65] Mean levels of factors V and VIII and fibrinogen (factor I) are within the normal adult range by 20 weeks of fetal development. Very low levels of these clotting proteins are never normal. The level of the VWF is elevated above adult normal values at birth, and the neonatal VWF *multimers* (assembled VWF protein subunits) include ultralarge forms, which makes the protein more adherent to platelets and vessel walls. **Fetal fibrinogen differs from the adult molecule in its increased content of sialic acid. This prolongs the thrombin time (TT) of the neonate,**[57] **but it is likely that this balances with other changes so there is no net change in bleeding risk.**[112,53] Vitamin K–dependent factors II, VII, IX, and X and protein C and protein S develop very slowly.[6,11] Factor IX does not reach its full adult potential until after 6 months of age; protein C may not reach adult levels until puberty. It is very difficult to determine if these proteins are genetically deficient during the neonatal period.

The clotting system is evaluated using a hemostasis screen, which includes testing for the activated partial thromboplastin time (aPTT), prothrombin time (PT), thrombin time (TT), fibrinogen activity, and platelet count. A test of platelet function, such as the PFA-100, can be included but is not standard. **The PT and aPTT are often prolonged in neonates compared with older children and adults**[7,8,112] **and more prolonged in preterm neonates than in term neonates.**[117,142,143] The TT is slightly prolonged because of fetal fibrinogen until 3 weeks of age. The fibrinogen mean is within the normal adult range at birth in stable term and preterm infants. **Normal ranges can vary with testing reagents, so all values should be interpreted using an age- and laboratory-specific reference range.**[68]

Global coagulation assays that measure thrombin generation over time or clot strength through thromboelastography have been studied to attempt to determine the clinical influences of differences in the neonatal coagulation system. Neonatal plasma generates less thrombin than adult plasma, but thrombin activity is generated after a shorter lag time than that determined in adult plasma.[34,35,171] Similarly, in thromboelastography, the maximum clot formation is lower in neonates than in adults, but the times to clot initiation and clot formation are shorter in neonates than in adults.[169]

The clinical significance of these differences between the neonatal coagulation system and older children and adults is unclear;[142] **treatment of abnormal laboratory values in the absence of clinical bleeding is not recommended.**[27]

BLEEDING

Pathophysiology

THROMBOCYTOPENIA

***Thrombocytopenia* is a general term that denotes a decreased number of platelets in the infant's blood. Thrombocytopenia is the most common coagulation disorder in the neonate.** Determining whether the infant appears well or ill will influence the diagnostic approach, as the causes of thrombocytopenia in an otherwise well infant differ from those in an acutely ill neonate (Box 20.6).

A well-appearing infant is likely to suffer from *neonatal alloimmune thrombocytopenia* (NAIT), in which the platelets are coated by circulating antibody and rapidly cleared from the circulation by the spleen and liver. Alloimmune thrombocytopenia develops when the mother is negative for a platelet antigen, usually PLA-1, for which the father is positive. **Fifty percent of recognized cases of NAIT occur in a mother's first infant.** Subsequent infants can be more severely involved. **Presentations of NAIT range from asymptomatic infants in whom a low platelet count is detected coincidentally on a blood count to fatal cases of intracranial hemorrhage with onset in utero.** Infants of mothers with ***idiopathic thrombocytopenic purpura (ITP)* may have a low platelet count because the maternal antibody crosses the placenta to the infant, but they do not usually develop life-threatening hemorrhage.**[20]

TABLE 20.4 COAGULATION FACTOR VALUES* FOR THE FETUS AND NEWBORN INFANT

AGE-GROUP	I (mg/dL)	II	V	VII	VIII:C	vWF:AG	IX	X	XI	XII	PK	HMWK	XIII	PLASMINOGEN	$ALPHA_2$-ANTIPLASMIN	AT-III	PROTEIN C: AG	PROTEIN S:AG
Fetus (~20 wk)	96	0.16	0.70	0.21	0.50	0.65	0.10	0.19	—	—	—	—	≈0.30	—	—	0.23	0.10	—
	(40)	(0.10)	(0.40)	(0.12)	(0.23)	(0.40)	(0.05)	(0.15)	—	—	—	—	—	—	—	(0.12)	(0.06)	—
Preterm newborn (25–32 wk)	250	0.32	0.80	0.37	0.75	1.50	0.22	0.38	0.20	0.22	0.26	0.28	0.11–0.40	0.35	74	0.35	0.29	—
	(100)	(0.18)	(0.43)	(0.24)	(0.40)	(0.90)	(0.17)	(0.20)	(0.12)	(0.09)	(0.14)	(0.20)	—	(0.20)	(≈50)	(0.20)	(0.21)	—
Preterm newborn (33–36 wk)	300	0.45	0.82	0.59	0.93	1.66	0.41	0.44	—	0.25	0.33	—	—	0.38	73	0.40	0.38	—
	(120)	(0.26)	(0.48)	(0.34)	(0.54)	(1.35)	(0.20)	(0.21)	—	(0.09)	(0.23)	—	—	(0.26)	(≈50)	(0.25)	(0.23)	—
Term newborn (37–41 wk)	240	0.52	1	0.57	1.50	1.60	0.35	0.45	0.42	0.44	0.35	0.64	0.61	0.49	83	0.56	0.50†	0.24†
	(150)	(0.25)	(0.54)	(0.35)	(0.55)	(0.84)	(0.15)	(0.30)	(0.20)	(0.16)	(0.16)	(0.50)	(0.36)	(0.25)	(≈65)	(0.32)	(0.30)	(0.10)
Older infant (age and level when adult value is approximated)	340	0.97	1	0.90	0.93	1.13	0.7	0.55	0.52	1	0.86	0.82	1	1	1	0.82	0.82	—
	(21 days)	(45–60 days)	(1 day)	(21 days)	(1–2 days)	(1 wk)	(6 mo)	(6 wk)	(6 wk)	(14 days)	(6 mo)	(6 mo)	(1 mo)	(6 mo)	(1 wk)	(3–6 mo)	(24 mo)	—

Values are expressed in units per milliliter compared with normal adult subject reference plasma (100% = 1 U/mL) unless otherwise noted; the mean is listed on the white lines, and the lower limit of the normal range, defined as mean minus 2 times standard deviation (or - 2 SD) is shown on the gray lines in parentheses.

*Clotting activity or chromogenic substrate methods (unless labeled with Ag [antigen]) in subjects in the first 24 hours of life.

†Cord blood. All other values are venous. All subjects received vitamin K at birth.

AT-III, Antithrombin III; *factor I,* fibrinogen; *HMWK,* high-molecular-weight kininogen; *mo,* month; *PK,* prekallikrein; *U,* units; *VWF,* von Willebrand factor; *wk,* week.

From Hathaway WE, Bonnar J. *Hemostatic Disorders of the Pregnant Woman and Newborn Infant.* New York, NY: Elsevier Science; 1987.

BOX 20.6 CAUSES OF THROMBOCYTOPENIA IN THE NEWBORN INFANT

1. Well infant
   a. Immune
      Neonatal alloimmune thrombocytopenia (NAIT)
      Maternal idiopathic thrombocytopenia purpura
   b. Constitutional
      Thrombocytopenia–absent radius syndrome
      Amegakaryocytic thrombocytopenia
      Wiskott-Aldrich syndrome
      Fanconi's anemia
      Bernard-Soulier syndrome
      Autosomal dominant thrombocytopenia
2. Sick infant
   a. Respiratory distress syndrome
   b. Bacterial sepsis
   c. Viral infection
   d. Necrotizing enterocolitis
   e. Hyperviscosity
   f. Disseminated intravascular coagulation
3. Infant appearing either well or sick
   a. Kasabach-Merritt (giant hemangioma) syndrome
   b. Trisomy 13, 18, 21
   c. Leukemia
   d. Thrombosis

NAIT, Neonatal alloimmune thrombocytopenia.

Constitutional thrombocytopenia is rare. Affected infants often manifest congenital skeletal malformations of the hands and arms. ***Thrombocytopenia–absent radius (TAR) syndrome*** is a rare but well-characterized platelet syndrome. A bone marrow examination is important to evaluate the megakaryocyte pool. In ***Bernard-Soulier syndrome,*** the platelet number is moderately decreased and giant platelets are seen on the peripheral smear. Infants with ***trisomy 21 (Down syndrome),*** trisomy 18, or trisomy 13 can manifest abnormal platelet counts without apparent illness. The bone marrow of infants with Down syndrome is highly reactive.

Infants with ***large-cavernous hemangiomas*** and ***arteriovenous malformations*** can also trap platelets and consume fibrinogen. Clues to these syndromes include skin hemangiomas; bruits over the liver, spleen, or brain; and high-output congestive heart failure with a structurally normal heart. ***Kaposiform hemangioendothelioma (KHE)*** is a specific vascular tumor associated with a severe, often life-threatening coagulopathy with platelet and fibrinogen trapping resulting in severe thrombocytopenia and hypofibrinogenemia, which is known as the *Kasabach-Merritt phenomenon (KMP)*. KHE presents with affected infants showing a very low platelet number and fibrinogen with elevated D-dimer. Bleeding, including intracranial hemorrhage, can be life-threatening.[1]

Sick infants usually manifest moderate thrombocytopenia. Bacterial and viral infections are the most common cause of thrombocytopenia in the newborn infant and must be excluded in any thrombocytopenic neonate. The infant of a mother with chorioamnionitis often demonstrates thrombocytopenia in the cord blood. Thrombocytopenia develops in most infants with respiratory distress severe enough to require mechanical ventilation. The lowest platelet counts are usually found on about day 3 of life, and normal counts recover by day 10 if the infant's course is not complicated by infection or thrombosis.[141] Infants less than 32 weeks' gestational age with respiratory distress syndrome and severe thrombocytopenia are at increased risk for intracranial hemorrhage.

VITAMIN K DEFICIENCY

The most important bleeding syndrome in the otherwise stable neonate is vitamin K deficiency bleeding (VKDB), previously called ***hemorrhagic disease of the newborn.***[162,172] There is at least a tenfold gradient in vitamin K concentration between the maternal and fetal plasma, with inefficient transmission across the placenta.[162,172] It is not known why fetal levels of vitamin K are maintained at low levels physiologically, but it has been speculated that because high levels of vitamin K are mutagenic in vitro, low levels of vitamin K may be protective during the rapid cellular proliferation and differentiation in utero. Marginal fetal vitamin K levels are further compromised by maternal use of anticonvulsants or warfarin. Approximately 3% of cord blood samples from normal term pregnancies show biochemical evidence of noncarboxylated clotting proteins related to vitamin K deficiency.[161] ***Early VKDB*** presents within the first 24 hours of life with skin bruising, massive cephalohematoma, GI bleeding, or intracranial hemorrhage. ***Classic VKDB*** presents between 1 and 7 days

of life; *late VKDB* occurs between 2 weeks and 6 months of life (predominantly by 2 months of age).[172] The recommendation of the American Academy of Pediatrics and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition is to **give every neonate 1 mg of vitamin K by intramuscular (IM) injection**[2,108]**; this is adequate to prevent bleeding in most infants (see** Table 5.3**).** Vitamin K prophylaxis can be achieved with use of an oral vitamin K preparation; however, it may be less effective than IM preparations at preventing late VKDB,[3,108,157,184] particularly because of difficulty adhering to multiple doses over the first 6 weeks of life.[172] Several different oral dosing regimens have been described,[69,108,136,184] including one discussed in Chapter 5. One study published in 1992 raised concerns that IM vitamin K could increase the risk of childhood leukemia; however, this study has been refuted.*

Vitamin K concentrations are physiologically very low in human breast milk; cow's milk and infant formulas contain significantly more vitamin K (≤15 and ≥60 μg/L, respectively),[108,162,153] **although the bioavailability of vitamin K is enhanced in infants receiving only breast milk.**[162] **Infants who are fed breast milk are at increased risk of vitamin K deficiency.**[172] **In addition, infants with fat malabsorption caused by cystic fibrosis, alpha$_1$-antitrypsin deficiency, or biliary atresia and infants treated with prolonged courses of antibiotics are at increased risk of late vitamin K deficiency. All infants with late-onset vitamin K deficiency should be evaluated for a fat malabsorption syndrome.**[162]

HEMOPHILIA AND OTHER CONGENITAL BLEEDING DISORDERS

The *hemophilias* are a group of lifelong bleeding disorders caused by genetic deficiencies of coagulation proteins. The most common congenital bleeding disorders are factor VIII deficiency (hemophilia A), with an incidence of 1:5,000 live births,[115] and factor IX deficiency (hemophilia B), with an incidence of 1:20,000 live births.[116] Both factors VIII and IX are encoded on the X chromosome; thus deficiency states are manifested primarily in males, with carriers manifesting no symptoms or mild symptoms.[144] Hemophilia can be severe (factor level <1% of normal), moderate (factor level 2% to 5%), or mild (factor level 6% to 40%).[144]

Most infants with even severe hemophilia appear to tolerate labor and a routine vaginal delivery with no undue problems. However, **newborns with hemophilia are 44 times more likely than the general population to experience intracranial hemorrhage at birth, with a higher incidence after vaginal-assisted births and a lower incidence with Caesarian delivery.**[40] **Current recommendations call for vaginal delivery in the absence of complications; however, cesarean delivery should be elected to avoid prolonged or difficult labor. Use of vacuum extraction or forceps to assist delivery should be avoided.**[105]

Approximately 50% of male infants with severe hemophilia will hemorrhage from a circumcision.[83] The absence of procedure-related bleeding in the neonatal period does not exclude hemophilia because hemostasis can be supported by physiologically increased platelet function around birth.

Deficiencies of other coagulation factors, including fibrinogen, or factors XI (hemophilia C), II, V, VII, X, or XIII, are inherited as autosomal traits with severe bleeding manifested with homozygous or compound heterozygous deficiency.[144] Heterozygous deficiencies are less likely to present during infancy. Prolonged bleeding from the umbilical cord stump is suggestive of factor XIII deficiency. ***Von Willebrand disease* is the most common inherited bleeding disorder;** however, only those with the most severe type of VWD (type 3) present in infancy and young childhood.[152,165]

LIVER FAILURE

The coagulopathy of liver failure is complex and includes thrombocytopenia, platelet dysfunction, decreased synthesis of coagulation proteins in the liver, and enhanced fibrinolysis. Severe liver disease is characterized by a markedly abnormal PT in excess of aPTT prolongation, along with other signs of liver dysfunction, such as hepatomegaly, jaundice, and elevated liver enzymes. **Liver failure in the neonatal period can result from viral hepatitis or rare metabolic disorders such as infantile hemochromatosis.**[14] **Infants with liver dysfunction manifest bleeding into the skin, GI tract, retroperitoneum, and cranium. Invasive procedures, such as liver biopsy, can provoke severe bleeding but have been shown to be generally safe with the precaution**

*References 3, 22, 46, 130, 131, 146, 148, 181.

of transfusing FFP if the international normalized ratio (INR) is greater than or equal to 1.5 before the procedure, or transfusing platelets if the platelet count is less than 50,000/μL.[23]

CONGENITAL PLATELET DYSFUNCTION

Genetic platelet function defects causing severe bleeding in the neonatal period are rare. ***Glanzmann's thrombasthenia*** is an autosomal recessive disorder resulting from a severe deficiency or dysfunction in the platelet fibrinogen receptor GPIIb/IIIa. Severe neonatal bleeding, including intracranial hemorrhage, can occur. Platelet number is normal in this syndrome. Absent receptors can be determined by flow cytometry, and genetic mutations have been determined, but all cases can be diagnosed by severe abnormalities on platelet aggregation studies or PFA-100 in the context of normal hematocrit and platelet count.[73] ***Bernard-Soulier*** is an autosomal recessive disorder from a defect in the platelet GPIb/IX/V receptor for VWF that also results in macrothrombocytopenia.[118]

Platelet storage pool disorders can be suspected from abnormal granule staining on the peripheral smear. ***Hermansky-Pudlak syndrome*** is a recessively inherited syndrome characterized by the absence of platelet-dense granules, often with oculocutaneous albinism.[73,118] ***Chédiak-Higashi disease*** is an autosomal recessive disease characterized by large, dysfunctional platelet granules and granulocytic cytoplasmic granules, with associated immunodeficiency.[73] ***Wiskott-Aldrich syndrome*** is an X-linked disease associated with small dysfunctional platelets, severe eczema, and immunodeficiency.[118] In *gray platelet syndrome,* the alpha granules are absent, the platelets have a pale appearance on the peripheral smear, and the bleeding phenotype is typically mild.[73] Acquired platelet dysfunction can cause bleeding in the first several days of life in an infant after maternal use of aspirin or other drugs affecting platelet function shortly before delivery.[172]

Diagnosis and Management

HISTORY

A history of maternal bleeding, medical and obstetric diagnoses, and medications should be elicited for every infant at birth. A careful family history for bleeding disorders in the parents, grandparents, siblings, aunts, uncles, and cousins should be taken as part of every admission evaluation. Specific questions must be asked about excessive bleeding with surgeries (including dental procedures), menses, childbirth, traumas, and spontaneous bleeding events. Efforts should be made to obtain confirmatory medical records for any positive response. Procedures, including circumcision, should not be performed until the possibility of a bleeding disorder in the infant is excluded. The administration of vitamin K to the infant should be confirmed by review of the chart.

SIGNS AND SYMPTOMS

Thrombocytopenia usually manifests with small, flat hemorrhages into the skin called ***petechiae*** that do not blanch with pressure. Petechiae may be concentrated in skin creases of the neck and axilla and around the site of a tourniquet or may be scattered over the entire body. More severe thrombocytopenia results in large ***ecchymoses,*** which are flat bruises. Infants with severe thrombocytopenia may hemorrhage into the central nervous system or GI tract.

Bleeding with coagulation disorders can manifest as palpable ***hematomas*** of the skin and scalp. Large cephalohematomas are common and can result in a decreased hematocrit. Intracranial, retroperitoneal, intraperitoneal, GI, and genitourinary bleeding may occur. Bleeding with surgeries or procedures may be immediate or delayed. Three-fourths of infants affected with severe hemophilia are diagnosed in the first month of life.

Hemangiomas are dark red raised lesions that blanch with pressure. KHE tumors are usually solitary indurated tumors with a pebbly rough surface and indistinct margins. The lesions may be associated with hypertrichosis or increased sweating. ***Arteriovenous malformations*** may not have skin manifestations but may have overlying swelling and warmth, and an overlying bruit may be heard.

LABORATORY DATA

Any infant with bleeding signs should be evaluated with a hemostasis screen and a platelet count. The CBC should be reviewed with attention to all cell lines. The peripheral smear should be carefully inspected for evidence of giant platelets or platelet clumping in the feathered edge of

the smear. **The results of the hemostasis screen in the healthy infant and during many states of illness are shown in** Table 20.5. **PT and/or PTT will be prolonged if any factor level is below the threshold of the test (typically around 30%).** Low factor levels caused by vitamin K deficiency can be confirmed with PIVKA (protein induced by vitamin K absence or antagonism, also called *des-gamma-carboxy-prothrombin*) testing, which examines the amount of prothrombin that has not been carboxylated with vitamin K.[62] **The possibility of hemophilia should be excluded by specific assay of factor VIII and factor IX. Severe *von Willebrand disease* can present with excessive bleeding in the neonatal period and is diagnosed by VWF activity that is less than 10% (IU/dL). In addition, fibrinogen and factors XIII, alpha2-antiplasmin, and plasminogen activator inhibitor-1 (PAI-1) should be assayed in a term infant with unexplained significant hemorrhage,** such as intracranial hemorrhage. If Glanzmann's or a similar congenital platelet dysfunction is suspected, **platelet function should be assessed with a screening test** (e.g., the PFA-100), platelet aggregation studies, or platelet receptor flow cytometry studies. **Heparin-induced thrombocytopenia (HIT) is rare in pediatrics[119] but should be considered in patients with a drop in platelet count greater than or equal to 50% to below 150,000/μL without an alternative cause, typically after 5 days of heparin administration.**[145]

Treatment

THROMBOCYTOPENIA

Therapy for thrombocytopenia depends on the overall health and stability of the neonate, as well as the cause of the thrombocytopenia. In immune thrombocytopenia, antibodies that are affecting neonatal platelets also may cause rapid destruction of transfused platelets. Platelet antibodies in infants with NAIT do not react against maternal platelets, and **washed maternal platelets are an effective therapy for affected infants with severe bleeding.**[168]

Thrombocytopenia in this disorder, as well as maternal autoimmune thrombocytopenia, responds well to IVIG. **Infants with alloimmune thrombocytopenia are likely to receive incompatible platelets from a random donor, and platelet transfusions, when needed, must be from a donor who shares the maternal antigen profile** if time and availability permit.

If HIT is suspected, heparin should be stopped promptly, a blood sample sent for HIT testing, and alternative anticoagulation (e.g., with *argatroban* or *bivalirudin*) should be substituted, until test results are obtained. Although there have been no prospective randomized clinical trials, infants with KHE and KMP have been treated with steroids and vincristine, either agent along with an antifibrinolytic agent (epsilon-aminocaproic acid or tranexamic acid), a platelet inhibitor (aspirin, ticlopidine, or clopidogrel), or

TABLE 20.5 COAGULATION RESULTS IN NORMAL NEONATES AND NEONATES WITH BLEEDING SYNDROMES

DESCRIPTION	PTT	PT	TT	FIB	D-DIMER	PLT CT
Healthy term	N-↑	N-↑	↑	NL	Neg	NL
Healthy preterm	↑↑	N-↑	↑	NL	Neg	NL
Vitamin K deficiency	↑↑	↑↑↑	↑	NL	Neg	NL
Liver disease	↑↑	↑↑↑	↑↑-↑↑↑	↓	Pos	↓
Hemophilia	↑↑↑	N-↑	↑	NL	Neg	NL
DIC	↑↑↑	↑↑	↑↑	↓	Pos	↓↓

DIC, Disseminated intravascular coagulation; *Fib,* fibrinogen; *N,* normal; *PLT CT,* platelet count; *PT,* prothrombin time; *PTT,* partial thromboplastin time; *TT,* thrombin time; ↑, mildly prolonged; ↑↑, moderately prolonged; ↑↑↑, severely prolonged; ↓, decreased.

interferon-α.[47] There is currently an ongoing clinical trial using sirolimus for vascular malformations that include KHE.

The primary support for most other thrombocytopenic infants is replacement transfusions of platelets, which are derived from CMV-reduced donor units. A stable, otherwise healthy infant can tolerate a platelet count as low as 20,000/μL without undue risk of serious bleeding. A recent prospective, randomized multicenter clinical trial in **preterm infants less than 34 weeks' gestational age found that patients who were transfused at higher platelet thresholds of 50,000/μL had significantly increased rates of mortality and severe bleeding events compared with preterm infants who were transfused at a lower platelet threshold of 25,000/μL at 1 month postrandomization.**[32] This suggests that a more restrictive approach to platelet transfusions may result in more favorable outcomes.

VITAMIN K DEFICIENCY

Infants with vitamin K deficiency bleeding are treated with 1 to 5 mg of vitamin K by slow IV push or IM injection. FFP, 10 to 15 mL/kg, may be given to control active bleeding, and **the use of four-factor prothrombin concentrates,** which are vitamin K–dependent clotting factors purified from human plasma, **have also been used off-label to control active bleeding.**[141,197]

Neonates with severe liver disease can be treated for active bleeding or prepared for liver biopsy using transfusions of FFP and platelet concentrates. Parenteral administration of vitamin K should be confirmed; ongoing replacement may be necessary if there is fat malabsorption. There is no benefit to treating babies with liver disease and abnormal clotting tests but without clinical bleeding signs.[61] **Recombinant factor VIIa has been used to control bleeding in children with liver failure,**[17] although there may be an associated risk of thrombosis.[194] **Prothrombin complex concentrates have also been used off-label in liver failure** in a few cases. Although a meta-analysis did not yield sufficient evidence to allow a recommendation for use of prothrombin complex concentrates for bleeding in neonates,[197] **these concentrates may be dosed at much smaller volumes than FFP and may be clinically useful for situations in which close attention must be paid to volume status. Consultation with a regional hemophilia treatment center about use and availability of these specialized products is strongly recommended.**

HEMOPHILIA AND OTHER CONGENITAL BLEEDING DISORDERS

Treatment of congenital coagulation factor deficiencies is based on the deficient factor. The most specific product available should be used. **Factor VIII or IX should be replaced in a bleeding neonate (or for surgery) using intravenously administered recombinant or plasma-derived factor concentrates.** Although recombinant factor VIII products have previously been recommended because of a presumed decrease in risk of viral transmission, **treatment of severe factor VIII deficiency with plasma-derived factor VIII products decreases the risk of inhibitory allo-antibody formation to factor VIII,**[132] **a major complication that occurs in 30% of those with severe hemophilia A.** New treatments for hemophilia A and B are developing rapidly. **In 2018, the U.S. Food and Drug Administration (FDA) approved *emicizumab,* a subcutaneously administered bispecific antibody that mimics the activity of factor VIII, for prevention of bleeding in patients with hemophilia A of any age, with or without inhibitors.**[93,124] **Gene therapy and other nonfactor treatments are currently in clinical trials.**[10]

Factor VII may be replaced using recombinant factor VIIa in low doses of 15 to 25 mcg/kg every 6 to 12 hours. Viral-inactivated, human plasma–derived concentrates are available for VWF, fibrinogen, factor X, factor XIII, AT, and protein C. **Factor II (prothrombin) may be replaced using prothrombin complex concentrates; a hemophilia center pharmacist should be consulted for factor concentrations in specific brands and lots.**

If factor-specific concentrates are not available, factor XIII, factor VIII, and fibrinogen may be replaced with cryoprecipitate. Replacement of factor V, XI and other clotting proteins usually requires FFP. *Desmopressin (DDAVP),* a synthetic vasopressin that stimulates release of endothelial stores of factor VIII and VWF, **is generally not used in the neonate because of the possibility of seizures related to hyponatremia in this age group. Antifibrinolytic agents**

are effective for infants with fibrinolytic defects, such as severe deficiency of PAI-1, or to supplement other bleeding treatments. A hemophilia center should be involved in the diagnosis and management of all infants with congenital bleeding disorders.

CONGENITAL PLATELET DYSFUNCTION

In congenital platelet function disorders, bleeding can be treated with platelet transfusions and antifibrinolytics such as aminocaproic acid. Because of concern about the increased risk for development of platelet antibodies and platelet refractoriness, recombinant factor VIIa is also approved for the treatment of bleeding in Glanzmann's thrombasthenia.[134]

Prevention and Parent Teaching

Mothers should be instructed during pregnancy that vitamin K deficiency is routinely prevented with an IM injection of vitamin K to the neonate. Nursery personnel and primary care providers should be careful to document administration of vitamin K, especially for infants born at home. For babies whose parents refuse IM vitamin K, even after education, oral supplementation should be offered.

Bleeding in an infant with a bleeding disorder can be minimized by exerting care to prevent undue trauma. IM injections and other invasive procedures should be avoided if at all possible, although vitamin K may be safely administered to infants with severe hemophilia if a small-bore needle is used, care is taken not to Z-track the needle under the skin, and pressure is held at the site for at least 15 minutes using a pressure dressing. The infant should be handled in as gentle a manner as possible. Pressure for holding and placement of a tourniquet should be minimized. Extreme care should be taken with arterial puncture.

Replacement platelet or clotting factor infusions should be considered before any necessary invasive procedure. Parents should be educated about the nature of the bleeding disorder and its cause in their infant. They should know whether this is a time-limited complication of the neonatal course or a long-term concern. Infants with constitutional bleeding disorders have a lifelong risk of bleeding. The benefits and any risks of treatment must be conveyed to the infant's parents. Any other family member at risk of having a genetic bleeding disorder should be identified, screened, and counseled.

Education of families about hemophilia or constitutional platelet disorders begins as soon as the diagnosis is established. Parents should be instructed about routine infant care and the recognition of possible bleeding events, in coordination with hemophilia treatment center staff.

Thrombosis

PATHOPHYSIOLOGY

Thrombosis is an uncommon problem in pediatric patients, with increased incidence noted both in the neonatal period and after puberty.[138] The incidence of venous thromboembolism in the neonatal population has been increasing over time, and the incidence is higher in preterm infants than in term infants.[64,156] Physiologic correlates of the neonate's increased predisposition to thrombosis are shown in Boxes 20.7 and 20.8. The most common risk factor for venous thromboembolism is a central venous catheter (CVC)[64]. CVC-associated thrombosis should be suspected in an infant with a malfunctioning central line, an idiopathic falling platelet count, or unexplained swelling or discoloration. In addition, an infected clot should be suspected in an infant with diagnosed catheter-related thrombosis and alterations in temperature, respiratory stability, or cardiovascular stability.

Thrombi not associated with a CVC in the newborn period most commonly manifest as renal vein thrombosis (RVT), cerebral

BOX 20.7 PROTHROMBOTIC CHARACTERISTICS OF NEONATAL BLOOD

- Increased hematocrit values
- Increased concentration and size of von Willebrand factor multimers
- Increased concentration of circulating tissue factor in preterm infants
- Low concentrations of physiologic anticoagulants, antithrombin, protein C, protein S, and tissue factor pathway inhibitor
- Low concentration of the fibrinolytic protein plasminogen
- Small-caliber, reactive blood vessels

BOX 20.8 PATHOLOGIC CONDITIONS PREDISPOSING TO THROMBOSIS IN THE NEONATE

- Hypotension
- Hyperviscosity
- Severe genetic and acquired deficiencies of antithrombin, protein C, protein S, and plasminogen[113,121]
- Genetic mutations in factor V and prothrombin; elevations in homocysteine and lipoprotein(a)
- Mechanical obstruction by catheters
- Maternal diabetes mellitus

sinovenous thrombosis (CSVT), or perinatal stroke. Thrombosis in the stable term infant most often presents in the first few days of life and may be of fetal onset. RVT and CSVT may also be provoked by dehydration or other illness.

Testing for an underlying thrombophilia in a neonate is controversial[64] and should be considered on a case-by-case basis. In general, thrombophilia testing is unlikely to be beneficial in neonates with provoked thrombi and without a family history of thrombosis.

Perinatal stroke (before 28 days of age; see Chapter 26) is typically multifactorial, including prenatal blood circulation and placental changes at delivery. Thus, extension and recurrence rates are low, and treatment with aspirin or anticoagulants is often not indicated (see Chapter 26). Although thrombophilia testing after stroke is controversial,[33,77,120] a recent large case-control study suggests that thrombophilia risk is not increased in children with perinatal stroke.[33]

PURPURA FULMINANS

Purpura fulminans is a syndrome of skin necrosis from thrombosis in the postcapillary venules caused by severe deficiencies of protein C or protein S.[92,94,95] Most cases are caused by homozygous or compound heterozygous genetic defects, so urgent testing for protein C and protein S deficiency is needed. Protein C or protein S is usually below the laboratory limit of detection. Screening coagulation tests are often normal initially, but DIC quickly develops and can be controlled only by replacement of the missing protein. Purpura fulminans is uniformly fatal if untreated. Rarely, acquired deficiencies from maternal lupus anticoagulants can mimic these genetic syndromes. ***Purpura fulminans*** complicating bacterial sepsis or meningitis has a similar pathophysiology to genetic deficiency and is caused by acquired consumption of protein C and protein S at the endothelial cell surface. Purpura fulminans associated with infection usually manifests at a later age and is less fulminant than the genetic syndromes.[30]

THROMBOCYTOSIS

Thrombocytosis is typically defined as a platelet count greater than 450,000/μL, with extreme thrombocytosis defined as a platelet count greater than 1,000,000/μL.[81] Inflammation after infection is the most common cause of ***thrombocytosis*** in the neonatal period.[104,183] After interruption of platelet consumption by a thrombus, which occurs with successful implementation of anticoagulation, infants may often manifest thrombocytosis from increased bone marrow synthesis and release.[176] Down syndrome,[58,78] iron-deficiency anemia,[52] and maternal drugs and medications (e.g., methadone)[18] may also be associated with thrombocytosis. *Primary thrombocytosis* is a very rare syndrome that is seldom diagnosed in the neonatal period.[81]

HEPARIN-INDUCED THROMBOCYTOPENIA

Heparin-induced thrombocytopenia (HIT) has been described in neonates, especially infants with significant heparin exposure associated with cardiac surgery, cardiopulmonary bypass, or extracorporeal membrane oxygenation (ECMO).[145] HIT is caused by antibodies that develop against a complex of heparin with platelet factor IV on the platelet surface. When HIT is suspected, all heparin must be promptly removed, including solutions used to flush catheters. ***Parenteral direct thrombin inhibitors (DTIs)*** can be used as an alternative anticoagulant; ***argatroban*** and ***bivalirudin*** have been studied in the neonate.[192,193] Although bleeding, including intracranial hemorrhage, is a risk with these parenteral DTIs, it is unclear if they have a higher bleeding risk than heparin, as the drugs have not been directly compared.

Diagnosis and Management

HISTORY

For neonates in whom thrombosis has been discovered, family history is important in

determining if a workup for hypercoagulability should be initiated. A history of thrombosis, including deep vein thrombosis, pulmonary embolism, heart attack, or stroke in persons younger than 50 years of age in the parents, grandparents, siblings, aunts, uncles, and cousins of the infant, raises suspicion of genetic thrombophilia. Many family members affected with heterozygous deficiencies of AT, protein C, or protein S are asymptomatic. A history of fetal or neonatal death with thrombosis is helpful. Maternal obstetric complications have been linked to thrombophilia. A maternal history of severe or recurrent preeclampsia, severe intrauterine growth restriction, three first-trimester losses, or any fetal death beyond 10 weeks of gestation could indicate potential thrombophilia. Maternal abnormalities of fibrinogen are associated with placental abruption and early pregnancy loss . Maternal diabetes mellitus and placental transfer of antiphospholipid antibodies are causes of acquired neonatal thrombophilia.

Signs and Symptoms

THROMBOSIS

Signs and symptoms of thrombosis are dependent on the site of thrombosis. Signs of decreased organ perfusion and subsequent dysfunction indicate the possibility of a thrombosis. The classic presentation of ***renal vein thrombosis*** includes hematuria, proteinuria, thrombocytopenia, and hypertension.[114] Palpably enlarged kidneys may be noted on physical examination, and prenatal RVT should be considered in patients with unilateral or bilateral flank masses on initial examination.[82] ***Stroke*** usually presents with seizures during the first 24 hours of life or with early handedness preference. ***Aortic thromboses*** present with cool, pale extremities, decreased pulses and capillary refill, and upper extremity hypertension. Classic signs of arterial emboli include purple toes or fingers. Thrombosis can also present with an idiopathic decrease in platelet count.

Confirmation of thrombosis is made with ultrasound examination of the vasculature or with computed tomography or magnetic resonance imaging and angiography of the brain if there is concern for intracranial clot.

Purpura Fulminans. Purpura fulminans from congenital protein C or protein S deficiency is a dramatic syndrome that usually manifests within hours of birth. Infants develop patchy areas of skin thrombosis over the trunk and buttocks, usually in dependent areas. The lesions are palpable and initially dark red and quickly become dusky purple and then black; an eschar forms. The lesions are exquisitely painful. Most infants with severe protein C deficiency manifest a white light reflex of the eyes from in utero thrombosis of the primary vitreal veins with subsequent retinal detachment, hemorrhage, and blindness.[94] Imaging studies of the brain show evidence of CNS infarction in many infants. Renal vein thrombosis is not uncommon.

Thrombocytosis. Infants rarely manifest signs of thrombocytosis. Occasionally, platelet counts of greater than 2,000,000/μL are associated with cerebral ischemia and may manifest as poor feeding, irritability, lethargy, or a focal neurologic deficit.

LABORATORY EVALUATION

Before initiation of anticoagulation, a CBC including platelets and coagulation studies should be obtained. Because infants have physiologically prolonged baseline aPTT values, low and variable levels of AT, and accelerated drug clearance, anticoagulation with heparin products should be monitored using an anti-Xa activity level, if at all possible. If anti-Xa levels are subtherapeutic on high doses of unfractionated heparin, consider checking the AT level. In addition, infants who are refractory to the anticoagulant effects of unfractionated heparin often manifest an enhanced response to low-molecular-weight heparin. Screening for inherited thrombophilia should be guided by clinical presentation and family history.

Treatment. The optimal therapy for neonatal thrombosis has not been determined. In the absence of any significant contraindications, anticoagulation remains the standard of care for most neonatal thromboses to prevent clot extension, end-organ damage, development of pulmonary embolism, or post-thrombotic syndrome.[111] Anticoagulation must be weighed against the risk of bleeding for each individual case. The duration of anticoagulation is typically 3

months for venous clots and 7 days for arterial clots.[111] Long-term anticoagulation is necessary only in the small proportion of infants who have an ongoing trigger for thrombosis or who have experienced a thrombus recurrence.

Neonates are relatively heparin resistant compared with older children and adults and have baseline AT levels about 50% of the predicted value for adults.[8] Additionally, heparin has accelerated clearance and increased volume of distribution in the neonate, which can make it more difficult to achieve therapeutic anti-Xa levels.[102] Off-label use of AT concentrate has been increasing to help achieve therapeutic anticoagulation in heparin-resistant neonates.[42,151,185,186] Parenteral DTIs, including ***bivalirudin*** and ***argatroban***, do not require AT for therapeutic action. Several prospective studies, which included infants younger than 6 months of age, have been conducted using either *bivalirudin* or *argatroban*.[195,196] These studies found low rates of clinically significant bleeding complications with early clot resolution, although severe bleeding, including intracranial hemorrhage, is an important risk of any anticoagulant, especially in sick preterm infants.[195,196] Large prospective trials into the use of bivalirudin and argatroban in the neonatal population are needed. DTIs should only be used in consultation with hematology.

Thrombolytic, or fibrinolytic, therapy, involves localized or systemic infusion of an activator of the fibrinolytic system, typically tPA. Thrombolytic therapy is intended to rapidly restore blood flow. However, the risk of hemorrhage is greater with thrombolytic therapy, especially in preterm infants. Oozing around catheters is the most common bleeding complication of fibrinolytic therapy, but the most important complication is CNS bleeding, which occurs most often in infants with brain ischemia from a previous episode of asphyxia or hypotension. Thrombolytic therapy, if deemed acceptably safe, may be indicated for life- or limb-threatening aortic thrombosis and thromboses affecting shunts in infants with complex congenital heart disease.[182]

Thrombolytic therapy can also be considered for bilateral renal vein thrombosis,[13] although it should be recognized that many episodes of renal vein thrombosis have onset in utero, and clots may be too organized for effective thrombolysis. Kidney enlargement and certain imaging features can be used to estimate the age of the clot.

Dosing schemes for anticoagulation and fibrinolytic therapy are shown in Box 20.9.

PURPURA FULMINANS

Treatment of neonatal purpura fulminans caused by genetic thrombophilia is replacement of the deficient regulatory protein. Viral-inactivated, human

BOX 20.9 ANTITHROMBOTIC THERAPY IN THE NEONATE

Anticoagulant Therapy

Unfractionated Heparin

Term infants: 75 to 100 U/kg bolus per micromedex.

maintenance of 25-30 U/kg per micromedex; adjusted to maintain anti-Xa activity level of 0.3 to 0.7 U/mL

Preterm infants: 50 U/kg bolus

15 to 35 U/kg/hr maintenance; adjusted to maintain anti-Xa activity level of 0.3 to 0.7 U/mL

Low-Molecular-Weight Heparin (Enoxaparin)

1.5 mg/kg subcutaneously every 12 hours; adjusted to maintain anti-Xa activity level of 0.5 to 1 U/mL 4 hours after injection

Fibrinolytic Therapy

Tissue Plasminogen Activator (tPA)

0.1 to 0.5 mg/kg/hr for 4 to 12 hours (bleeding risk is greater at the higher doses) or 0.06 to 0.12 mg/kg/hr for 12 to 48 hours

Fibrinolytic therapy has been given to neonates both as higher-dose, shorter infusions and lower-dose, longer-term infusions. The higher-dose infusions may be more effective in thromboses that are acute, arterial, and smaller in volume (e.g., aortic or cardiac). Lower, longer infusions may be more efficacious in larger, older, or venous thromboses (e.g., subclavian or extensive vena cava).

Contraindications to tPA: Intracranial hemorrhage, surgery, or ischemia (poor Apgar scores) in previous 10 days; surgery within 7 days; invasive procedures within 72 hours; seizures within 48 hours; active bleeding

Concomitant with tPA, may give heparin 10 U/kg/hr (no bolus) or enoxaparin 0.5 mg/kg every 12 hours subcutaneously

Consider FFP 10 mL/kg every 24 hours to replace plasminogen.

Term infants show the highest dose requirements for unfractionated and low-molecular-weight heparin with increased volume of distribution and more rapid plasma elimination. Extremely preterm infants show the lowest dose requirements.

AT, Antithrombin; *FFP,* fresh frozen plasma; *tPA,* tissue plasminogen activator; *U,* units.

plasma–derived protein C concentrate is FDA approved for severe protein C deficiency. Protein S is currently available only in FFP. The hemophilia center staff members are the best resources for information on the availability and safety of existing replacement proteins. FFP may be administered while confirmatory laboratory assays are being performed, using 10 mL/kg every 8 to 12 hours. Prophylactic replacement with protein C concentrate is currently available for infants with severe genetic protein C deficiency, although some infants may be medically managed with anticoagulation alone after the neonatal period and up until puberty.

Infants with acquired deficiencies of protein C or S caused by autoantibodies may respond to IVIG or steroids in addition to plasma replacement. Infants with sepsis and purpura fulminans may require FFP or protein concentrate until antibiotics have successfully controlled their infection.

Parent Teaching

Parents of infants with severe genetic deficiencies of protein C or S require intensive education regarding the administration and monitoring of anticoagulation therapy, observation for early lesions of purpura fulminans or bleeding, and care and rehabilitation of early lesions. Parents of children without severe thrombophilia, but who will be discharged to home on anticoagulation, require similar teaching about the administration and monitoring of anticoagulation therapy and observation for bleeding complications.

DISSEMINATED INTRAVASCULAR COAGULATION

In DIC, the activation of blood-clotting proteins is initiated by tissue factor from bacterial products (endotoxin) or inflammation (cellular expression through protease activatable receptors) or through the contact system.[139] The activation of clotting proteins leads to a hypercoagulable state, and thromboses form, especially in the small vessels of the liver, spleen, brain, lungs, kidneys, and adrenal glands. The bone marrow and liver partially compensate by releasing platelets and clotting factors into circulation. However, the regulatory system of coagulation is immature in term and preterm neonates. The capacity to neutralize activated clotting proteins is quickly exhausted, and the resulting deficiency of platelets and clotting factors is called ***consumptive coagulopathy***. Thrombocytopenia in an ill infant is often part of the larger syndrome of DIC. DIC predisposes a preterm infant to intracranial hemorrhage.[178] Venous thrombosis of the germinal matrix occurs as the initial lesion, followed by post-thrombotic hemorrhage. Bleeding is also seen in the skin around indwelling catheters, endotracheal tubes, and chest tubes; into the lungs and other parenchyma; and in the urine and stool.

TREATMENT

Transfusion of platelets for infants with thrombosis or DIC may aggravate the platelet consumption unless specific therapy for the underlying condition is also administered. The primary treatment of DIC is reversal of the trigger (Box 20.10). Adequate ventilation, support of circulation and perfusion, treatment of sepsis, and general supportive care usually interrupt the DIC process within 48 hours. Routine infusion of FFP into infants with DIC without clinical bleeding does not improve infant outcomes, although infants with active bleeding require replacement of coagulation proteins and platelets to maintain minimal hemostatic levels.[61] Replacement of coagulation regulatory proteins in FFP or AT concentrate or inhibition of coagulation activation with low-dose heparin have been recommended in various guidelines and may be helpful in some situations.

BOX 20.10 THERAPY OF DISSEMINATED INTRAVASCULAR COAGULATION

1. Reverse the trigger: Treat the underlying disorder.
2. In bleeding infants, maintain hemostatic levels of fibrinogen (>100 mg/dL) and platelets (50,000/μL) using cryoprecipitate, FFP, and platelet concentrates (10 mL/kg). FFP is also indicated to treat bleeding infants with PT greater than 3 seconds above the upper limit of normal.
3. If necessary, replace regulatory proteins; antithrombin or protein C concentrate (50 to 150 U/kg).
4. Consider low-dose heparin therapy 10 U/kg/hr if survival of infused fibrinogen and platelets is less than 12 hours.

FFP, Fresh frozen plasma.

However, in a recent meta-analysis of 1340 adult patients, heparin was found to increase bleeding risk without improving mortality,[190] so coagulation inhibitors should be used with caution.

WHITE BLOOD CELLS

Physiology

White blood cell production in the fetus begins relatively late in human gestation (14 to 16 weeks) and appears to be limited to the bone marrow, in contrast with erythropoiesis, which is found earlier in the liver, spleen, and lymph nodes. The neutrophil reserve pool size is extremely small during the second trimester and increases slowly during gestation. At 18 to 20 weeks, the total fetal white cell count is approximately 4000 with 5% neutrophils.[133] This increases to 8.5%, or 350 absolute neutrophil count, by 26 to 30 weeks. Developmental levels of total granulocytes and neutrophils are shown in Fig. 20.5. Thus a baby born extremely premature has severely limited neutrophil capacity and is at increased risk for overwhelming bacterial infection.

White cell counts rise after normal delivery, with a peak at 12 hours, and gradually decline over the subsequent 48 hours, as shown in Fig. 20.6. Neutrophil counts must be evaluated with respect to postconceptual and postnatal age.

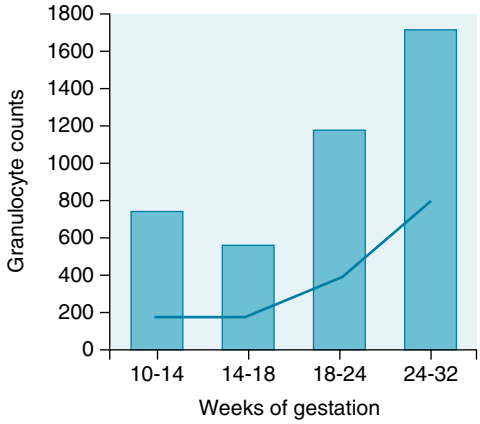

FIGURE 20.5 Mean and range of neutrophil counts at 10 to 14, 14 to 18, 18 to 24, and 24 to 32 weeks of gestation. (From Thomas DB, Yoffe JM. The cellular composition of foetal blood. *Br J Haematol.* 1962;8:290.)

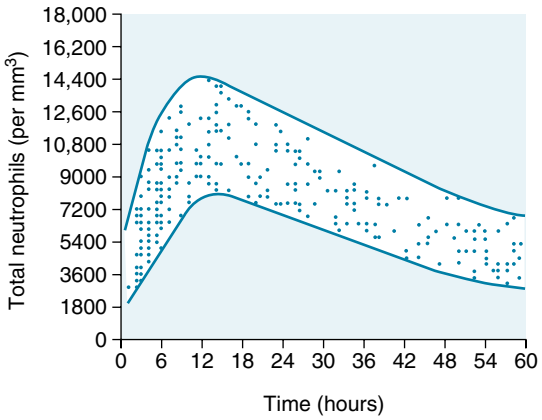

FIGURE 20.6 The total neutrophil count reference range in the first 60 hours of life. (From Monroe BL, Weinberg AG, Rosenfeld CR, et al. The neonatal blood count in health and disease. I. Reference values for neutrophilic cells. *J Pediatr.* 1979;95:89.)

Pathophysiology of Neutropenia

Neonatal neutropenia may be congenital or acquired and result from a decrease in production or survival of neutrophils. The two most common causes of neonatal neutropenia are infection and medication exposure.

Congenital causes of neutropenia include a variety of rare genetic conditions. Severe congenital neutropenia is characterized by myeloid hypoplasia in the bone marrow with an early arrest in maturation and has been linked to mutations in more than 20 genes (e.g. *ELANE, HAX1, GFI1, G6PC3, WAS*).[44] These are usually inherited in an autosomal recessive fashion and may present with isolated neutropenia complicated by severe recurrent bacterial and fungal infections or may be syndromic. Patients with ***Shwachman-Diamond syndrome*** typically present with failure to thrive and exhibit all or part of the classic triad of neutropenia (or other cytopenias), exocrine pancreatic insufficiency, and skeletal anomalies (metaphyseal dysplasia).[48] Patients with ***Chédiak-Higashi syndrome*** have oculocutaneous albinism, peripheral neuropathies, and characteristic large cytoplasmic inclusion granules on a peripheral blood smear. ***Reticular dysgenesis*** is a severe defect leading to absent production of all myeloid cells, including neutrophils, monocytes, macrophages, and lymphocytes. ***Myelokathexis*** is a disorder of intramedullary destruction and release of small numbers of neutrophils with abnormal morphology into

the peripheral circulation. In *dyskeratosis congenita,* an X-linked disorder consisting of nail dystrophy, hyperpigmented dystrophic skin, and leukoplakia, one-third of children develop neutropenia. In *cartilage-hair hypoplasia,* an autosomal recessive syndrome of short-limbed dysostosis, one-fourth of children develop neutropenia or lymphopenia. There are genetic forms of *familial neutropenia* that are more mild and less symptomatic. Most benign congenital neutropenia is not associated with infection and is not often detected in the neonatal period.

Increased destruction of neutrophils is mediated by antibodies, infection, or inflammation. *Congenital acquired neutropenia* can result from maternal lupus or drugs and is found in severe isoimmune hemolytic anemia. *Neonatal isoimmune neutropenia,* similar to NAIT, occurs in about 1 in 1000 live births and is often an incidental finding on CBC. **Most neutropenia developing in the neonatal period results from infection or other stresses, including respiratory distress syndrome and intracranial hemorrhage. Over one-half of infants born to mothers with preeclampsia may be neutropenic. The neutropenia is usually self-limited and may last more than 7 days. Neutropenia in the setting of very low birth weight infants with a history of maternal preeclampsia is associated with increased mortality.**[135] G-CSF can be successfully used to increase the absolute neutrophil count in these patients.[84] However, it is not clear whether cytokine treatment decreases the rates of culture-positive sepsis or mortality.[80,197]

The **most common severe congenital disorder of neutrophil function is *chronic granulomatous disease (CGD).*** CGD results from a mutation impairing NADPH oxidase, which is responsible for the normal oxidative burst within neutrophil phagosomes, rendering them unable to kill ingested bacteria or fungi.[25] Classic CGD is inherited in an X-linked recessive manner and primarily affects male infants, and less common variant forms of CGD are inherited in an autosomal recessive manner. **CGD is characterized by development of recurrent severe infections, primarily with catalase-positive organisms** (e.g. *Staphylococcus aureus, Pseudomonas aeruginosa,* Aspergillus) despite a normal absolute neutrophil count. The **presence of certain types of unusual infections** (e.g. *Burkholderia cepacia, Serratia marcescens, Nocardia*) **should raise suspicion for CGD.** The types of infections typically seen include pneumonias, abscesses, adenitis, and, less commonly, bacteremias.

Leukocyte adhesion deficiency (LAD) may also present during the neonatal period with recurrent bacterial infections of the skin and mucosa, impaired wound healing, absence of pus formation, and delayed separation of the umbilical cord.[43] LAD usually results from a deficiency in the integrins that are involved in the adhesion of neutrophils so they cannot migrate out of the endothelium to the site of infection in the tissue. Laboratory evaluation typically demonstrates neutrophilia with an elevated white blood cell count.

Data Collection

HISTORY

History should include questioning about maternal gestational complications, hypertension, collagen vascular disorders, and medications. Family history of previously affected infants and information about predisposition to or death during childhood from infections are important.

SIGN AND SYMPTOMS

Signs and symptoms of neutropenia follow primarily from related secondary infections. Although older infants may manifest fevers and aphthous ulcers with neutropenia, these are rarely apparent in newborn infants. **Delayed umbilical cord separation can be seen in LAD.**

LABORATORY DATA

The CBC should be obtained with attention to all cell lines. The peripheral smear should be carefully inspected for evidence of abnormal neutrophil morphology. **A bone marrow aspirate and biopsy may be needed** in certain circumstances if there is a high clinical suspicion of severe congenital neutropenia. **Testing of maternal blood for neutrophil antibodies can help confirm the presence of neonatal isoimmune neutropenia.** In patients with suspected neutrophil dysfunction, **a dihydrorhodamine test may be performed to measure the neutrophil oxidative burst.**[98] LAD can be diagnosed based on peripheral blood flow cytometry demonstrating decreased CD18 expression.

Treatment

Infants with neutropenia must be evaluated for sepsis and other infections and **treated with appropriate antimicrobial agents while cultures are pending.**

Immune neutropenia usually does not require any specific therapy in the absence of severe or invasive infections. **Granulocyte–colony stimulating factor (G-CSF) may be used in patients with severe neutropenia who have serious or recurrent infections to increase the absolute neutrophil count.**[37] **CGD is primarily treated with prophylactic antibiotics and antifungals, along with administration of-γ interferon.**[25] Replacement IVIG has a role in defects that also affect the lymphocyte production of antibodies. The role of transfused granulocytes is controversial, and its use is mostly indicated for overwhelming infections with gram-negative organisms in severely neutropenic infants.

Prevention and Parent Teaching

The sequelae of some severe genetic neutropenias can be prevented with bone marrow transplantation. Important **adjuvant approaches for all neutropenic babies include careful attention to hygiene when touching babies, infant skin care to prevent infections and avoid skin trauma, and recognition of early signs.** Most acquired neutropenias in neonates are of short duration. Parents of babies with congenital neutropenia must be instructed about the diagnosis, underlying defect, available treatments, and long-term prognosis.

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21 NEONATAL HYPERBILIRUBINEMIA

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Unconjugated hyperbilirubinemia is the most common condition requiring evaluation and treatment in neonates, but for most newborns, it is a benign postnatal transitional phenomenon. Neonatal hyperbilirubinemia manifests as jaundice, the yellow-orange tint usually detected visually in the sclera and skin of infants with total serum bilirubin (TSB) concentration between 6 and 7 mg/dL. Despite the cause-and-effect relationship, the terms *neonatal hyperbilirubinemia* and *neonatal jaundice* are used fairly interchangeably. All infants experience a rise in their serum bilirubin concentration after birth because of brisk red cell turnover and bilirubin formation paired with an immature liver that cannot adequately clear the bilirubin from the blood. It is estimated that about 60% to 80% of normal newborns will appear clinically jaundiced during the first week of life.[55,77] Despite this, the incidence of extreme hyperbilirubinemia and kernicterus is low[17,99] (Box 21.1).

Severe hyperbilirubinemia, defined as TSB above the 95th percentile for age in hours, occurs in 8% to 9% of infants during the first week of life.[14,15] Experience has shown the dangers of excessive concentrations of unconjugated bilirubin, such as the development of bilirubin encephalopathy and the devastating and irreversible effects of kernicterus. An understanding of the pathophysiology and clinical significance of hyperbilirubinemia is critical in the care of newborn infants. This chapter provides the reader with a basic overview of the multiple causes and contributing factors in the development of hyperbilirubinemia; describes the diagnosis, clinical significance, and complications of hyperbilirubinemia; and discusses current treatment modalities and their complications.

PATHOPHYSIOLOGY

Understanding the pathophysiology and clinical significance of hyperbilirubinemia requires an appreciation of normal bilirubin metabolism in the newborn (Fig. 21.1). A newborn produces bilirubin at a rate of 8 to 10 mg/kg/24 hr, which is 2 to 2.5 times the rate in adults. Red blood cells in newborns have a shortened life span of 70 to 90 days, compared with 120 days in adults, and the newborn has a higher red cell mass per kilogram weight compared with the adult. Because the catabolism of *1 g of hemoglobin yields 35 mg of bilirubin,* this accelerated red blood cell breakdown

BOX 21.1 PREVALENCE OF EXTREME HYPERBILIRUBINEMIA AND KERNICTERUS

- TSB >15 mg/dL: 8%–10% of newborns
- TSB >20 mg/dL: 1.2% of newborns
- TSB >25 mg/dL: 1/770 (0.13%) newborns
- TSB >30 mg/dL: 1/10,000 (0.01%) newborns
- Kernicterus (approx.): 1/100,000 (0.001%)
  - TSB >25 mg/dL: 1/18 (5%)
  - TSB >30 mg/dL: 1/7 (15%)
  - TSB >35 mg/dL: all have sequelae (100%)

TSB, Total serum bilirubin.

Data modified from Bhutani VK, Johnson LH, Keren R. Diagnosis and management of hyperbilirubinemia in the term neonate: towards a safer first week. *Pediatr Clin North Am.* 2004;51(4):843; Bhutani VK, Johnson L. Synopsis report from the pilot USA Kernicterus Registry. *J Perinatol.* 2009;29(suppl 1):S4; U.S. Preventive Services Task Force. Screening of infants for hyperbilirubinemia to prevent chronic bilirubin encephalopathy. US Preventive Services Task Force recommendation statement. *Pediatrics.* 2009;124(4):1172.

BLUE type highlights content that is particularly applicable to clinical settings.

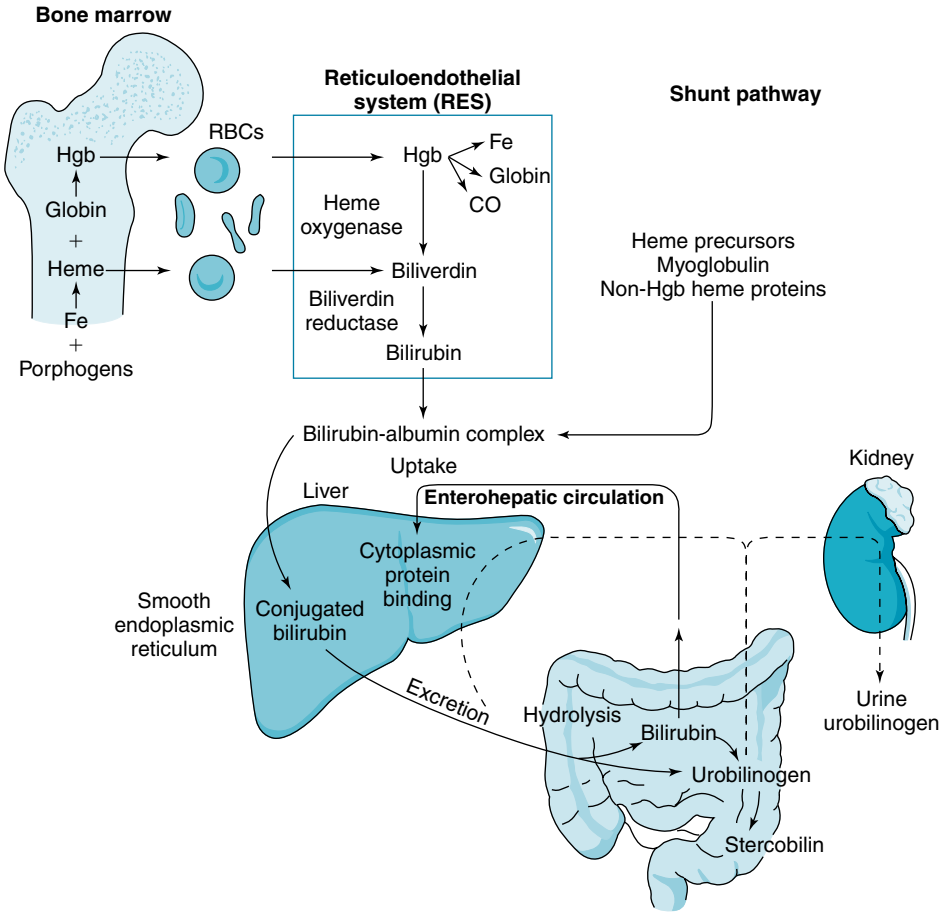


FIGURE 21.1 Bilirubin physiology: pathways of bilirubin production, transport, and metabolism. *Fe,* Iron; *Hgb,* hemoglobin; *RBC,* red blood cells; *CO,* carbon monoxide. (Modified from Gartner LM, Hollander M. Disorders of bilirubin metabolism. In: Assali NS, ed. *Pathophysiology of Gestation.* Vol 3. New York, NY: Academic Press; 1972.)

produces most of the bilirubin (75% to 85%) in newborns. The remaining 15% to 25% of bilirubin is derived from nonerythroid heme proteins found principally in the liver, and heme precursors in the marrow and extramedullary hematopoietic areas that do not go on to form red blood cells (referred to as "early peak" or "shunt" bilirubin).

Bilirubin metabolism begins in the reticuloendothelial system, principally in the liver and spleen, as senescent or abnormal red blood cells are removed from the circulation. The enzyme *heme oxygenase* acts on heme to produce biliverdin, and *biliverdin reductase* then converts biliverdin into bilirubin. This **bilirubin, in its unconjugated or indirect-reacting form, is released into the plasma**, where it is bound to albumin for transport. Exhaled carbon monoxide is a by-product of these pathways.

At a normal plasma pH, bilirubin is very poorly soluble and binds tightly to the circulating carrier protein albumin. Albumin contains one high-affinity site for bilirubin and one or more sites of lower affinity. **Bilirubin binds to albumin in a molar ratio of between 0.5 and 1 mole of bilirubin per mole of albumin. A bilirubin/albumin molar ratio of 1 corresponds to approximately 8.5 mg bilirubin/g of albumin. This ratio is likely to be lower in a sick very-low-birth-weight (VLBW) infant, who is also likely to have a lower serum albumin concentration**[26] than a healthy term newborn. It is important to note that the TSB is

the concentration of albumin-bound bilirubin; the concentration of unconjugated, unbound bilirubin ("free bilirubin") is potentially more important in prediction of neuronal injury, but measurement is not yet commercially available.[4]

Bilirubin bound to albumin is carried to the liver and dissociates from circulating albumin before entering the liver cell. The process of entering the liver cell occurs partly by passive carrier-mediated diffusion involving the sinusoidal transporter SLCO1B, and partly by mediation of organic anion transporter proteins (OATPs). In the liver cell cytoplasm, the unconjugated bilirubin binds to glutathione-S-transferase A, also known as *ligandin,* or with B-ligandin (Y protein). These are major intracellular transport proteins, and their bilirubin binding ability helps keep the potentially toxic unbound portion low. Z protein, another hepatic cytoplasmic carrier, also binds bilirubin, but with lower affinity.[96] Conjugation occurs within the smooth endoplasmic reticulum of the cell. This reaction, catalyzed by the enzyme *uridine diphosphate glucuronosyltransferase (UGT-1A1),* leads to the formation of water-soluble compounds called *bilirubin glucuronides.* UGT-1A1 is the predominant isoenzyme and arises from the *UGT1* gene complex on chromosome 2 (2q37).[95] In addition to UGT-1A1, conjugation requires glucuronic acid synthesized from glucose. Conjugated bilirubin is then actively secreted into bile and passes into the small intestine.

Conjugated bilirubin is not reabsorbed from the intestine, but the mucosal brush border of the newborn contains the enzyme *beta-glucuronidase,* which can convert conjugated bilirubin back into glucuronic acid and unconjugated bilirubin, which may then be absorbed. This pathway constitutes the enterohepatic circulation of bilirubin and contributes significantly to an infant's bilirubin load.

Factors That Affect Bilirubin Levels

A number of different factors affect the ability of albumin to bind bilirubin, including plasma pH, free fatty acid concentrations, and certain drugs, particularly sulfonamides and ceftriaxone. Albumin binding of unconjugated bilirubin may be important in the prevention of bilirubin toxicity, by limiting the amount of unbound, unconjugated bilirubin available for causing neuronal damage.[4,60,73] Consequently, serum albumin concentration may be measured as an estimate of available binding capacity, perhaps allowing a better estimation of the concentration at which aggressive phototherapy and exchange transfusion should be considered in a particular infant.[8]

A rise in bilirubin levels shortly after birth is partially attributable to a relative deficiency of UGT-1A1 activity (0.1% of adult levels at 30 weeks of gestation, 1% of adult levels by 40 weeks of gestation). Enzyme activity increases rapidly after birth independent of the infant's gestational age, achieving adult concentrations by 14 weeks of age.[95] Newborn monkeys have been shown to be deficient in the intracellular Y and Z proteins for the first few days of life, and this also may occur in the human newborn. The hormonal (estrogen) environment of the infant may also inhibit liver function and bilirubin secretion.

Certain ethnic groups, including Eskimo, Asian, and Native American, have an increased incidence and severity of hyperbilirubinemia for reasons that are not completely understood, but are likely related to genetic polymorphisms involving UGT-1A1 activity.[43,96] The presence of *beta-glucuronidase* in the bowel lumen during fetal life enables bilirubin to be reabsorbed and transported across the placenta for excretion by the maternal liver; its presence in the neonate, however, contributes to an excessive enterohepatic circulation of bilirubin.

Physiologic Jaundice

Debate and controversy remain over efforts to define normal or physiologic ranges of TSB concentrations in full-term newborn infants, because the data are affected by multiple variables. Traditionally, a distinction has been made between physiologic jaundice and hyperbilirubinemia that is either pathologic in origin or severe enough to warrant further evaluation and intervention. **Data from multiple studies consider that the 97th percentile of maximal TSB concentration in healthy mature newborns is 12.4 mg/dL for formula-fed infants and 14.8 mg/dL for breastfed infants.[6,9,65] Any TSB elevation exceeding 17 mg/dL should be presumed pathologic and warrants investigation** for a cause and possible therapeutic intervention, such as phototherapy.

In the normal full-term newborn, the clinical course of physiologic jaundice is characterized by a progressive increase in TSB concentration from about 2 mg/dL in cord blood to a mean peak of 5 to 6 mg/dL between 3 and 4 days of life *(phase I physiologic*

jaundice). This is followed by a decline to about 3 mg/dL toward the end of the first week of life and then continues with a period of very slowly declining TSB concentration until reaching the normal adult level of less than 2 mg/dL at the end of the second week of life *(phase II physiologic jaundice)*. **Several criteria have been proposed that can be used to exclude the diagnosis of physiologic jaundice in a full-term infant: (1) clinical jaundice in the first 24 hours of life, (2) TSB concentration that increases more than 0.2 mg/dL per hour, (3) TSB concentration exceeding the 95th percentile for age in hours, (4) direct-reacting bilirubin levels exceeding 1.5 to 2 mg/dL, or (5) clinical jaundice persisting for more than 2 weeks.** However, absence of these criteria does not guarantee that the jaundice is physiologic.

ETIOLOGY OF HYPERBILIRUBINEMIA

Excessive bilirubin concentrations occur in newborn infants by three main mechanisms: increased production (accelerated red blood cell breakdown), decreased excretion (transient UGT-1A1 insufficiency),[80] and increased reabsorption (enterohepatic circulation) (Box 21.2). The normal pathways of bilirubin metabolism described earlier account for much of the increase in bilirubin concentrations in newborn infants; however, there are circumstances that deserve evaluation in infants who have a more prolonged hyperbilirubinemia.

From a management perspective, **it is helpful to describe nonphysiologic hyperbilirubinemia according to its time of onset, early (first 24 to 48 hours) or late (after 48 to 96 hours), to determine its specific etiology.** In general, early-onset nonphysiologic hyperbilirubinemia is associated with increased bilirubin production, whereas later-onset hyperbilirubinemia is often associated with delayed bilirubin elimination with or without increased bilirubin production (Fig. 21.2).[50]

Overproduction of Bilirubin

HEMOLYTIC DISEASE OF THE NEWBORN

Hemolytic disease of the newborn may occur when blood group incompatibilities in Rh,

BOX 21.2 CAUSES OF HYPERBILIRUBINEMIA

Overproduction
- Hemolytic disease of the newborn (antibody-mediated hemolysis: Rh, ABO, Kell, Duffy)
- Hereditary hemolytic anemia
  - Membrane defects (spherocytosis, elliptocytosis, pyknocytosis)
  - Hemoglobinopathies
  - Enzyme defects (G6PD deficiency)
- Polycythemia
- Extravascular blood
  - Swallowed
  - Bruising or enclosed hemorrhage (e.g., cephalohematoma)
- Increased enterohepatic circulation (prematurity, delayed feedings, bowel obstruction)

Slow Excretion
- Decreased hepatic uptake
  - Decreased sinusoidal perfusion
  - Ligandin deficiency and SLCO1B1 deficiency
- Decreased conjugation
  - UGT-1A1 deficiency (Crigler-Najjar syndrome, Gilbert syndrome)
  - Enzyme inhibition, such as Lucey-Driscoll syndrome
- Inadequate transport out of hepatocyte
- Biliary obstruction (Dubin-Johnson syndrome, Rotor syndrome, biliary atresia)

Combined (Overproduction and Slow Excretion)
- Bacterial infection
- Congenital intrauterine infection

Breastfeeding
- Breastfeeding jaundice ("lack of breast milk" jaundice)
- Breast milk jaundice

Physiologic

Miscellaneous
- Galactosemia
- Hypothyroidism
- Infant of diabetic mother

<table>
<tr><th colspan="2">Early-onset hyperbilirubinemia
(age < 72 hours)</th><th>Late-onset hyperbilirubinemia
(age >72 hours and <2 weeks)</th></tr>
<tr><th>First 24 hours of life</th><th colspan="2">First week of life</th><th>>1 week of life</th></tr>
<tr><td rowspan="3">Direct Coombs' positive:
• Isoimmune erythroblastosis fetalis
• Rhesus disease
• Minor blood group incompatibilities
• ABO (often the direct Coombs' is negative)</td><td colspan="2">Benign idiopathic jaundice
(physiologic; <40th percentile)</td><td>Prolonged idiopathic jaundice
(breast milk jaundice;
TSB <13 mg/dL)</td></tr>
<tr><td colspan="2">Sepsis (viral or bacterial)</td><td>Sepsis (viral or bacterial)</td></tr>
<tr><td colspan="2">Increased enterohepatic circulation</td><td>Functional gastrointestinal tract abnormality</td></tr>
<tr><td rowspan="2">Direct Coombs' negative:
• G6PD deficiency
• Intrinsic red blood cell defect
• Spherocytosis
• Elliptocytosis
• Hemoglobinopathies</td><td colspan="3">Disorders of bilirubin metabolism:
• UGT1A1 gene polymorphisms (delayed conjugation)
• Co-inheritance of UGT1A1 polymorphism with G6PD deficiency, ABO incompatibility, spherocytosis
• Crigler-Najjar syndrome: I and II
• Gilbert syndrome
• Others
Metabolic disorders:
• Galactosemia
• Alpha$_1$-antitrypsin deficiency
• Storage diseases
• Others</td></tr>
<tr><td colspan="2">Enclosed hemorrhages:
• Cephalohematoma
• Subaponeurotic hemorrhage
• Bruising</td><td>Cystic fibrosis
Hypothyroidism</td></tr>
</table>

FIGURE 21.2 Differential diagnosis of severe neonatal hyperbilirubinemia based on pathophysiology and timing at presentation. *G6PD,* Glucose-6-phosphate dehydrogenase; *TSB,* total serum bilirubin. (Modified from Smitherman H, Stark AR, Bhutani VK. Early recognition of neonatal hyperbilirubinemia and its emergent management. *Semin Fetal Neonatal Med.* 2006;11(3):214.)

ABO, or minor blood groups exist between a mother and her fetus (see Chapter 20). The classic example of hemolytic disease of the newborn has been erythroblastosis fetalis occurring as a result of Rh incompatibility. Fifteen percent of the white population is Rh negative. When an Rh-negative mother is sensitized to the Rh antigen after a blood transfusion or a fetal-maternal sensitization during pregnancy, delivery, abortion, or amniocentesis, the presence of the Rh antigen induces maternal antibody production. **Because prior sensitization with the Rh antigen is necessary for maternal antibody production, the first Rh-positive infant usually is not affected. Once a mother is sensitized, an anamnestic response to further exposure causes maternal immunoglobulin G (IgG) to cross the placenta into the fetal circulation, where it reacts with the Rh antigen on fetal erythrocytes. These antibody-coated cells are recognized as abnormal and destroyed by the fetal spleen.** This results in increased production of heme requiring metabolic degradation. As the destruction of erythrocytes and production of bilirubin progress, severe anemia and congestive heart failure can ensue, progressing to hydrops fetalis. **Fortunately, the use of anti-D gamma globulin (RhoGAM), particularly antenatal administration at 26 to 28 weeks of gestation to prevent sensitization of nonsensitized pregnant Rh-negative women, has markedly decreased the incidence of Rh isoimmunization in newborn infants.**

After the widespread use of RhoGAM, the most frequent cause of hemolytic disease of the newborn is now ABO blood group incompatibility. ABO incompatibility is limited to mothers of blood group O and affects infants of blood group A or B. All group O individuals

have naturally occurring anti-A and anti-B (IgG) antibodies, so specific sensitization is not necessary. The resulting hyperbilirubinemia in the newborn is highly variable and generally milder than that seen with Rh incompatibility. Although some 15% of pregnancies are a "set-up" for ABO incompatibility (mother O, baby A or B), only 33% of these infants show a positive direct antiglobulin test (DAT), and only 15% of these have clinically significant hemolysis and hyperbilirubinemia. If the DAT is negative, these infants, as a group, do not have an increased incidence of significant hyperbilirubinemia compared with non–ABO-incompatible infants.[95]

HEREDITARY HEMOLYTIC ANEMIAS

Erythrocytes with abnormal membranes or containing abnormal hemoglobin variants have increased rates of destruction. Individuals with *membrane defects,* such as spherocytosis, elliptocytosis, stomatocytosis, and pyknocytosis, cannot maintain the integrity of red blood cells because of abnormal osmotic fragility (generally increased) and an increased rate of splenic destruction (see Chapter 20). A mean corpuscular hemoglobin concentration (MCHC) greater than 36.5 to 37 g/dL or a ratio of MCHC:MCV (the HS index) greater than 0.36 may be clues to the diagnosis of hereditary spherocytosis.[27,95]

***Glucose-6-phosphate dehydrogenase (G6PD) deficiency* is the most common enzyme defect and is more commonly found in certain racial and ethnic groups, including East Asian, Mediterranean, and African peoples.** Pyruvate kinase deficiency is much less common. G6PD deficiency affects some 400 million individuals worldwide.[19] **In areas where G6PD is prevalent, it is the most common and most severe risk factor for hyperbilirubinemia.[5] G6PD deficiency is also common in the United States, with an estimated overall incidence of 3.4%.** Up to 12.5% of African-American males and 4% of African-American females are G6PD deficient.[20] Although G6PD deficiency is an X-linked recessive disease affecting primarily males and homozygous females, heterozygous females may also be phenotypically deficient as a result of X chromosome inactivation. **Affected infants may occasionally present with acute hemolysis and severe hyperbilirubinemia in response to exposure to an oxidative trigger (infection, starvation, or drug exposure, notably sulfonamides), but more commonly present with later-onset (end of first week of age) hyperbilirubinemia without significant anemia.**[100] The combination of G6PD deficiency with Gilbert's disease (another common genetic variation involving partial UGT-1A1 deficiency) makes infants especially prone to the development of later-onset severe hyperbilirubinemia without significant hemolysis or anemia.[47,94]

Individuals with *hemoglobinopathies,* which can be diagnosed by hemoglobin electrophoresis, may also have increased splenic destruction of red blood cells, although most of these do not manifest clinically in the newborn period. The exceptions are the alpha-thalassemia syndromes wherein three or four of the four alpha globin genes are affected, resulting in hemoglobin H disease (three genes affected) or homozygous alpha-thalassemia (absence of all four genes). Hemoglobin H disease can manifest as hemolysis and anemia in the neonate, and homozygous alpha-thalassemia regularly causes severe hemolysis, anemia, hydrops fetalis, and death.[95] Family history is positive in as many as 80% of cases.

POLYCYTHEMIA

In the presence of *polycythemia (a central venous hematocrit greater than 65%),* an increased red blood cell mass, coupled with the shortened life span of red blood cells in newborns, results in an increased bilirubin load. Polycythemia may be idiopathic, or it may occur as a result of a placental transfusion, twin-to-twin transfusion, or chronic in utero hypoxia.

EXTRAVASCULAR BLOOD

Enclosed hemorrhage includes cephalohematoma, subgaleal hemorrhage, cerebral hemorrhage, adrenal hemorrhage, intraabdominal or retroperitoneal bleeding, or extensive bruising. As these enclosed hemorrhages resolve, red blood cells trapped within are broken down and add to bilirubin production. Swallowed maternal blood is another possible source of increased bilirubin load.

INCREASED ENTEROHEPATIC CIRCULATION

As mentioned earlier, the intestinal brush border contains the enzyme *beta-glucuronidase,* which can convert conjugated bilirubin back into its unconjugated (absorbable) form plus glucuronic acid. **Meconium contains a substantial amount of bilirubin, estimated at 1 mg of bilirubin per 1 g of meconium, or a total load of 100 to 200**

mg. Any delay in the passage of meconium, as can occur with prematurity, delayed feedings, or bowel obstruction, increases the bilirubin load that must be metabolized. Hyperbilirubinemia requiring treatment due to these causes is rarely evident in the first 24 to 48 hours of life.

Slow Excretion of Bilirubin

Infants with normal bilirubin production rates may be unable to excrete it efficiently for a variety of reasons, as described in the following conditions.

DECREASED HEPATIC UPTAKE OF BILIRUBIN

Diminished hepatic uptake of bilirubin may be a result of inadequate perfusion of hepatic sinusoids or of deficient carrier proteins (Y and Z). *Inadequate perfusion* of hepatic sinusoids occurs when there is a shunt through a persistent ductus venosus or there is an extrahepatic portal vein thrombosis, or with hyperviscosity, hypovolemia, or severe congestive heart failure. *Functional deficiency* of the transporter proteins may be caused by certain drugs and compounds (e.g., steroid hormones, free fatty acids, chloramphenicol) that competitively bind to them. Although Y and Z proteins are decreased in some newborn primates, no actual deficiency has yet been demonstrated in the human newborn.

DECREASED BILIRUBIN CONJUGATION

Decreased bilirubin conjugation may be a result of *UGT-1A1 deficiency,* as in Crigler-Najjar syndrome or Gilbert syndrome.[86] These disorders are caused by defects in the *UGT-1A1* gene complex on chromosome 2. These diseases may represent a continuous spectrum of severity. *Crigler-Najjar syndrome* is rare and exists in two forms with either complete (type I) or partial (type II) absence of enzymatic activity. Type I is an autosomal recessive disorder, resulting in an inactive UGT-1A1 enzyme, putting the infant at significant risk of bilirubin encephalopathy. Lifelong phototherapy becomes ineffective in preventing toxicity, and liver transplantation is the only possible cure. Type II Crigler-Najjar syndrome is characterized by low but detectable concentrations of the enzyme and more moderate degrees of hyperbilirubinemia.[95] It is inherited as an autosomal dominant disorder and responds to enzyme induction with phenobarbital.

Gilbert syndrome is a milder and very common autosomal dominant disorder with partial UGT-1A1 enzyme activity caused by a number of polymorphisms in the *UGT-1A1 promoter sequence,* usually involving the number of TA base pair repeats. As the number of TA repeats increases above the normal 6, UGT-1A1 activity declines.[94] Approximately 9% of the US population is homozygous for the promoter sequence polymorphism responsible for Gilbert's syndrome and shows a 50% reduction in UGT-1A1 activity, whereas 42% of the population is heterozygous and shows a 37% reduction in enzyme activity. **Although Gilbert syndrome generally manifests after the newborn period with mild bilirubin elevation during times of stress, fasting, or intercurrent illness, it is also an important contributing factor in cases of later-onset severe hyperbilirubinemia, even in the absence of significant hemolysis.[86]** In the neonate, where TSB is a delicate balance between production and elimination, even a small decrease in bilirubin elimination can have a major impact on degree of hyperbilirubinemia. **Although neither G6PD deficiency nor Gilbert syndrome alone is associated with an increased incidence of hyperbilirubinemia, both occurring together are associated with severe hyperbilirubinemia.[20,99]**

INADEQUATE TRANSPORT OUT OF THE HEPATOCYTE

Dubin-Johnson syndrome (DJS) and Rotor syndrome[82] are genetically inherited conditions that are both autosomal recessive and have a similar phenotype in which individuals can conjugate bilirubin normally but cannot excrete it, leading to a mixed hyperbilirubinemia. In DJS, there is impairment in the biliary excretion of organic anions (except bile acids). Rotor syndrome has a different underlying mechanism, with impaired hepatocellular storage of conjugated bilirubin. **Both conditions are considered benign and do not require treatment.** Liver biopsy is not recommended as it will be unlikely to show abnormalities. Urine coproporphyrin excretion is helpful to differentiate the two disorders: in DJS, coproporphyrin concentrations will be normal, but composed predominantly of coproporphyrin I, as opposed to coproporphyrin III as seen in normal individuals. In Rotor syndrome, the total urine coproporphyrin concentration is 2 to 5 times the normal amount, with the majority being coproporphyrin I.

BILIARY OBSTRUCTION

Biliary obstruction often presents a diagnostic challenge requiring differentiation between generalized hepatocellular damage and mechanical obstruction.

A variety of disorders can cause hepatocellular damage, including infections, such as hepatitis, and metabolic disorders, such as galactosemia. **In the neonatal intensive care unit (NICU), the most common cause of hepatocellular damage is the use of parenteral nutrition.** The mechanism is not well established, but the injury takes at least 2 weeks to develop and is especially prominent in VLBW infants. Biliary atresia or, much less frequently, a choledochal cyst, can cause mechanical obstruction to bile flow, resulting in a conjugated hyperbilirubinemia with *light-colored stools*.

Combined Overproduction and Slow Excretion

INFECTIONS

Bacterial infections (sepsis neonatorum, especially necrotizing enterocolitis and urinary tract infection caused by toxin-producing organisms such as certain strains of *Escherichia coli*) or intrauterine viral infections can result in increased bilirubin production and decreased hepatic clearance.

Intrauterine infections, including syphilis, toxoplasmosis, rubella, cytomegalovirus, herpes simplex, coxsackie B virus, and hepatitis virus, cause clinical jaundice with evidence for hepatocellular damage (elevated liver enzymes, poor synthetic function, coagulopathy). Infants with these infections often have additional clinical signs of their infection such as thrombocytopenia and rash.

INFANT OF A DIABETIC MOTHER

The cause of hyperbilirubinemia in an infant of a diabetic mother (IDM) appears to be multifactorial. **In addition to prematurity and a tendency to feed poorly, leading to delayed intestinal motility and enhanced enterohepatic circulation, an IDM may have an increased bilirubin load as a result of an expanded red blood cell mass.** Erythrocyte membrane composition may be altered, and macrosomic infants often are bruised during labor and delivery. Evaluation of exhaled carbon monoxide (CO) in IDM infants has consistently shown evidence for increased production of bilirubin.[82]

Jaundice Associated With Breastfeeding

Numerous studies have reported an association between exclusive breastfeeding and an increased incidence and severity of hyperbilirubinemia, both during the first few days of life and as a cause of prolonged neonatal jaundice.[8,41,95] Breastfed infants are several times more likely to have TSB concentrations greater than 12 mg/dL than infants who are formula fed (13% vs. 4%). As such, **exclusive breastfeeding, particularly if nursing is not going well and weight loss is excessive, is listed as a major hyperbilirubinemia risk factor. Promotion and support of successful breastfeeding constitute key elements of the American Academy of Pediatrics (AAP) clinical practice guideline on the management of hyperbilirubinemia.**[5] **Ideally, a trained observer should evaluate all breastfed infants within 48 to 72 hours of discharge in either a home or office setting.** Early discharge of breastfed infants with inadequate follow-up may result in extreme hyperbilirubinemia and kernicterus, even in the absence of hemolysis.[17]

Two separate patterns of jaundice in breastfeeding infants have been described. The first has been termed *breastfeeding-associated jaundice* and the second *breast milk jaundice*.

BREASTFEEDING-ASSOCIATED JAUNDICE

It is important to recognize that not all breastfed infants will receive optimal milk intake during the first few days of life; as many as 10% to 18% of exclusively breastfed newborns lose more than 10% of birth weight.[32] **It has been postulated that this early jaundice is related to decreased caloric and fluid intake from colostrum (sometimes called "lack of breast milk" jaundice)**[41] **and increased enterohepatic circulation resulting from low stool output and breast milk containing beta-glucuronidase.**[8,72] Many studies show a relationship between the degree of hyperbilirubinemia and the amount of weight lost by the infant after birth.[1,94] Breastfeeding-associated jaundice, however, is not caused by increased bilirubin production.

Optimal management of a breastfeeding mother and infant includes early (initiation in the first hour after birth) and frequent nursing

(8 to 12 times each day). If the infant is unable to feed this frequently, the mother should be instructed in the regular use of a mechanical breast pump to improve her milk supply, and the infant should be supplemented with expressed breast milk or formula to improve nutritional status and intestinal motility.

BREAST MILK JAUNDICE

Breast milk jaundice is a benign condition that resolves without treatment. Such infants have an unconjugated hyperbilirubinemia (less than 12 mg/dL) that becomes exaggerated and persistent toward the end of the first week of life.[71] **Infants with breast milk jaundice are otherwise healthy, with normal weight gain, normal stool and urine output, a normal physical examination, and no other underlying etiology for the hyperbilirubinemia.** If concentrations are higher than 12 mg/dL and persist for several weeks, or if there is an elevation of direct or conjugated bilirubin concentration, other causes of hyperbilirubinemia need to be investigated. For the vast majority of infants, it is not necessary to interrupt breastfeeding, even if the bilirubin increases to concentrations that require phototherapy.

Lactation failure is not present in affected infants, suggesting that other possible mechanisms may be operative in breast milk jaundice. No specific inhibitor or inhibitory substance has been identified in mother's breast milk, but animal models suggest that mature breast milk may increase unconjugated bilirubin concentration by enhancing the enterohepatic circulation. **Breast milk may act as an environmental modifier for selected genotypes (for example, those with Gilbert polymorphism and/or G6PD deficiency)** and thereby potentially predispose to the development of marked neonatal jaundice.[90,91,94]

HYPERBILIRUBINEMIA IN PREMATURE INFANTS LESS THAN 35 WEEKS' GESTATIONAL AGE

Preterm infants are at higher risk for hyperbilirubinemia because of increased bilirubin production, delays in bilirubin elimination, and altered bilirubin-albumin binding.[21,98] Immaturity of UGT-1A1 activity is the primary cause of hyperbilirubinemia in preterm infants.[48] UGT-1A1 is progressively less active with decreasing gestational age.[48]

Prematurity in association with bilirubin toxicity can lead to long-term neurodevelopmental impairments.[21,48] These impairments can be manifested by the syndrome of bilirubin-induced neurologic dysfunction (BIND), which includes auditory neuropathy and visuomotor processing disorders.[21] **Bilirubin may have a higher propensity to cross the blood-brain barrier in preterm infants than in term infants because of differences in albumin binding and lower concentrations of albumin, potentially leading to kernicterus, even with bilirubin levels below usual treatment thresholds.[48]**

Late-preterm infants are overrepresented in the Pilot USA Kernicterus Registry.[44] Neonatal hyperbilirubinemia in late-preterm newborns is more prevalent, more pronounced, and more protracted than in their term counterparts. Late-preterm gestation (34 0/7 to 36 6/7 weeks) is one of the most prevalent identified risk factors for the development of severe hyperbilirubinemia and kernicterus,[15, 25] because these infants have an approximately eightfold increased risk of developing a TSB greater than 20 mg/dL (5.2%) compared with those born at 41 or more weeks of gestation (0.7%). **Many late-preterm infants will also be breastfed, and they frequently are cared for in normal newborn nurseries,** despite the fact that they remain relatively immature compared with term newborns in their capacity to handle unconjugated hyperbilirubinemia.[16]

Miscellaneous Causes

The following causes of hyperbilirubinemia are uncommon but important to consider in infants who have no other clear etiology to explain their elevated bilirubin levels. These conditions include **hypothyroidism and galactosemia.** Newborn genetic screening now routinely includes these conditions, because early detection allows intervention before permanent adverse neurologic injury occurs. **Hyperbilirubinemia, unconjugated or mixed, may be the initial sign of these conditions.**

MECHANISMS OF BILIRUBIN NEUROTOXICITY

Identification of infants at risk for severe hyperbilirubinemia enables clinicians to provide timely intervention to prevent neuronal injury. The AAP has described risk factors for hyperbilirubinemia, which are shown in Box 21.3.[8] **The most**

BOX 21.3 RISK FACTORS FOR HYPERBILIRUBINEMIA IN NEWBORNS

Major Risk Factors

- Predischarge TSB or TcB level in the high-risk zone
- Jaundice observed in the first 24 hours of life
- Blood group incompatibility with positive direct antiglobulin test, other known hemolytic disease (e.g., G6PD deficiency), elevated ETCOC
- Gestational age 35 to 36 weeks
- Previous sibling received phototherapy
- Cephalohematoma or significant bruising
- Exclusive breastfeeding, especially if nursing is not going well and weight loss is excessive
- East Asian race*

Minor Risk Factors

- Predischarge TSB or TcB level in the high intermediate-risk zone
- Gestational age 37 to 38 weeks
- Jaundice observed before discharge
- Previous sibling with jaundice
- Macrosomic infant of a diabetic mother
- Maternal age ≥25 years
- Male gender

Decreased Risk

These factors are associated with decreased risk for significant jaundice, listed in order of decreasing importance.

- TSB or TcB level in the low-risk zone
- Gestational age ≥41 weeks
- Exclusive bottle feeding
- Black race*
- Discharge from the hospital after 72 hours

*Race as defined by mother's description.

ETCOC, End-tidal carbon monoxide corrected; *G6PD,* glucose-6-phosphate dehydrogenase; *TcB,* transcutaneous bilirubin; *TSB,* total serum bilirubin.

From American Academy of Pediatrics. Subcommittee on Hyperbilirubinemia. Clinical Practice Guideline. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 2004;114(1):297.

important determinants of brain injury caused by hyperbilirubinemia are the concentrations of unconjugated bilirubin and free bilirubin, the concentration of serum albumin and its ability to bind unconjugated bilirubin, the concentration of hydrogen ion (pH), and neuronal susceptibility.[78] Although the TSB concentration alone is of limited value in predicting neurologic impairment and kernicterus, the use of the bilirubin:albumin ratio does not appear to predict neurodevelopmental outcomes in preterm infants better than TSB alone.[95] Although levels of unbound or free bilirubin seem to be more associated with abnormal hearing tests and may prove to be a better predictor of bilirubin toxicity than TSB, this measurement is not available clinically.[3] There is also no agreement on a "threshold" above which injury always occurs.[4] Finally, photoisomers, which account for up to 25% of circulating TSB during phototherapy, may affect albumin binding and the amount of unbound bilirubin available to enter the central nervous system, but the presence and effects of these compounds are largely unknown.

Nevertheless, unbound bilirubin appears to induce a variety of cellular events that result in neurotoxicity. Unbound bilirubin affects neurons, astrocytes, microglia, and oligodendrocytes, resulting in increased apoptosis in all cell lines, decreased arborization by neurons, release of proinflammatory cytokines by astrocytes and microglia, and decreased myelin synthesis by oligodendrocytes.[23,96]

Interpretation of High Bilirubin Concentrations

All bilirubin concentrations should be interpreted according to the infant's age in hours. The AAP recommends a nomogram that designates risk for newborn infants at 35 weeks or greater according to TSB obtained at varying postnatal ages in hours. The nomogram (Fig. 21.3), based on work by Bhutani et al., designates whether an infant is at high, intermediate, or low risk for requiring further intervention for hyperbilirubinemia, based on the TSB concentration.[8,14] **Universal screening combined with use of the hour-specific bilirubin nomogram has been shown to accurately predict and prevent severe hyperbilirubinemia.[12]** However, the nomogram includes only infants at and above 35 weeks' gestational age from a single institution with a primary outcome of TSB greater than 20 mg/dL, not bilirubin encephalopathy.[39] More premature infants have a slightly later peak and are at risk for adverse neurologic outcomes at lower levels of bilirubin than mature infants.

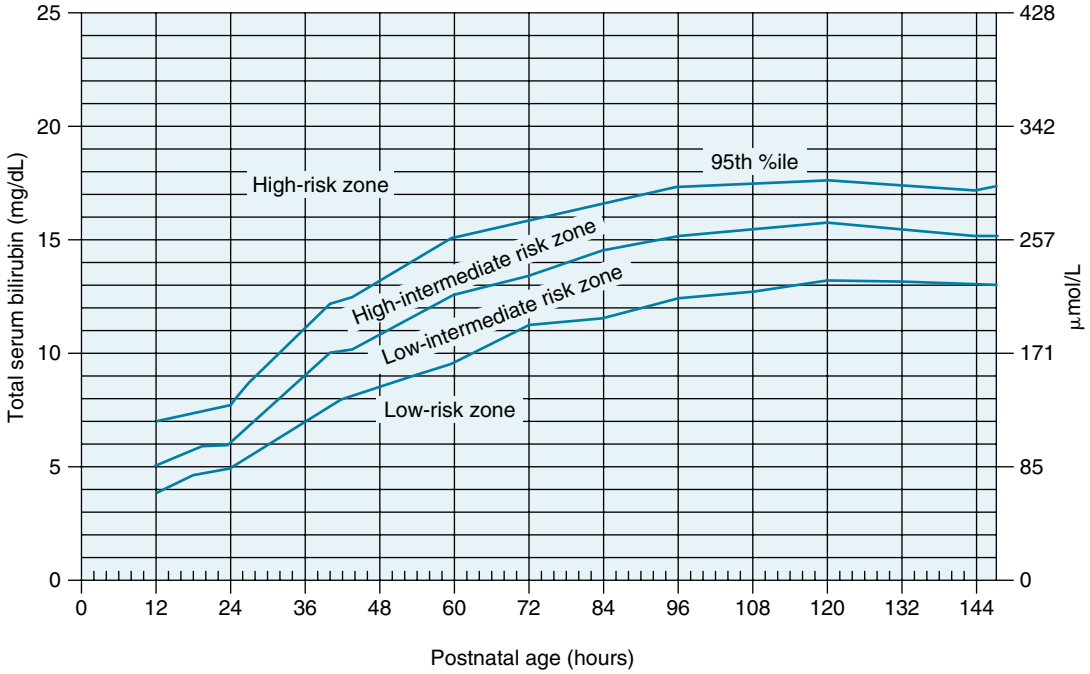


FIGURE 21.3 Nomogram for designation of risk in 2840 well newborns at 36 or more weeks' gestational age with birth weight of 2000 g or more or 35 or more weeks' gestational age with birth weight of 2500 g or more based on hour-specific serum bilirubin levels. The serum bilirubin level was obtained before discharge, and the zone in which the value fell predicted the likelihood of a subsequent bilirubin level exceeding the 95th percentile (high-risk zone). *%ile,* Percentile. (From Bhutani VK, Johnson L, Sivieri EM. Predictive ability of a predischarge hour-specific serum bilirubin for subsequent significant hyperbilirubinemia in healthy term and near-term newborns. *Pediatrics.* 1999;103(1):6.)

PREVENTION OF HYPERBILIRUBINEMIA

Early Feeding

Compared with infants not fed during the first 24 to 48 hours of life, infants fed earlier have lower peak bilirubin levels, likely related to a decrease in intestinal transit time and decreased enterohepatic circulation. Early initiation of breastfeeding in the first hour helps establish lactation and set a pattern of frequent feeding.[51]

RhoGAM

As described earlier, widespread use of RhoGAM has proven effective in preventing the sensitization of Rh-negative mothers after delivery or abortion of Rh-positive infants. RhoGAM, or anti-D gamma globulin, provides passive protection by preventing maternal production of anti-Rh antibodies that might affect subsequent Rh-positive pregnancies, causing destruction of fetal red blood cells. Failures may occur if the amount of RhoGAM administered is insufficient compared with the load of fetal red blood cells received, or if a significant fetal-maternal hemorrhage occurred before prophylaxis. Routine management of the Rh-negative mother now includes the administration of antenatal RhoGAM in the second trimester (26 to 28 weeks), at the time of amniocentesis, and after delivery if the neonate is Rh positive.

Phenobarbital

Phenobarbital acts to induce microsomal enzymes, increasing the levels of UGT-1A1. It also stimulates bile secretion in infants with nonobstructive cholestasis and increases the concentration of ligandin. When used in conjunction with phototherapy, however, phenobarbital does not increase the rate of decline in bilirubin

levels.[29] Phenobarbital treatment is indicated in infants with Crigler-Najjar syndrome type II, but is otherwise not used on a routine basis.

Heme Oxidase Inhibitors

Metalloporphyrins, compounds that are potent competitive inhibitors of the enzyme *heme oxygenase,* the initial and rate-limiting step in bilirubin production, have been investigated as possible interventions for prevention of hyperbilirubinemia by modulating bilirubin production.[83] Only tin protoporphyrin (SnPP) and tin mesoporphyrin (SnMP) have been studied in humans for prevention of neonatal unconjugated hyperbilirubinemia. Although highly efficacious, SnPP had photosensitizing properties that made it less appealing. Although SnMP is also photosensitizing, its use at lower doses reduces photoreactivity. **Human trials with SnMP in preterm neonates have shown a dose-dependent reduction in peak bilirubin levels irrespective of gestational age and a reduction in the need for phototherapy.**[49,62,89] The efficacy of SnMP has been well described in patients with Crigler-Najjar syndrome. Other alternative metalloporphyrins and nonmetalloporphyrins are currently being investigated; however, further trials in humans to determine long-term safety and effectiveness are necessary before widespread use can be recommended.

EVALUATION OF THE INFANT WITH HYPERBILIRUBINEMIA

The history, physical examination, and laboratory data play an important role in the evaluation of the infant with hyperbilirubinemia (Box 21.4).

History

The evaluation of a jaundiced infant begins with a complete family, perinatal, and neonatal history. The family history should include the occurrence of disorders associated with hyperbilirubinemia in other family members, particularly siblings. **Need for phototherapy in a sibling is a risk factor for hyperbilirubinemia requiring intervention in the current child.** A family history of early gallstones, splenectomy, or chronic anemia may indicate inherited hemolytic diseases. The infant's course during labor and delivery should be assessed for possible infection during the pregnancy, the use of oxytocin induction for delivery, or the occurrence of an asphyxial episode during labor or delivery. A history of medications used and the infant's feeding and elimination patterns should also be obtained. **The time of onset of jaundice is important, because clinical jaundice in the first 24 hours of life is abnormal, and likely indicates a hemolytic process.**

BOX 21.4 EVALUATION OF UNCONJUGATED HYPERBILIRUBINEMIA IN THE NEONATE

History
- Family
- Perinatal and obstetric
- Neonatal

Physical Examination
- Pallor
- Hepatosplenomegaly
- Enclosed hemorrhage
- Petechiae
- Congenital anomalies

Laboratory Data

All Jaundiced Infants
- Maternal and infant blood type
- Coombs' test on cord blood
- Total/direct bilirubin (serial measurements)
- Complete blood count, including hematocrit, red blood cell indices, reticulocyte and platelet counts, white blood cell differential, and peripheral smear for red blood cell morphology
- Urinalysis, test for reducing substances
- Serum albumin concentration

Sepsis Evaluation
- IgM
- Urine cytomegalovirus culture and polymerase chain reaction
- Viral cultures

New Techniques
- Transcutaneous bilirubinometry
- Bilirubin-binding tests

Signs and Symptoms and Clinical Approach

A wide spectrum of signs and symptoms may occur in a jaundiced infant, often depending on the cause

of the jaundice. **Jaundice in a newborn usually can be detected visually at a level between 6 and 7 mg/dL. Visible icterus appears first on the head and face and progresses in a cephalocaudal manner.** The skin of the extremities, particularly the palmar and plantar surfaces, are the last skin surfaces to be affected; once the TSB approaches 15 mg/dL, all body surfaces are affected, and further elevation causes no difference in appearance. **However, multiple studies show the inaccuracy of visual estimation of the degree of jaundice, even by experienced health care workers; thus all newborns should be assessed for hyperbilirubinemia with a serum or transcutaneous measurement whenever concern exists.**

An infant with hemolytic disease of the newborn may show jaundice and pallor, or may appear entirely normal at birth. *Hepatosplenomegaly* resulting from congestion and extramedullary hematopoiesis may be present. **Infants affected by severe hemolytic disease of the newborn may also have pancreatic islet cell hyperplasia and an increased risk for hypoglycemia.** Physical examination may reveal the presence of a cephalohematoma or other lesion resulting from enclosed hemorrhage. The occurrence of petechiae or purpura raises the possibility of intrauterine infection or sepsis. Congenital anomalies or syndromic appearance should be noted, because an increased incidence of jaundice is noted in aneuploidy syndromes. Jaundice and umbilical hernia may be associated with congenital hypothyroidism.

SIGNS OF BILIRUBIN TOXICITY

Hyperbilirubinemia is of clinical concern because of the potential for brain injury. Neurons are the principal target of bilirubin toxicity. The spectrum of BIND ranges from acute bilirubin encephalopathy to the irreversible syndrome of kernicterus.[50] **More recently, the overarching term *kernicterus spectrum disorders (KSDs)* has been proposed to encompass all the neurologic sequelae of bilirubin neurotoxicity, with further subclassifications based on the principal disabling features (e.g., motor or auditory deficits).[53] KSDs include all of the following conditions:**

Acute bilirubin encephalopathy (ABE) describes the effects of hyperbilirubinemia seen during the hyperbilirubinemia and immediately thereafter. **Clinical signs of ABE include progressive changes to an infant's mental and behavioral status, including lethargy, poor feeding, and hypotonia, followed by hypertonia, a poor Moro reflex with incomplete flexion of the extremities, and a high-pitched cry.** Opisthotonos and retrocollis occur in the later stages.[19,77] As the symptoms of ABE worsen, apnea, seizures, and coma occur, which can result in death.

Kernicterus, or chronic bilirubin encephalopathy, is an irreversible and devastating brain injury[46] evidenced pathologically by yellowish staining in the deep nuclei of the central nervous system, particularly in the globus pallidus of the basal ganglia, central and peripheral auditory pathways, pontine and brainstem nuclei, subthalamic nuclei, cerebellum, and hippocampus. Compared with other forms of perinatal brain injury, kernicterus shows a clear correlation among etiology, pathogenesis, and symptomatology. **Based on multiple studies, kernicterus has a mortality rate of 10% and a 70% or higher risk of long-term morbidity.**[43] **The clinical signs of kernicterus include extrapyramidal movement disorder, including dystonia and choreoathetoid movements (rapid, highly complex, involuntary, spasmodic movements); gaze abnormalities (especially paralysis of upward gaze); auditory disturbances (deafness); dysplasia of the enamel of deciduous teeth; and mild cognitive defects.** The neuromotor abnormalities may be subtle, with the auditory abnormalities most apparent because the auditory pathways are the neural system most sensitive to bilirubin injury.[19]

Survivors with kernicterus may exhibit choreoathetosis, spastic cerebral palsy, cognitive delay, sensory and perceptual deafness, and visual-motor incoordination. Although it is not likely that significant cognitive delay alone, without the other features, is caused by bilirubin encephalopathy, it is possible, though not yet proven, that subtle neurologic signs may occur, including learning and behavioral problems, awkwardness, gait abnormalities, or minimal fine and gross motor incoordination.[44]

A syndrome of BIND can occur in the absence of classic kernicterus.[18] Bilirubin toxicity can result in neuronal cell death, astrocytic reactivity, and microglia activation that cause both subtle and obvious clinical manifestations.[24] These clinical manifestations can include abnormal neuromotor signs, muscle tone abnormalities, hyperexcitable neonatal reflexes, neurobehavioral manifestations, speech and language abnormalities, and central processing abnormalities (including sensorineural

audiologic and visuomotor dysfunction). There are concerns that vulnerable infants can acquire BIND, even without a history of severely elevated bilirubin levels, or with prolonged elevation of bilirubin levels that are subthreshold for treatment.[18]

Brain lesions identified on magnetic resonance imaging after extreme hyperbilirubinemia have been linked to dyskinetic cerebral palsy.[74] Newer imaging techniques, including diffusion tensor imaging or single-photon emission computed tomography allow for quantification of subtle white matter injury after exposure to unbound bilirubin.[74]

Bilirubin Toxicity in Very-Low-Birth-Weight Infants. Infants with hemolytic disease and premature (especially VLBW) infants should receive phototherapy and exchange transfusion at lower bilirubin concentrations than full-term and otherwise healthy infants. **Unfortunately, the "critical level" at which bilirubin toxicity occurs in either preterm or term infants has not been established. Preterm infants are more susceptible to elevated bilirubin concentrations because they have less efficient hepatic conjugation, lower albumin binding capacity, and increased central nervous system sensitivity to unbound bilirubin.** Some studies have shown significant neurodevelopmental impairment in preterm infants despite only modest elevations in bilirubin concentration. Such studies are difficult to interpret because of the many confounders (e.g., gestational age, concurrent illness) in this population of infants.

Laboratory Data

The TSB level remains the recommended test on which to base clinical decisions. *Transcutaneous bilimeters* are commonly used in newborn nurseries and outpatient settings to screen for hyperbilirubinemia and work by emitting light onto the skin and measuring the light reflected, which is not absorbed by bilirubin in the skin.[36] **Transcutaneous bilirubin measurements (TcB) have been shown to be valid and to result in reduced blood draws;[15,90] however, regular monitoring for quality assurance by comparison with TSB measurements is necessary. TcB measurements are not reliable during or after phototherapy because of the bleaching effect of the phototherapy on skin.[19]** Other studies indicate that discrepancies between TcB and TSB are increased in African-American and black African newborns.[67,86] In low-resource settings, TcB may identify a high proportion of false positives that may lead to unnecessary and burdensome treatment.[69]

Newer devices (e.g., the BiliCheck [Andover, MA] device by Phillips-Respironics or the JM-103 [Loganville, GA] device by Konica Minolta/Air-Shields) **are able to correct for skin melanin content and give results within 2 to 3 mg/100 mL of the TSB.** Although transcutaneous devices are currently approved and recommended for the evaluation of jaundice in infants greater than or equal to 35 weeks' gestational age, some studies indicate that TcB is also useful in premature infants, and consistently measures about 1 mg % less than TSB.[28]

Because TcB is not an exact measure of TSB, a TSB level should be obtained whenever therapeutic intervention is considered (Box 21.5). Other noninvasive methods of determining jaundice include jaundice color cards, or icterometers. In one study in China, measurements from the newborn's cheek had a correlation coefficient of 0.985 with TSB.[99] Another two-color icterometer (Bilistrip, Advanced Instruments, Norwood, MA) tested in Africa showed a sensitivity and negative predictive value for newborns requiring phototherapy of 95.8%.[68] These studies need to be replicated in larger and ethnically variable populations.

New complete bilirubin binding panels are under development and include plasma total bilirubin binding concentration, bilirubin binding capacity, and the concentration of nonalbumin bound or free bilirubin. A bilirubin-albumin equilibrium dissociation constant can be calculated from these variables that can be used in comparison with the other variables to determine the risk for bilirubin toxicity.[2] The additional use of the

BOX 21.5 INDICATIONS FOR TSB LEVEL TESTING[58]

- The TcB level is at 70% of the TSB level at which phototherapy would be instituted.
- The TcB value is above the 75th percentile on the AAP nomogram or the 95th percentile on the TcB nomogram.
- At follow-up after discharge, the TcB value is greater than 13 mg/dL.

TSB, Total serum bilirubin.

bilirubin:albumin ratio in jaundiced premature infants was evaluated in the Bilirubin Albumin Ratio Trial (BARTrial) but failed to demonstrate better correlation with neurodevelopmental outcome in preterm infants less than 32 weeks' gestational age assigned to the study group.[42]

ADDITIONAL LABORATORY EVALUATION

In addition to a bilirubin level, **the minimum laboratory evaluation of the newborn with significant jaundice requiring treatment should include the mother's and infant's blood types, Rh status, and antiglobulin testing on cord blood. A complete blood count (CBC), including hematocrit, reticulocyte count, red cell indices, platelet count, white blood cell count and differential, and peripheral smear for red blood cell morphology, should be performed, seeking evidence of hemolysis.** Microspherocytosis is characteristic of ABO incompatibility and hereditary spherocytosis (MCHC/MCV >0.36).[27]

Bilirubin concentration (TSB) should be measured serially, preferably at the same clinical laboratory facility because of significant interlaboratory variation, and interpreted based on the infant's age in hours at the time of measurement (see Fig. 21.3). **A fractionated bilirubin should be obtained if the jaundice is severe, prolonged, or associated with light-colored stools.** Serum albumin level may be helpful at higher bilirubin concentrations, with the bilirubin:albumin ratio considered as an additional factor in interpretation of bilirubin concentrations.

Evaluation for other potential causes of hyperbilirubinemia is essential when the etiology is not immediately clear. An elevated direct fraction of bilirubin, abnormal white blood cell count, left-shifted differential, or thrombocytopenia may suggest infection. Urinalysis, including evaluation for reducing substances, may be helpful. Infants suspected of having bacterial sepsis should receive antibiotic treatment and have a complete sepsis evaluation performed. Infants suspected of having intrauterine infection should have additional tests, including immunoglobulin M (IgM), as well as blood, cerebrospinal fluid, and/or exudate from skin vesicles for viral cultures and urine for cytomegalovirus as indicated.

Infants with hemolytic disease are at risk for late anemia after discharge from the nursery. These infants require close follow-up for anemia from their primary care provider, as they may require treatment with erythropoietin or transfusion.

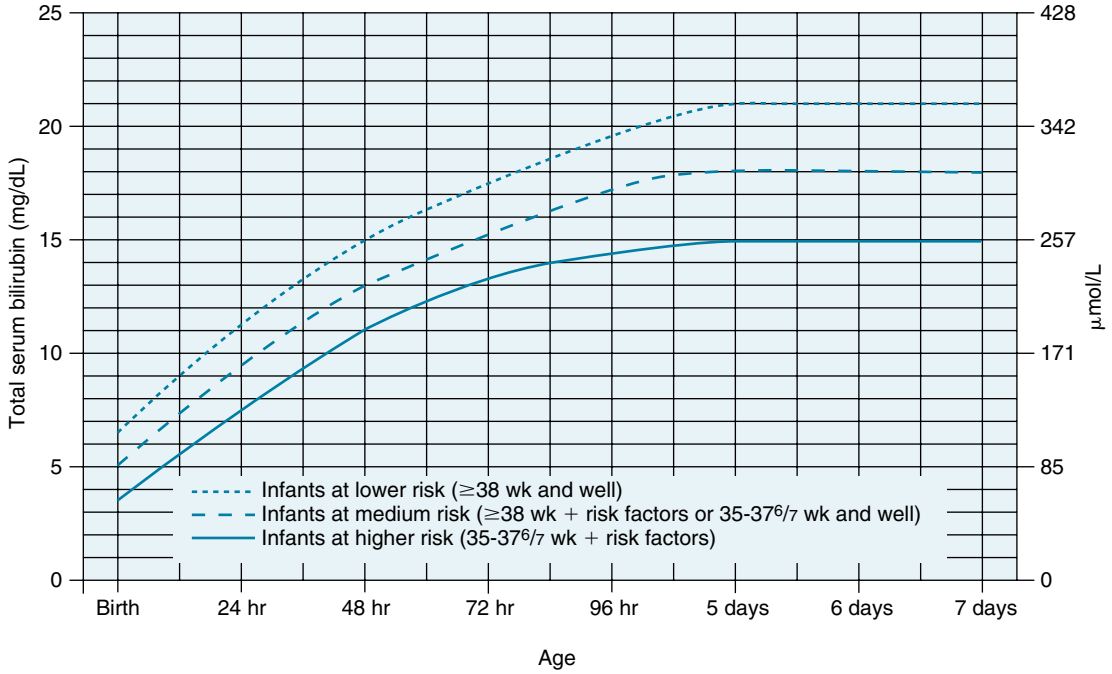
TREATMENT

Treatment aims at lowering the concentration of circulating bilirubin or keeping it from increasing, thereby preventing acute bilirubin encephalopathy and kernicterus. In 2004, the AAP Subcommittee on Hyperbilirubinemia published clinical practice guidelines on the management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation that lend direction regarding the use of phototherapy and exchange transfusion (Table 21.1).[8] These guidelines and recommendations are outlined in Fig. 21.4 *(phototherapy)* and Fig. 21.5 *(exchange transfusion)*. Since the publication of these guidelines, several other studies suggested that combining clinical risk factors analysis with the predischarge measurements of TSB or TcB improves prediction of subsequent hyperbilirubinemia risk;[16,25,50,52,64] consequently,

TABLE 21.1 PHOTOTHERAPY AND EXCHANGE TRANSFUSION CRITERIA FOR VERY-LOW-BIRTH-WEIGHT AND EXTREMELY LOW-BIRTH-WEIGHT INFANTS

WEIGHT (G)	INITIATE PHOTOTHERAPY (mg/dL)	CONSIDER EXCHANGE TRANSFUSION (mg/dL)
500–750	5–8	12–15
751–1000	6–10	>15
1001–1250	8–10	15–18
1251–1500	10–12	17–20

Modified from Cashore WJ. Bilirubin and jaundice in the micropremie. *Clin Perinatol* 2000;27(1):178.



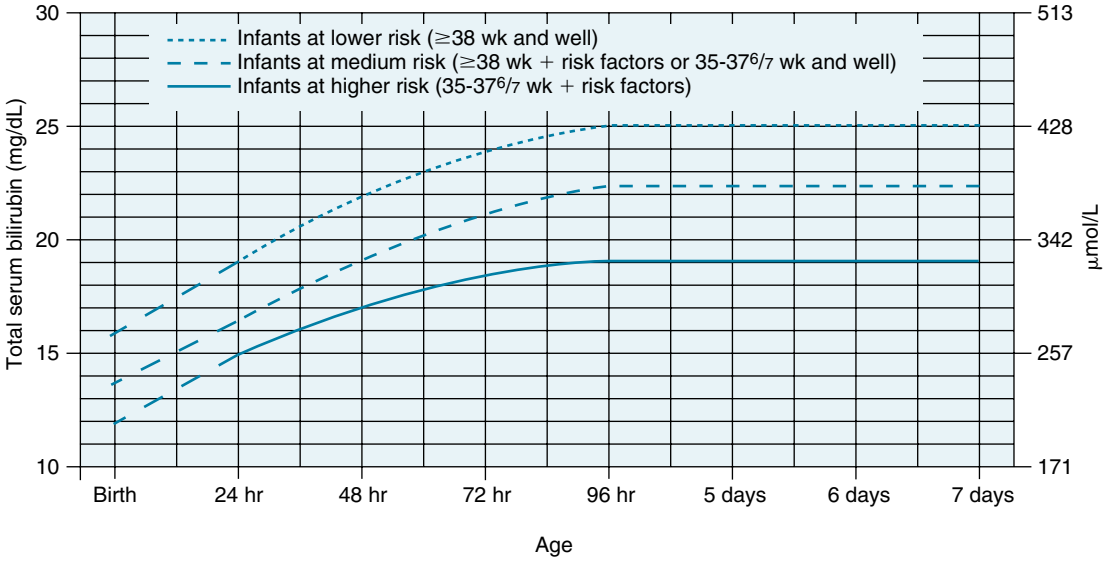
- Use total bilirubin. Do not subtract direct-reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin <3.0 g/dL (if measured).
- For well infants 35-37⁶/₇ weeks, can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 weeks and at higher TSB levels for those closer to 37⁶/₇ weeks.
- It is an option to provide conventional phototherapy in the hospital or at home at TSB levels 2-3 mg/dl (35-50 mmol/L) below those shown, but home phototherapy should not be used in any infant with risk factors.

FIGURE 21.4 American Academy of Pediatrics (AAP) guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestational age. (NOTE: These guidelines are based on limited evidence, and the levels shown are approximations. The guidelines refer to the use of intensive phototherapy that should be used when the total serum bilirubin [TSB] exceeds the line indicated for each category. Infants are designated as "higher risk" because of the potential negative effects of the conditions listed on albumin binding of bilirubin, the blood-brain barrier, and the susceptibility of the brain cells to damage by bilirubin.) *G6PD,* Glucose-6-phosphate dehydrogenase. (From American Academy of Pediatrics. Subcommittee on Hyperbilirubinemia. Clinical Practice Guideline. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 2004;114(1):297.)

these recommendations were updated in a consensus-based guideline in 2009.[58] **The outlined *algorithm* in Fig. 21.6 represents the proposed consensus-based guidelines for the management and follow-up of hyperbilirubinemia in the newborn infant 35 or more weeks' gestational age, according to predischarge bilirubin measurements, gestation, and risk factors. Similarly, a consensus-based guideline has been developed for the suggested use of phototherapy in infants less than 35 weeks' gestational age.**[59] Subsequently, in 2013 Wallenstein and Bhutani published an expanded form of **these recommendations for the management of hyperbilirubinemia in the moderately preterm infant of 32 to 34 weeks' gestational age (Fig. 21.7).**

Phototherapy

Phototherapy is the most frequently used treatment for hyperbilirubinemia. The widespread availability and use of phototherapy in high-resource



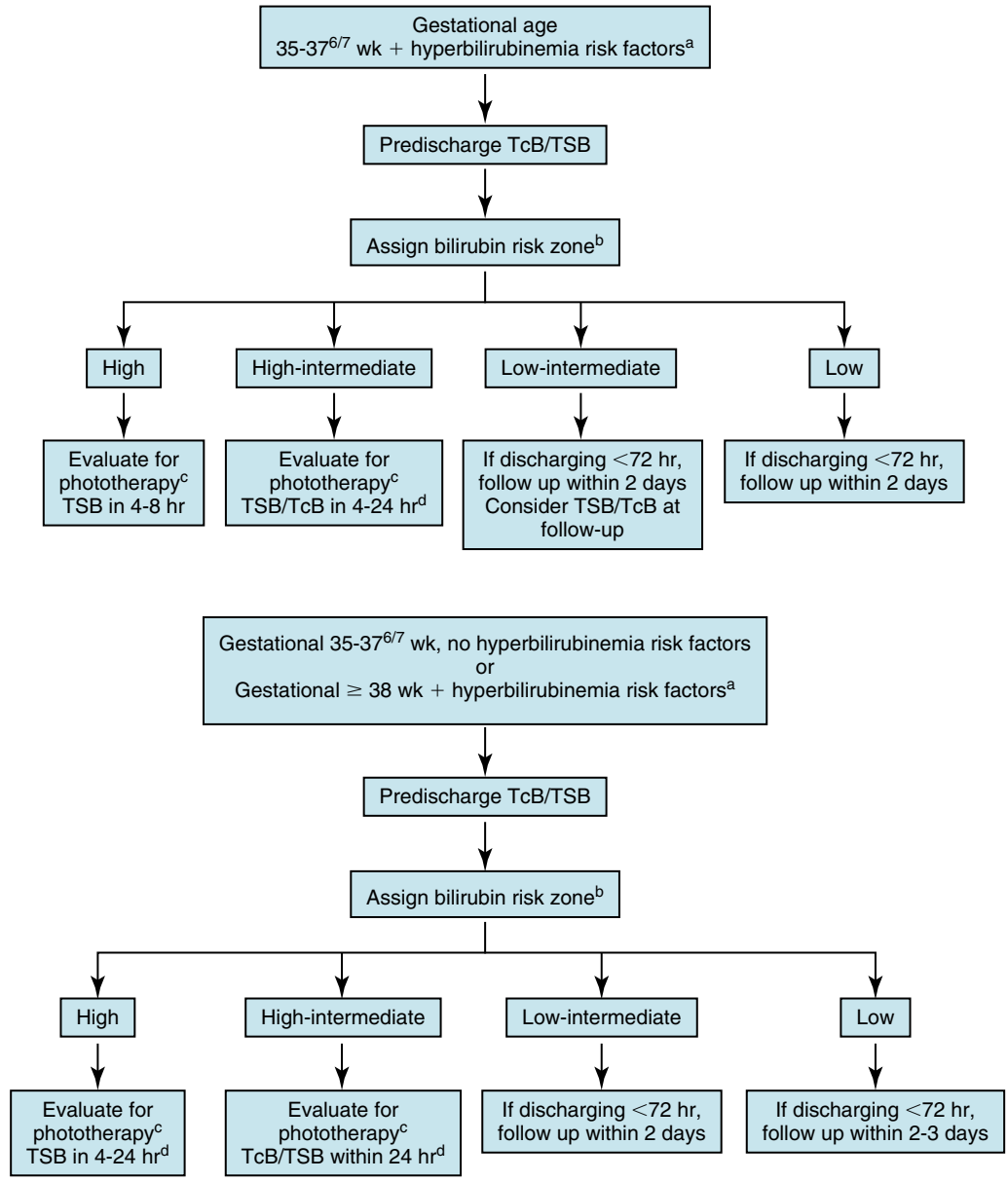
- The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.
- Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high-pitched cry) or if TSB is ≥5 mg/dl (85 μmol/L) above these lines.
- Risk factors: isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.
- Use total bilirubin. Do not subtract direct-reacting or conjugated bilirubin.
- If infant is well and 35-37⁶/₇ weeks (median risk), can individualize TSB levels for exchange based on actual gestational age.

FIGURE 21.5 American Academy of Pediatrics (AAP) guidelines for exchange transfusion in infants of 35 or more weeks' gestational age. (NOTE: These suggested guidelines represent a consensus of most of the American Academy of Pediatrics Subcommittee on Hyperbilirubinemia but are based on limited evidence, and the levels shown are approximations. During birth hospitalization, exchange transfusion is recommended if the total serum bilirubin [TSB] rises to these levels despite intensive phototherapy. For readmitted infants, if the TSB level is above the exchange level, repeat TSB measurement every 2 to 3 hours and consider exchange if the TSB remains above the levels indicated after intensive phototherapy for 6 hours.) *G6PD,* Glucose-6-phosphate dehydrogenase; *TSB,* total serum bilirubin. (From American Academy of Pediatrics. Subcommittee on Hyperbilirubinemia. Clinical Practice Guideline. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics.* 2004;114(1):297.)

settings have nearly eliminated the need for exchange transfusion in infants with nonhemolytic hyperbilirubinemia. Hospital-based studies in the United States have shown that 5 to 40 infants per 1000 term and late-preterm infants receive phototherapy before discharge from the nursery, and an equal number are readmitted for phototherapy after discharge.[55] The decision to initiate phototherapy must be individualized for each newborn and should be based on the AAP guidelines (see Fig. 21.4).

RATE OF BILIRUBIN DECLINE UNDER PHOTOTHERAPY

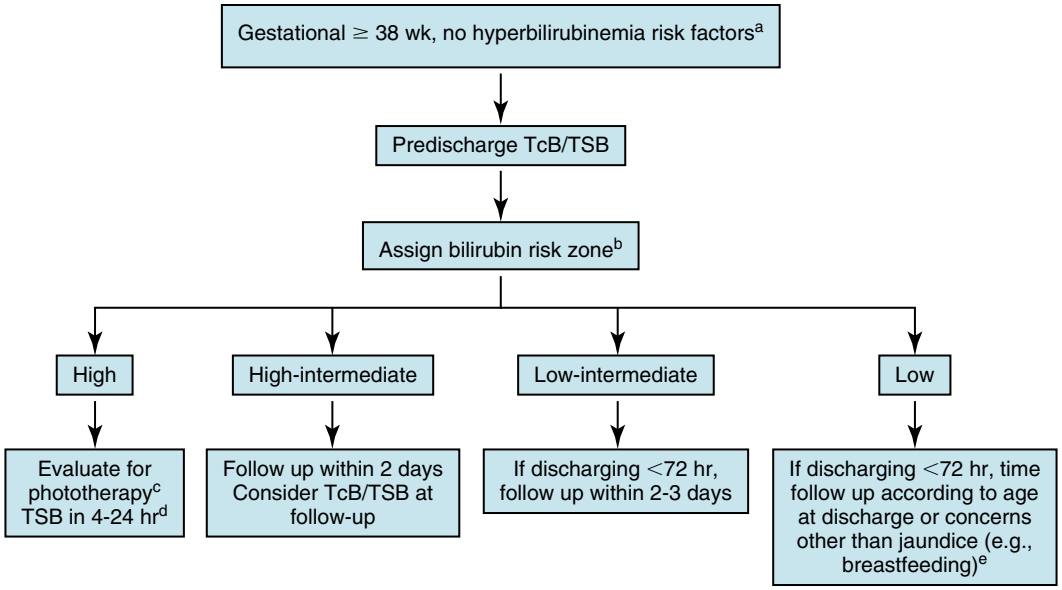
With effective phototherapy, the infant's bilirubin level should drop at a rate of 0.5 to 1 mg/dL (8.5 to 17 mmol/L) per hour, and by 30% to 40% after 24 hours of treatment, when applied at several days of age. **The rate of decline of bilirubin in the first days (early hyperbilirubinemia, likely the result of increased bilirubin production) will not be as brisk, but the rate of rise will be significantly slowed.** Bilirubin best absorbs light in the blue-green spectrum, particularly in the blue region near 460 nm[55]; light at 425 to 475 nm is therefore most effective. **The light energy supplied by phototherapy changes the shape and structure of bilirubin, converting it to photoisomers that can be excreted in the bile and urine without conjugation.[55]** Configurational isomers are formed most rapidly (Z, E and E, Z isomers), but the reaction



- Recommendation for timing of repeat TSB measurement depends on age at measurement and how far the TSB level is above the 95th percentile (Figure 21-3). Higher and earlier initial TSB levels require an earlier repeat TSB measurement.
- (a) Risk factors, (b) Figure 21-3, (c) Figure 21-4, (d) in hospital or as outpatient, (e) follow-up recommendations can be modified according to level of risk for hyperbilirubinemia.

FIGURE 21.6

Algorithm providing recommendations for management and follow-up according to predischarge bilirubin measurements, gestation, and risk factors for subsequent hyperbilirubinemia. Provide lactation evaluation and support for all breastfeeding mothers. (From Maisels MJ. Neonatal hyperbilirubinemia and kernicterus—not gone but sometimes forgotten. *Early Hum Dev.* 2009;85(11):727. Reproduced with permission from Maisels MJ, Bhutani VK, Bogen D, Newman TB, et al. Hyperbilirubinemia in the newborn infant 35 or more weeks' gestation. *Pediatrics.* 2009;124(4):1193.)



- Recommendation for timing of repeat TSB measurement depends on age at measurement and how far the TSB level is above the 95th percentile (Figure 21-3). Higher and earlier initial TSB levels require an earlier repeat TSB measurement.
- (a) Risk factors, (b) Figure 21-3, (c) Figure 21-4, (d) in hospital or as outpatient, (e) follow-up recommendations can be modified according to level of risk for hyperbilirubinemia.

FIGURE 21.6, cont'd

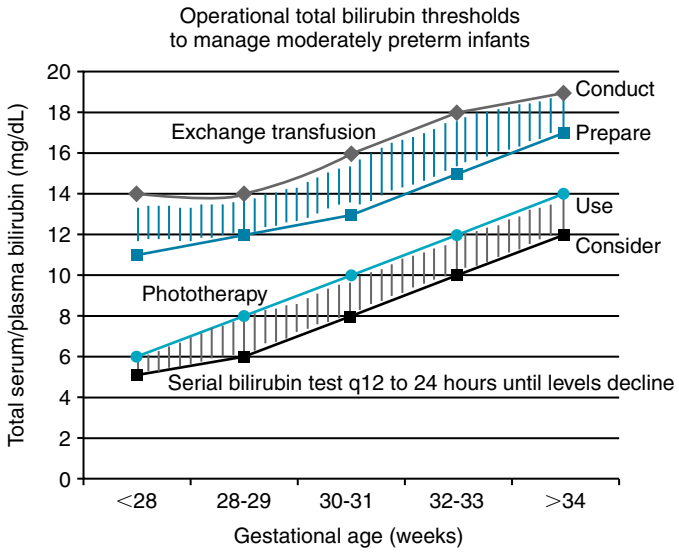


FIGURE 21.7 Suggested use of phototherapy and exchange transfusion in preterm infants less than 35 weeks' gestational age. The operational thresholds have been demarcated by recommendations of an expert panel. The *shaded bands* represent the degree of uncertainty. Recommended threshold to prepare for exchange transfusion assumes that these infants are already being managed by effective phototherapy. Increase in exposure of body surface area to phototherapy may inform the decision to conduct an exchange transfusion based on patient response to phototherapy. (From Wallenstein MB, Bhutani VK. Jaundice and kernicterus in the moderately preterm infant. *Clin Perinatol* 2013;40(4):679. Modified with permission from Maisels MJ, Watchko JF, Bhutani VK, et al. An approach to the management of hyperbilirubinemia in the preterm infant less than 35 weeks of gestation. *J Perinatol* 2012;32[9]:660.)

is reversible.[41] The most important of these isomers is ***lumirubin,*** **a stable structural photoisomer. Lumirubin does not require conjugation and is rapidly excreted in both bile and urine. The production of lumirubin is an irreversible reaction that appears to be dose-related,** but occurs more slowly than formation of the configurational isomers. Photo-oxidation of bilirubin occurs much more slowly and is not as important as photoisomerization.

The efficacy of phototherapy depends on the energy output *(irradiance)* of the light source (measured with a radiometer in units of microwatts per square centimeter per nanometer of light over a given wavelength band), **the distance of the light source from the infant, and the surface area of the skin exposed to the light. Intensive phototherapy consists of 30 μW/cm²/nm or more.[8]** Of concern, several studies show that irradiance of phototherapy devices worldwide may be suboptimal.[22] Barriers to appropriate irradiance levels may include distance of infant from the light source, skin surface area exposed, type of light source used, and protocols to standardize correct phototherapy practices and equipment maintenance.[22] **Fiber-optic blankets deliver phototherapy from a high-intensity light source either alone or in conjunction with other sources of phototherapy;** alone they are unlikely to expose adequate surface area on a term infant to provide intensive phototherapy.[55]

LIGHT SOURCES

The AAP describes the most commonly used phototherapy units in its 2004 guidelines. These include daylight, cool white, blue, or "special blue" fluorescent tubes or tungsten-halogen lamps in different configurations, either freestanding or as part of a radiant warming device. Most of these devices deliver enough output in the blue-green region of the visible spectrum to be effective for standard phototherapy use. **The most effective light sources commercially available for phototherapy are blue fluorescent tubes or specially designed light-emitting diode (LED) lights** (Natus Inc., San Carlos, CA). The special blue fluorescent tubes are labeled *F20T12/BB* (General Electric, Westinghouse, Sylvania) or *TL52/20W* (Phillips, Eindhoven, The Netherlands). It is important to note that special blue tubes provide much greater irradiance than regular blue tubes (labeled *F20T12/B*) because they provide light predominantly in the blue-green spectrum. At these wavelengths, light penetrates skin well and is absorbed maximally by bilirubin.[8]

Currently, LEDs are more frequently used than florescent tubes.[34] Super LEDs are high-intensity blue lights grouped together in small capsules that emit a high intensity blue light with a narrow band that produces low heat.[78] One study showed a **significant reduction in TSB in hemolytic and nonhemolytic neonates treated with the super blue light when contrasted with similar patients treated with florescent phototherapy.[79]**

Fiber-optic phototherapy blankets (Wallaby Phototherapy System, Fiberoptic Medical Products, Inc., Allentown, PA; Biliblanket, Ohmeda, Columbia, MD) use a high-intensity halogen light source for transmission of light by fiber-optic bundles. Irradiance and efficacy appear comparable with those for standard phototherapy. **Purported advantages of these systems are elimination of the need for eye patches, exposure of greater surface area, and provision of phototherapy outside of the nursery or hospital with less interference in mother-infant bonding.**

Double-bank phototherapy has been shown to reduce the TSB significantly faster than single-bank phototherapy because of the increase in body surface area that is exposed.[33]

Physical and laboratory evaluation should be performed before initiating phototherapy in any infant. **Once phototherapy has been initiated, TSB must be monitored as TcB measurement is no longer valid.** Hematocrit also must be followed serially in infants with hemolytic disease.

There are conflicting data in the literature on whether continuous or intermittent administration of phototherapy is most effective. **Phototherapy may be interrupted during brief periods for feeding, laboratory draws, assessment of the eyes, visual stimulation, and parental contact. Intermittent phototherapy has been shown to be as effective as continuous phototherapy in nonhemolytic term and late-preterm neonates.[75]** Although it only takes a few nanoseconds for the photochemical reaction (isomerization) to occur, it may take several hours for the migration and elimination of bilirubin to occur; during this time, phototherapy's role is minimal.[75] Neonates with nonhemolytic hyperbilirubinemia in the intermittent phototherapy (12 hours on, 12 hours off) arm had bilirubin levels that fell faster and a shorter duration of phototherapy compared with neonates in the continuous phototherapy arm.[75] Table 21.2 outlines some of

TABLE 21.2 NURSING MANAGEMENT OF INFANTS UNDERGOING PHOTOTHERAPY

NURSING ASSESSMENT

AREA	PARAMETER
Physical status	Intake and output Color Location of jaundice Skin integrity Stools (character, consistency) Vital signs Infant/environmental temperature Hydration status Signs of phototherapy side effects Eye discharge and tearing Position Activity
Neurobehavioral status	Sleep-wake states Sensory threshold Behavioral responsiveness Feeding behaviors Consoling abilities Stress responses Interactive capabilities

NURSING MANAGEMENT

NURSING DIAGNOSIS	INTERVENTION
Deficient fluid volume (actual or potential)	Monitor intake and output. Monitor hydration status (weight, specific gravity, urine output). Monitor stooling pattern, character. Maintain adequate fluid intake (oral or parenteral).
Imbalanced nutrition: less than body requirements	Assess feeding behavior and activity. Monitor fluid and caloric intake, weight, and abdominal girth. Remove eye shields during feeding. Hold during oral feedings as health and thermal status permit. Bring to alert state before feeding. Feed on demand if possible.
Impaired skin integrity	Observe color, rashes, excoriation. Clean skin with warm water. Clean perineal area after stooling. Turn frequently (also increases skin exposure to phototherapy). Ensure Plexiglas shield is in place between light source and infant to reduce exposure to ultraviolet light.

Continued

TABLE 21.2 NURSING MANAGEMENT OF INFANTS UNDERGOING PHOTOTHERAPY—CONT'D

NURSING MANAGEMENT	
NURSING DIAGNOSIS	**INTERVENTION**
Risk for injury	Observe for side effects associated with phototherapy. Observe for signs of sepsis. Provide care to minimize side effects of phototherapy. Shield eyes from lights with opaque patches. Ensure eyelids are closed when shield is applied to prevent corneal injury. Remove eye shield and observe eyes regularly. Monitor position of eye shield to prevent occlusion of nose. Avoid tight headband on eye shield to reduce risk of increased intracranial pressure, especially in preterm infants. Observe for eye discharge and tearing. Shield testes and possibly ovaries (data unclear about need to do this) with diaper.
Ineffective thermoregulation	Place in warm, thermoneutral environment. Monitor environmental and infant temperature. Observe for hypothermia and hyperthermia. Reduce heat losses from environmental sources. Use servocontrol for infants in incubator or under radiant warmer. Shield servocontrol thermistor from direct exposure to phototherapy lights.

From Blackburn S. Hyperbilirubinemia and neonatal jaundice. *Neonatal Netw.* 1995;14(7):15.

the nursing assessments and management to be performed in infants undergoing phototherapy.

REBOUND

After phototherapy is discontinued, TSB should be followed for at least 24 hours to assess for significant rebound. Infants most likely to experience significant rebound are those less than 37 weeks' gestational age, those with a hemolytic process, and those treated with phototherapy for early hyperbilirubinemia during the birth hospitalization, because the bilirubin is still rising at the time phototherapy is discontinued.[55]

SAFETY

Despite widespread use since 1958, questions about the safety and side effects of phototherapy remain. However, reports of clinically significant toxicity are rare.[57] Animal studies have demonstrated a potential retinal toxicity of light. Although it is not established that this occurs in the human newborn, the **infant's eyes should be covered while phototherapy is in use.** Patches should completely cover the eyes without placing excessive pressure on the eyes and should be carefully positioned to avoid occluding the nares. **Eye patches should be removed every 4 hours to permit evaluation of the infant's eyes. The patches should be left off during feedings and parental visits.**

HEAT BALANCE

Infants exposed to phototherapy, particularly low-birth-weight infants and infants under a radiant warmer, may have significant increases in their insensible water losses. Infants in incubators or servocontrolled care centers may become overheated. **The servocontrol probe should be shielded by an opaque covering.**

Infants treated in open cribs may become cold stressed. Fluid balance must be monitored carefully in an infant receiving phototherapy. Infants under phototherapy may also have increased stool water losses and may develop temporary lactose intolerance. **The infant's temperature, weight,**

and intake and output should be monitored frequently. Liquid stools containing reducing substances can be treated with a non–lactose-containing formula.

PHOTOTHERAPY IN PREMATURE INFANTS

Little evidence exists for management of hyperbilirubinemia in preterm infants less than 35 weeks' gestational age.[21,70] Consensus-based management continues to be the recommendation (see Fig. 21.7).[21,70] Extremely low-birth-weight (ELBW) infants have thinner and more translucent skin. The light from phototherapy interacts with bilirubin, but can also interact with many other molecules in the ELBW infant's tissues. Because the head represents a large expanse of their total body surface area, brain tissue is one of the most concerning areas of interaction.[84] **Therefore, generalizing the safety and efficacy of phototherapy to ELBW infants may not be appropriate.**

Because the concentration of bilirubin that is detrimental to ELBW preterm infants has not been well defined, a randomized controlled trial attempted to determine whether aggressive versus conservative phototherapy led to improvement in neurodevelopmental outcome at 18 to 22 months for infants between 501 and 1000 g.[62] **Although there was no difference in survival between groups overall, of the surviving infants, the aggressive phototherapy group had significant decreases in rates of neurodevelopmental impairment.** Of concern, however, was that in a **subgroup analysis of the smallest infants, 501 to 750 grams, the mortality rate was increased by 5% in the aggressive versus conservative phototherapy group.** Although not statistically significant, this increased mortality rate was worrisome to the authors and may offset any potential benefit of aggressive phototherapy in this weight category. Future directions may include evaluation of other novel interventions for prevention or treatment of hyperbilirubinemia in these most vulnerable infants.[10]

CHOLESTATIC JAUNDICE AND PHOTOTHERAPY

Infants who have cholestatic jaundice and are exposed to phototherapy may develop the "bronze baby syndrome," presumably caused by a breakdown product of bilirubin produced by phototherapy, although the mechanism is unclear. **An infant with bronze baby syndrome develops a dark gray-brown discoloration of the skin, urine, and serum.** There are generally no other clinical symptoms, but at least one death has been reported. After phototherapy ceases, the bronzing gradually resolves.

TRANSIENT SIDE EFFECTS

Transient skin rashes and tanning resulting from increased melanin production have been reported, as have bullous skin eruptions in infants treated with SnMP who are subsequently exposed to sunlight or daylight fluorescent bulbs.[55] A study published in 2008 suggested that intensive phototherapy might increase the number of melanocytic nevi identified at school age.[55] Other potential problems include **interference with biologic (circadian) rhythms and maternal-infant bonding.** Although there may be some transient, short-term growth effects, long-term growth effects and development appear unaffected by phototherapy.

PHOTOTHERAPY IN LOW-RESOURCE SETTINGS

Optimal phototherapy can be difficult to achieve in settings with limited resources and leads to higher rates of exchange transfusion in these settings. Barriers to optimal phototherapy include light sources that deliver a suboptimal light emission spectrum and irradiance level, maintenance constraints, lack of consistent electricity, and lack of education and awareness among medical staff administering phototherapy about how it works or the requirements for effective treatment.[13] A recent randomized, controlled, noninferiority trial was performed in a maternity hospital in Lagos, Nigeria, to determine if filtered sunlight and conventional phototherapy produced similar reductions in mild-to-moderate hyperbilirubinemia.[80] The study showed that filtered sunlight was noninferior to conventional phototherapy, that filtered sunlight achieved higher means of irradiance, but also that higher numbers of infants had elevated temperatures with filtered sunlight compared with conventional phototherapy. A subsequent study confirmed noninferiority of filtered sunlight for moderate to severe hyperbilirubinemia as well.[81] Although this is promising for future management of hyperbilirubinemia in low-resource settings, more evidence is needed on how to do this safely and effectively.

Intravenous Immunoglobulin

When immune-mediated hemolysis is present and the TSB is rising, despite intensive phototherapy or is approaching the exchange level, intravenous immunoglobulin should be administered to the infant to decrease the severity of hemolysis. The dose of 500 mg/kg to 1 g/kg IV over 2 to 4 hours may be repeated one time after 12 hours. This intervention has been shown in multiple trials to decrease the need for exchange transfusion by approximately 70% and is recommended for Rh isoimmunization as soon as the diagnosis is established, and for ABO isoimmunization if the TSB continues to rise despite intensive phototherapy.[8,9] Immunoglobulin is of no benefit in non–antibody-mediated hyperbilirubinemia such as occurs in G6PD deficiency, Gilbert syndrome, or spherocytosis.

Exchange Transfusion

An exchange transfusion is indicated for correction of anemia and removal of antibody-coated red blood cells in severe hemolytic disease, or for treatment of signs of acute bilirubin encephalopathy regardless of its cause or TSB level. Phototherapy cannot be used in place of an exchange transfusion in such infants, although use of intensive phototherapy while preparing for exchange transfusion is essential.

It must be stressed that the decision to perform an exchange transfusion is individualized for each patient. Particularly in VLBW infants, evidence-based guidelines are lacking. **The recent AAP guidelines for performing exchange transfusion in infants of 35 or more weeks of gestation are shown in** Fig. 21.5 **(see discussion in legend). Similar guidelines have recently been proposed for the preterm infant, as shown in** Fig. 21.7. Exchange transfusions are much more commonly performed in low- and middle-income countries; however, the criteria for making this decision have not been systematically explored nor a guideline written.[66]

A double-volume exchange transfusion is performed using 160 mL/kg of appropriate whole-blood product. If fresh whole blood is not available, reconstituted whole blood can be requested that can be mixed to a desired hematocrit. ABO type–specific Rh-negative blood should be used in cases with Rh incompatibility. Type O Rh-specific cells are indicated when ABO incompatibility exists. **Whereas a single-volume exchange (80 mL/kg) will replace 63% of the infant's blood, a double-volume exchange will replace 86%.** Further increase in the amount exchanged gives little additional benefit.

The blood bank can prepare reconstituted whole blood for the infant with a predetermined hematocrit, usually 50% to 55%. **An exchange transfusion will reduce bilirubin levels by approximately 45% to 85%,** according to various sources. Administration of 1 g/kg of 25% albumin 1 hour before the exchange transfusion has been shown in some studies to increase the efficiency of exchange by about 40%. **As plasma and tissue bilirubin levels equilibrate post-transfusion, the bilirubin rises to about 60% of the pre-exchange level.**

PROCEDURE

Exchange transfusion trays are commercially available and include a four-way stopcock, necessary tubing and syringes, a vial of 10% calcium gluconate, and a plastic bag for discarded blood.

The infant should be in the NICU for close observation during and immediately after the procedure. **Feedings should be held for 2 to 3 hours before the procedure and for some time afterward.** The procedure is performed by removing small aliquots of the infant's blood and replacing similar small aliquots of transfused blood product through the umbilical vein while blood pressure, heart rate, and general condition are monitored. Generally, 5 mL to 20 mL aliquots of blood are used, depending on the size and condition of the infant. Each aliquot should be 5% to 8% of the estimated blood volume or 5 mL/kg, withdrawn or infused at a rate of approximately 5 mL/kg/min. **The entire procedure should take 60 to 90 minutes and encompass 30 to 35 cycles of withdrawal and infusion.[38] In general, a slower exchange will result in less rebound of TSB than a rapid exchange because the extravascular bilirubin may equilibrate with the plasma bilirubin more extensively during the procedure.[38]** The initial aliquot should be withdrawn and sent to the laboratory for determination of bilirubin, hematocrit, and calcium. Blood used in the exchange must be warmed in a carefully controlled fashion to prevent "cold heart syndrome," which may cause arrhythmia and cardiac arrest, or overheating.[38]

The final aliquot from an exchange should be sent for determination of CBC, fractionated bilirubin, calcium ion, and electrolytes. In addition to the individuals performing the exchange, another person must keep an accurate record of time, volumes withdrawn and infused, vital signs, and medications administered.

POTENTIAL COMPLICATIONS

Exchange transfusion is a procedure with many potential complications and carries a mortality risk of about 0.5%. For this reason and because so few exchange transfusions are performed in highly resourced countries today (estimated at 3/100,000 live births in the United States),[64] this procedure should be done only by personnel who are familiar with the technique and its complications, preferably in a tertiary care unit. Vascular complications are related to the use of umbilical catheters (discussed in Chapter 7). **Necrotizing enterocolitis has been reported as a postexchange complication, probably as a result of bowel ischemia during the procedure,** and may be related to a more rapid exchange and use of larger aliquots of blood.[38,63]

Electrolyte and glucose disturbances are related to the blood preparation used for the exchange. Citrate used as part of the anticoagulant solution binds divalent ions such as calcium and magnesium; thus laboratory evaluation of calcium and magnesium during the procedure is essential. **The infant should be evaluated for hypocalcemia after each 100 mL of the exchange has been completed.** Although symptomatic hypocalcemia is rare, clinical signs and symptoms include irritability, tachycardia, or prolongation of the Q-Tc interval. **If hypocalcemia is detected, 1 mL of a 10% calcium gluconate solution is infused slowly through the umbilical vein catheter under continuous electronic cardiac monitoring.**

Acid-citrate-dextrose and citrate-phosphate-dextrose blood have high levels of sodium and glucose and sometimes potassium. **Initial hyperglycemia may be followed by reactive hypoglycemia as a result of an insulin response.** Although the blood is acidic at the time of infusion, a postexchange alkalosis may occur as citrate is metabolized to bicarbonate in the liver. Many of the electrolyte and acid-base disturbances may be avoided by the use of fresh, heparinized whole blood. **Bleeding may occur in an overheparinized infant but is reversible with protamine sulfate.**

Thrombocytopenia is very likely to occur after any exchange transfusion, but especially in the infant needing repeated exchange transfusions. Bacterial infection is rare, and routine antibiotic prophylaxis is not indicated. Most complications, other than thrombocytopenia, are avoidable if careful attention to technique is observed.

LONG-TERM OUTCOMES

Apart from kernicterus, recent studies have looked at other long-term outcomes associated with hyperbilirubinemia itself and with phototherapy treatment. Prediction of outcome is difficult, although a recent study evaluated the use of a 9-point BIND score that assesses mental status, muscle tone, and cry patterns and demonstrated that a BIND score greater than or equal to 4 had a specificity of 87.3% and a sensitivity of 97.4% for predicting poor neurologic outcome at 3 to 5 months.[35]

Several observational studies have suggested a possible association between hyperbilirubinemia and other conditions, such as autism spectrum disorder or childhood allergic diseases, although these studies also caution that further prospective evaluation of such links is needed.[7,31,54]

Recent studies have raised concerns that both conventional and intensive phototherapy are associated with DNA damage that could result in adverse long-term outcomes and that duration of phototherapy was positively correlated with markers of genotoxicity.[73] Several studies indicate a possible increased risk of cancer, although results are attenuated when confounding variables are eliminated.[65]

PARENT TEACHING

Providing parents with written information about jaundice and its treatment may be a beneficial adjunct to verbal explanations and forms a key element of the AAP guidelines on management of hyperbilirubinemia (Box 21.6). Because early discharge policies (less than 48 hours of age) have increased the need for outpatient evaluation or management of neonatal hyperbilirubinemia, it is important that **parents feel empowered to ask questions about hyperbilirubinemia and its symptoms so that they can bring any concerns to the attention of health care providers.[93]** This is especially true for the nursing mother, who may be

BOX 21.6 KEY ELEMENTS OF AAP CLINICAL PRACTICE GUIDELINE (2004): MANAGEMENT OF HYPERBILIRUBINEMIA IN THE NEWBORN INFANT 35 OR MORE WEEKS OF GESTATION

Important Points for the Management of Jaundice

- Promote and support successful breastfeeding.
- Establish nursery protocols for the identification and evaluation of hyperbilirubinemia.
- Measure the total serum bilirubin (TSB) or transcutaneous bilirubin (TcB) level on infants jaundiced in the first 24 hours.
- Recognize that visual estimation of the degree of jaundice can lead to errors, particularly in darkly pigmented infants.
- Interpret all bilirubin levels according to the infant's age in hours.
- Recognize that infants at less than 38 weeks' gestation, particularly those who are breastfed, are at higher risk of developing hyperbilirubinemia.
- Screen all infants before discharge with a TSB or TcB measurement, combined with clinical risk factors, to guide the need for additional testing to identify a cause for hyperbilirubinemia and for additional TSB measurements.
- Provide parents with written and verbal information about newborn jaundice.
- Provide appropriate follow-up based on the time of discharge and risk assessment.
- Treat newborns, when indicated, with phototherapy or exchange transfusion.

From American Academy of Pediatrics. Subcommittee on Hyperbilirubinemia. Clinical Practice Guideline. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics.* 2004;114(1):297.

questioning her ability to provide adequate nourishment for her infant. **Indeed, early discharge of infants has led to hyperbilirubinemia being the most common cause for hospital readmission in term infants.**

Providing parents and families with consistent information, reassurance, and support is essential. **The use of phototherapy can be distressing for parents and should be explained to them before they see their infant under phototherapy lights for the first time.**

In addition, **incubators, bili-masks, and phototherapy lights can all contribute to a sense of separation between parents and their infant by creating a physical and emotional barrier.** Parents may avoid coming to the nursery to be with their infant. If they do come to their infant's bedside, they may be reluctant to touch or participate in care for fear of interfering with phototherapy and potentially hindering their infant's progress.

As with many disorders in newborn infants, time and energy spent providing parents with information and support can alleviate much fear, guilt, and anger. It also can help facilitate the development of a healthy family relationship in a time of stress. **Signs and symptoms of jaundice should be explained in a manner that is understandable and meaningful for parents, emphasizing that neonatal hyperbilirubinemia is usually a transient condition and one to which all infants must adapt after birth.**

HEALTH SYSTEMS APPROACH TO BILIRUBIN

Recently, rising rates of kernicterus have called attention to potential systems failures in neonatal services, because most infants currently developing kernicterus are term and late-preterm babies who have been discharged postnatally and return to a pediatrician or emergency department with symptoms of kernicterus.[11,16,46] For this reason, the Joint Commission on Accreditation of Healthcare Organizations issued Sentinel Event Alerts on kernicterus in 2001 and again in 2004.[17,37,44,45,93] However, neither hyperbilirubinemia nor kernicterus has been a reportable disease, and no reliable information source exists to produce national annual estimates.[17] Most estimates range from 0.4 to 2.7 cases per 100,000 live births among infants born at or after 35 weeks of gestation in the United States[59,60] (see Box 21.1).

The root cause analysis for the reappearance of kernicterus revealed several factors. First, **multiple providers at multiple sites** deliver health services, and some providers may not have sufficient understanding of bilirubin and its potential for toxicity. **Early discharge of newborn infants in the first 72 hours after birth** occurs before the natural peak of bilirubin rise in term infants and before the establishment of adequate breastfeeding; these risks are potentiated even more in the late-preterm infant. **Limited parental and provider knowledge regarding hyperbilirubinemia and the early symptoms of acute bilirubin encephalopathy, and failures within health care systems to provide appropriate predischarge screening of at-risk infants,**

only serve to complicate issues.[16,87] Inadequate screening, the inability to measure TSB easily, and a high prevalence of medical conditions that increase the risk of severe hyperbilirubinemia (UGT-1A1 polymorphisms and G6PD deficiency) may cause infants at risk for significant hyperbilirubinemia to be overlooked.[79] In addition, issues related to patient referrals, challenges with implementation of phototherapy, limited availability of whole blood, or lack of experienced personnel to perform exchange transfusions may cause delays in the treatment of infants with acute bilirubin encephalopathy.[98]

The overall aim of the published guidelines[8,58] was to promote an approach that would (1) reduce the frequency of severe hyperbilirubinemia and bilirubin encephalopathy, (2) minimize the risk for unintended harm (e.g., increased anxiety, decreased breastfeeding, unnecessary treatment for the general population), and (3) avoid excessive cost and waste. **These guidelines emphasize the importance of universal predischarge screening combined with clinical risk assessment, close follow-up, and prompt intervention when indicated.** By obtaining a TcB or TSB on all infants before discharge, a systems-based approach to reducing the occurrence of acute bilirubin encephalopathy is achievable. **Infants with bilirubin levels above the 75th percentile for age in hours can be identified, and ongoing tracking of those with rapid rates of rise (greater than 0.2 mg/dL/hr)[19] can be arranged.** Although evidence that universal predischarge screening will reduce the incidence of kernicterus is lacking, published data suggest that predischarge screening can reduce the incidence of TSB levels of 25 mg/dL or greater by facilitating the early recognition of those infants at greatest risk, but may lead to overuse of phototherapy. Furthermore, universal screening is not associated with an increase in neonatal length of stay or postdischarge hospital use.[30] When possible overuse of phototherapy is balanced against the permanent and devastating, though rare, occurrence of kernicterus, such a widespread approach may be seen as conferring a small, but still worthwhile, benefit.[56,58]

The 10 key elements of the 2004 AAP practice guidelines are listed in Box 21.6. Bhutani and Johnson[16] went further to recommend a **five-step nationwide strategy to prevent severe neonatal hyperbilirubinemia:**

- An institutional curriculum for the systems approach, including universal prenatal, predischarge, and postdischarge risk assessment for severe neonatal hyperbilirubinemia
- Advocacy for on-site services that promote breastfeeding in the context of supervised and seamless health care delivery during the first month of life
- Effective parent-provider partnerships for safer management of neonatal jaundice
- Statewide (or regional) reporting of birthing institution outcome assessment for severe neonatal hyperbilirubinemia along with outcomes for neonatal screening for other inherited disorders
- Nationwide surveillance in which all cases of severe neonatal hyperbilirubinemia are reported

On a global scale, research is needed to better define the burden and causes of severe neonatal jaundice and its consequences, along with aggressive educational programs for families and health personnel to facilitate timely care-seeking, accurate diagnosis, and effective phototherapy.[40]

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22 INFECTION IN THE NEONATE

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A newborn infant is uniquely susceptible to infectious diseases. This chapter presents causes of infectious diseases with particular emphasis on prevention, history, presenting signs and symptoms, laboratory data, treatment, and parent teaching methods of prevention applicable to the care of the neonate. Abbreviations for this chapter are listed in Box 22.1.

PATHOPHYSIOLOGY AND PATHOGENESIS

An infection occurs when a susceptible host comes in contact with a potentially pathogenic organism. When the encountered organism proliferates and overcomes the host defenses, infection results. **Sources of infection in a newborn can be divided into three categories: (1) transplacental acquisition (intrauterine infection), (2) perinatal acquisition during labor and delivery (intrapartum infection), and (3) hospital acquisition in the neonatal period (postnatal infection) from the mother, hospital environment, or hospital personnel.**

In general, most infecting organisms can, under the proper circumstances, cross the placenta or ascend from the birth canal and invade the at-risk neonate. These infections may result in abortion, stillbirth, and disease present at birth or in the neonatal period.

The main goal is to prevent infections in the fetus and newborn. Unfortunately, few proven measures exist for the prevention of infections acquired via the placenta or in the perinatal period. Preventive measures are important, because most nonbacterial infections (except syphilis and possibly toxoplasmosis, cytomegalovirus [CMV] infection, and herpes simplex) do not respond to current therapy.

ETIOLOGY

Thorough data collection for the diagnosis of infectious diseases includes a review of the perinatal history, signs and symptoms, and laboratory data. Intrauterine, intrapartum, or neonatal disease may be caused by a wide variety of organisms, many of which are discussed in this chapter.

SPECIFIC INFECTIOUS DISEASES

The following specific infectious diseases are grouped according to their source of infection.[119]

Transplacental (Intrauterine) Acquisition

HUMAN IMMUNODEFICIENCY VIRUS INFECTION AND ACQUIRED IMMUNODEFICIENCY SYNDROME

Prevention. **The primary risk to infants for infection with human immunodeficiency virus (HIV), the causative agent of acquired immunodeficiency syndrome (AIDS), is intrauterine, intrapartum, and postpartum exposure to a mother with HIV infection.** HIV has been isolated from blood and many body fluids. Epidemiologic evidence has implicated only blood, semen, vaginal secretions, and breast milk

BLUE type highlights content that is particularly applicable to clinical settings.

BOX 22.1 ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
CF	Complement fixation (test)
CIE	Counterimmunoelectrophoresis
CRP	C-reactive protein
CRS	Congenital rubella syndrome
CSF	Cerebrospinal fluid
DFA	Direct fluorescent antibody
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
FA	Fluorescent antibody (test)
FAMA	Fluorescent antibody to membrane antigen
FTA-ABS	Fluorescent treponemal antibody absorption (test)
GBS	Group B *Streptococcus*
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
IAHA	Immune adherence hemagglutination
IFA	Indirect fluorescent antibody (test)
IHA	Indirect hemagglutination inhibition (test)
IPV	Inactivated poliovirus vaccine
IUGR	Intrauterine growth restriction
LA	Latex agglutination (test)
MHA-TP	Microhemagglutination test for *Treponema pallidum* infection
NAAT	Nucleic acid amplification test
OPV	Oral poliovirus vaccine
PCP	*Pneumocystis jiroveci* pneumonia*
PCR	Polymerase chain reaction
RNA	Ribonucleic acid
RPR	Rapid plasma reagin (test)
RT-PCR	Reverse transcriptase PCR
VDRL	Venereal Disease Research Laboratory (test)

*Formerly *Pneumocystis carinii* pneumonia.

in transmission. **Some recommendations consider breast milk feedings contraindicated in developed countries where safe alternatives are available.[9,11,155] However, the most recent recommendations from the World Health Organization address exclusive and nonexclusive breastfeeding in mothers receiving anti-retroviral therapy (see Table 18.4).** HIV testing should be recommended and encouraged to all pregnant women.[9,10,155]

Because the medical history and examination cannot reliably identify all patients infected with HIV (or other blood-borne pathogens) and because during delivery and initial care of the infant, perinatal care providers are exposed to large amounts of maternal blood, **standard precautions (e.g., gloves) should be consistently used for all patients when handling the placenta or infant until all maternal blood has been washed away.**[9137]

Data Collection

History. HIV infection in the mother is acquired primarily sexually or by intravenous (IV) drug abuse. **Infection may be asymptomatic. Transmission from an untreated infected mother to the fetus or infant occurs in 13% to 39% of births. Approximately 40% of transmissions occur before birth, and the rest occur around the time of delivery.** Two-thirds of infections occurring before delivery are caused by transmission within the 14 days before delivery.[9] A high maternal plasma viral load, high cervicovaginal viral load, low $CD4^+$ lymphocyte count, advanced maternal illness, an increase in exposure of the fetus to maternal blood, premature delivery, prolonged labor, longer duration of rupture of membranes before delivery, and mode of delivery all increase perinatal transmission of HIV infection.[1079] Globally there has been a 48% reduction in pediatric HIV infection.[154] The rate of perinatal transmission of HIV has decreased to 1% or less in Europe and the United States.[155]

Signs and Symptoms. **Infants with perinatally acquired HIV infection uncommonly have symptoms in the neonatal period,** but the majority of these infants present with clinical illness by 24 months of life (median age at onset of symptoms is 11 to 12 months). One-fifth of infants infected with HIV perinatally develop serious disease or die in the first year of life.[149] Symptoms include failure to thrive, developmental disabilities, neurologic dysfunction, hepatosplenomegaly, generalized lymphadenopathy, parotitis, persistent oral candidiasis (thrush), and chronic or recurrent diarrhea. Lymphoid interstitial pneumonia is frequently seen in these infants. HIV-infected infants commonly have osteomyelitis, septic joints, pneumonia, sepsis, meningitis, and otitis media with common organisms (e.g., *Streptococcus pneumoniae, Haemophilus influenzae* type b), and these infections may be recurrent.[79,149]

Laboratory Data. **HIV nucleic acid detection by polymerase chain reaction (PCR) of DNA extracted from peripheral blood mononuclear cells is the gold standard for early diagnosis of infected infants, and results are available within 24 hours.**[149] About 30% of HIV-infected infants have a positive DNA PCR assay from samples obtained within 48 hours of age; 93% have detectable HIV DNA by 2 weeks; and almost all have it by 1 month of age. The primary serologic laboratory test for HIV antibody is the enzyme-linked immunosorbent assay (ELISA). The Western blot test is used for confirmation of positive ELISA results. **Differentiation of the child with passively acquired antibody from the infant with active infection is critical but difficult.** Acquired antibody is undetectable in 75% of infants by 12 months of age and in most infants by 15 to 18 months of age. Infants have also been described with negative serology but active infection. Virus isolation by culture is difficult and expensive, and p24 antigen detection is less sensitive.[79,86] The plasma HIV RNA PCR assay is currently used for quantifying the viral load but not routinely used for diagnosis. Although hypogammaglobulinemia has been reported (less than 10% of patients), hypergammaglobulinemia usually is present.

Treatment. **Antiretroviral therapy with zidovudine (ZDV) or highly active antiretroviral therapy (HAART), a combination of three or more drugs, reduces viral replication and is recommended for pregnant women to reduce perinatal HIV transmission (to <2% of births by women with HIV).**[10,28] Antiretroviral medications are administered for prophylaxis, for intravenous empirical therapy, and for treatment of newborns with documented HIV infection.[32]

ZDV should be given to infants of infected women beginning as soon as possible after birth (i.e., within 6 to 12 hours) and should be continued for 4 to 6 weeks.[10,32,155] **ZDV is administered orally at 2 mg/kg body weight/dose twice daily for 2 weeks and then increased to 3 mg/kg for next 4 weeks for infants born before 35 weeks of gestation. For infants born after 35 weeks of gestation, give a 4 mg/kg/dose twice daily for 6 weeks.**[79]

Infants born to untreated HIV-infected women should receive ZDV for 6 weeks, and three doses of nevirapine (NVP) in the first week of life (at birth, 48 hours later, and 96 hours after the second dose), beginning as soon after birth as possible. NVP is administered orally at 8 mg/dose (for infants 1.5 to 2 kg) or 12 mg/dose (infant >2 kg). If the infant is confirmed to be HIV positive, ZDV is changed to a multidrug antiretroviral regimen. Management guidelines for multidrug antiretroviral regimens are available online.[155] Infants who are perinatally infected with HIV are at high risk for developing *Pneumocystis jiroveci* pneumonia (PCP, formerly known as *Pneumocystis carinii* pneumonia) early in the first year of life. Guidelines recommend initiating prophylaxis for the prevention of PCP for all HIV-exposed infants at 4 to 6 weeks of age, regardless of their $CD4^+$ cell count. For infants receiving ZDV, PCP prophylaxis should begin after completion of the 6-week course of ZDV. The recommended PCP prophylaxis may be provided by 150 mg/m^2/day (5 mg/kg/day) of trimethoprim (TMP) and 750 mg/m^2/day (25 mg/kg/day) of sulfamethoxazole (SMX) administered in two divided doses for 3 consecutive days in a week.[10,79] TMP/SMX prophylaxis should be continued through the first year of life or until HIV infection is reasonably excluded.[6]

Parent Teaching. **Care of an infant at risk for HIV requires close and long-term follow-up. Involvement of the parents is essential to this process.** Education of the parents will maximize the success of such a care plan, and utilization of all available community resources should provide additional support. In addition to the rationale for and importance of the medical management just outlined, the parents should be counseled concerning the need for the following:

- Immunizations following the American Academy of Pediatrics schedule
- Rapid consultation with the infant's physician if he or she is exposed to varicella (may need treatment with varicella-zoster immune globulin [VariZIG]) within 96 hours of exposure) or measles (needs immune globulin intramuscularly regardless of immunization status)
- Rapid consultation with the physician for tetanus-prone wounds (requires tetanus immune globulin irrespective of immunization status)
- Rapid consultation with the physician for thrush, a diaper rash, or any other signs or symptoms of illness

Prevention of infections is important, and this requires good handwashing, regular bathing, appropriate food preparation skills (wash bottles, nipples, and pacifiers), and good skin care (changing diapers and moisturizing skin in other areas to prevent drying and cracking).[79]

CYTOMEGALOVIRUS INFECTION

Prevention. There are no practical methods for preventing CMV infection. Avoiding exposure is virtually impossible because of the ubiquitous and asymptomatic nature of the infections. **Avoiding unnecessary blood transfusions or using CMV-seronegative blood donors, white blood cell–depleted blood products, or frozen deglycerolized blood cells has proved to be important in minimizing the occurrence of postnatally acquired CMV, particularly in premature infants.[9,79]** Short-term or Holder pasteurization of mother's milk (if CMV positive) may be considered for infants born before 32 weeks of gestation.[79]

The question frequently arises about assignment of staff to infants with a possible diagnosis of CMV infection. Staff members who may be pregnant have heightened concern about this issue. Staff members should be aware that many infants with CMV infection are asymptomatic and therefore not identified while in the hospital. **To avoid any problems, staff members should employ good handwashing technique with all infants. Wearing gloves when handling urine and other secretions is a strategy that can also be employed by staff members who are working in the neonatal intensive care unit (NICU) and are pregnant or of childbearing age.** The actual risk for an infected infant's transmitting disease to a susceptible health care worker is unknown but probably small.[79]

Data Collection

History. **Congenital infections are represented by a wide spectrum of disease from asymptomatic disease to profoundly symptomatic disease.** CMV infection in the mother is usually asymptomatic.[92,125]

Signs and Symptoms. **An infant with CMV infection is usually asymptomatic.** Infants less than 32 weeks' gestational age are at greater risk of symptomatic CMV than term infants.[79] Congenital manifestations include intrauterine growth restriction (IUGR), neonatal jaundice (increased direct fraction), purpura, hepatosplenomegaly, microcephaly, seizures, intracerebral calcification, chorioretinitis, and progressive sensorineural hearing loss.[92,125]

Laboratory Data. CMV may be cultured from urine, pharyngeal secretions, and peripheral leukocytes. **Isolation of the virus within 3 weeks of birth indicates transplacental acquisition.** A paired sera demonstration of a fourfold titer rise or histopathology demonstration of characteristic nuclear inclusions in certain tissues can confirm infection. Examining the urine for intranuclear inclusions is not helpful. **PCR detection of viral DNA in tissues and cerebrospinal fluid is available.**[79]

Treatment. Ganciclovir, foscarnet, valganciclovir, and cidofovir are the only licensed antiviral agents effective against CMV. These drugs are approved only for treatment of life- and sight-saving disease. In a randomized controlled trial (RCT) that evaluated 42 neonates with congenital CMV infection involving the central nervous system (CNS), 6 weeks of IV ganciclovir therapy prevented hearing deterioration at 6 months. However, two-thirds of neonates treated with ganciclovir had significant neutropenia.[92,125] **Antiretroviral therapy for congenital CMV infection with antiviral agents is recommended in infants with evidence of CNS involvement, including sensorineural hearing loss, and should be considered in infants with serious end-organ disease (hepatitis, pneumonia, thrombocytopenia).**[92,125]

Parent Teaching. The need for good handwashing technique by parents and caregivers of infants with suspected CMV should be included in discharge instructions.

RUBELLA

Prevention. Medical personnel should ensure that all mothers have a protective hemagglutination titer before conception. If the woman is susceptible, vaccinate her with rubella vaccine before conception, and advise her that she should avoid conception for 28 days after receiving the vaccine.[79,91] If a woman is found to lack immunity to rubella during pregnancy, she should receive rubella immunization in the postpartum period, even if she is breastfeeding.[91]

All perinatal health care workers should have rubella titers drawn to identify immunity status, and they should be re-immunized if this is not adequate. Women of childbearing age who do not have protective immune titers should be encouraged to have rubella immunization.[9,79]

Data Collection

History. **Rubella in the first 4 to 5 months of pregnancy is associated with a high incidence of sequelae in the infant.**[9] A mother with rubella may be relatively asymptomatic or mildly ill with respiratory symptoms with or without a rash.[79]

Signs and Symptoms. Congenital manifestations of rubella include IUGR, sensorineural deafness, cataracts, neonatal jaundice (increased direct fraction), purpura, dermal erythropoiesis, hepatosplenomegaly, microcephaly, chronic encephalitis, chorioretinitis, and cardiac defects (especially patent ductus arteriosus and peripheral pulmonic stenosis). Less frequent manifestations include bone lesions and pneumonitis.[79]

Laboratory Data. The virus may be isolated from the throat, blood, urine, and cerebrospinal fluid (CSF). A paired sera demonstration of a fourfold rise in titers, such as an indirect hemagglutination (IHA) inhibition test or an indirect fluorescent antibody (IFA) test, is diagnostic. The IHA test generally has been replaced by one of several more sensitive methods, including ELISA, or latex agglutination, and reverse transcriptase polymerase chain reaction (RT-PCR) assays.[27,79]

Treatment. Supportive care is needed for transient manifestations such as hepatitis, jaundice, and thrombocytopenia. Cardiovascular and CNS abnormalities should be followed by the appropriate specialists. The infant should be monitored for failure to thrive. Serial hearing screens are indicated as deafness may develop or increase over time. Developmental follow-up should be included in the plan of care as psychomotor difficulties may develop, including autism.[126]

Parent Teaching. **Infants with congenital rubella syndrome may secrete the virus for many years. This requires that discharge instructions include preventive strategies that should be employed to decrease the chance of contact of susceptible pregnant women with the infant. Parents should be informed of their responsibility to ensure that potentially seronegative women of childbearing age avoid direct contact with the infant.**[79] The challenge arises to impress this on the family and at the same time avoid ostracizing the infant or negatively affecting the parent-infant attachment process. In discharge planning with these families, a collaborative approach should be employed, using community health, medical, nursing, and social work input and support. Another challenge is to impress on parents that an infant exposed to rubella during pregnancy may appear normal at birth, but the first appearance of some CNS symptoms may extend into childhood. Thus families and clinicians should keep a watchful eye on these children during the early childhood years.[91]

SYPHILIS

Prevention. Pregnant women should avoid exposure to syphilis. Monitor the serum early and late in pregnancy, and treat the mother for the appropriate stage of disease. Erythromycin, previously used in penicillin-sensitive women, is not considered adequate treatment during gestation because of 30% treatment failure rates in adults and failure to establish a cure in newborns as a result of poor transplacental passage of erythromycin. **Infants born to women treated with erythromycin should be considered at high risk for infection and appropriately evaluated and treated.** If penicillin allergy is confirmed in the pregnant woman, acute desensitization is necessary. Desensitization can be accomplished using increasing doses of oral penicillin over 4 to 6 hours.[151]

Data Collection

History. **A congenital infection may be manifested by a multisystem disease.** A primary syphilitic chancre on the cervix or rectal mucosa in a mother may be unnoticed.[151]

Signs and Symptoms. An infant exposed to syphilis may be asymptomatic at birth, or virtually all organ systems may be involved. Clinical findings may include hepatitis, pneumonitis, bone marrow failure, myocarditis, meningitis, nephrotic syndrome, rhinitis (snuffles), a rash involving the palms and soles, and pseudoparalysis of an extremity.[79,151]

Laboratory Data. The microscopic darkfield examination identifies spirochetes from nonoral lesions.

Nonspecific, nontreponemal reaginic tests, such as Venereal Disease Research Laboratory (VDRL) tests and rapid plasma reagin (RPR) tests, followed serially with a rise or absence of fall after birth, are useful for screening.[79,151] Specific treponemal antibody serologic tests, such as a fluorescent treponemal antibody absorption (FTA-ABS) test or a microhemagglutination test for *Treponema pallidum* (MHA-TP), provide diagnostic confirmation of a reactive nontreponemal test, but an FTA-ABS immunoglobulin M (IgM) test is unreliable.[79] False-positive results may occur with nontreponemal tests secondary to other medical conditions or other spirochetal diseases. Therefore confirmation of diagnosis is necessary.[79] **A long-bone x-ray examination showing metaphysitis or periostitis may help in diagnosing syphilis. VDRL tests on CSF are mandatory in all infants suspected of having congenital syphilis.** When the diagnosis of active congenital syphilis is equivocal, often it is best to treat and ascertain the diagnosis by serial serologic determinations.[79]

Treatment. Table 22.1 outlines the treatment of syphilis.[79]

Parent Teaching. Adequate follow-up of both symptomatic and asymptomatic neonates is very important. A physical evaluation should be conducted at 1, 2, 3, 6, and 12 months. Serologic testing should be performed at 3, 6, and 12 months after completion of therapy regimen, or until titer decreases fourfold. Noninfected or adequately treated infants' titers should be decreased by 3 months and nonreactive by 6 months. If titers fail to decline or if they increase or are still present after 6 to 12 months of age, the infant should be reevaluated and retreated. Infants with neurosyphilis should have a repeat CSF examination every 6 months until it is normal and VDRL nonreactive. If CSF VDRL is still reactive at 6 months or CSF white cell count is not decreasing at each reexamination or is abnormal at 24 months, retreatment is indicated.[79]

TOXOPLASMOSIS

Prevention. Women should avoid unnecessary exposure to raw meat, cat feces, and eating fruits or vegetables not peeled or washed thoroughly. Using a pair of gloves when emptying the litter box may provide protection if the pregnant woman (or a woman attempting to become pregnant) must empty the litter box.[79] A pregnant woman (or woman attempting to become pregnant) should use hot soapy water to wash her hands immediately after exposure to any infectious source, even after wearing gloves.[26]

Data Collection

History. Congenital infections are represented by a wide range of disease, from asymptomatic disease to profound symptomatic disease, and all require treatment.[66,79,139] Mothers may have noted an influenza-like illness or posterior cervical adenitis. Toxoplasmosis should be considered in the differential diagnosis if chorioretinitis is present, even if there are no other symptoms. A history of exposure to cat feces or ingestion of raw meat may occasionally be obtained.[66,79,139]

Signs and Symptoms. Manifestations in a newborn may be prematurity, IUGR, hydrocephalus, chorioretinitis, seizures, cerebral calcifications, hepatosplenomegaly, thrombocytopenia, jaundice, generalized lymphadenopathy, and rash.[66,79,139]

Laboratory Data. Isolating *Toxoplasma gondii* from blood or body fluids is difficult and tedious. Cysts may be found in the placenta or tissues of a fetus or newborn.[66,139] Most congenitally infected infants have a Sabin-Feldman dye test titer greater than 1:1000 at birth.

Treatment. Table 22.1 outlines the treatment of toxoplasmosis.[79]

Parent Teaching. Parents of infants with congenital toxoplasmosis should know that the majority of neurologic problems are identified in early infancy and will need ongoing management and follow-up for visual impairment.[55]

ZIKA VIRUS

Prevention. Women who are contemplating pregnancy should avoid travel to areas known to have Zika virus (ZKV) present and avoid intercourse with male partners who are at risk for exposure to ZKV. Pyriproxyfen, a mosquito larvicide, has been introduced into drinking water in Brazil and is considered nontoxic at recommended levels.[156]

Data Collection

History. Zika virus is an arbovirus transmitted by Aedes mosquitos (particularly *Aedes Aegypti* mosquitoes, known for spreading yellow fever

TABLE 22.1 RECOMMENDED THERAPY FOR INDICATED CONDITION

CONDITION	TREATMENT
Sepsis and/or Meningitis	
Initial Therapy	
Early onset	IV ampicillin and gentamicin or IV amikacin (if gentamicin-resistant organisms are present in nursery, ampicillin plus cefotaxime is a suitable alternative, particularly if meningitis is present).
Late onset	IV vancomycin plus cefotaxime or IV aminoglycoside (see "Early onset").
Once Specific Organisms Are Identified	
Group B *Streptococcus*	IV ampicillin and gentamicin for 10-14 days (gentamicin may be discontinued if strain is susceptible to ampicillin or with penicillin G alone once identified and shown to be susceptible).
Coliform species	IV ampicillin and gentamicin for 10-14 days (cefotaxime may replace gentamicin).
Listeria monocytogenes	IV ampicillin and IV gentamicin for 14-21 days.
Enterococcus	Same as for *Listeria monocytogenes*. For ampicillin resistance, use vancomycin.
Group A *Streptococcus*	IV penicillin G for 10-14 days.
Group D *Streptococcus* (non-enterococcus)	Same as for group A *Streptococcus*.
Staphylococcus aureus	IV nafcillin for 10-14 days; IV vancomycin for methicillin-resistant strains.
Staphylococcus epidermidis	IV vancomycin for 10-14 days.
Pseudomonas aeruginosa	IV ceftazidime and aminoglycoside for 10-14 days.
Anaerobes	IV metronidazole, clindamycin, or meropenem.
Pneumonia	
Group B *Streptococcus*	Same as for sepsis (respiratory distress syndrome may mimic pneumonitis and vice versa).
Staphylococcus aureus	Same as for sepsis.
Chlamydia trachomatis	PO erythromycin for 14 days or with azithromycin for 3 days.
Pneumocystis jiroveci	PO or IV trimethoprim and sulfamethoxazole, or IV pentamidine isethionate.
Pertussis	PO or IV azithromycin for 5 days (clinical course is unchanged, but shedding of organism is diminished significantly).
Ureaplasma spp.	PO or IV azithromycin 20/kg/day for 3 days
Other organisms	Same as for sepsis.
Skin and Soft Tissue Infections	
Impetigo	IV or IM nafcillin; PO cephalexin for 7 days (depending on clinical severity). For methicillin resistance, use vancomycin. Also consider topical mupirocin.
Group A *Streptococcus* infections	IV penicillin G for 7 days.
Breast abscess	IV nafcillin and gentamicin for 7 days pending identification of etiologic agent (change to IV penicillin if *Streptococcus* is etiologic agent; IV ampicillin or gentamicin should be used for coliform species pending sensitivities); value of surgical drainage is individualized; vancomycin for methicillin-resistant strains.
Omphalitis and/or funisitis	Cefotaxime or gentamicin, and clindamycin for ≥10 days (penicillin may be used if infection is caused by group A or B streptococci); if gram-negative rods, consider gentamicin or cefotaxime also.

TABLE 22.1 RECOMMENDED THERAPY FOR INDICATED CONDITION—CONT'D

Gastrointestinal Infections	
Salmonella species	IV ampicillin for 7-10 days; or IV cefotaxime or ceftriaxone for 7-10 days depending on sensitivities (focal complications of meningitis and arthritis should be monitored closely).
Shigella species	PO trimethoprim/sulfamethoxazole or PO or IV ampicillin, depending on susceptibilities.
Necrotizing enterocolitis	IV ampicillin and IV gentamicin for 2-3 weeks, (if *Pseudomonas* is isolated, IV ceftazidime or piperacillin/tazobactam combination may be substituted for ampicillin); supportive measures (gastrointestinal suction) are appropriate.
Osteomyelitis or Septic Arthritis	
Group B *Streptococcus*	IV penicillin G or ampicillin for 21 days minimum.
Staphylococcus aureus	IV oxacillin for 21 days minimum. Vancomycin for methicillin-resistant strains.
Coliform species	IV gentamicin for 21 days (IV ampicillin for 21 days minimum if organism is sensitive).
Gonococcus species	IM, IV ceftriaxone for 7-14 days
Unknown	IV oxacillin and gentamicin or cefotaxime for 21 days minimum.
Urinary tract infections	Suspect predisposing anatomic defect if urinary tract infection; individualize workup and follow-up.
Enterococcus species	Ampicillin, 150 mg/kg/day divided q 8 hr for 10 days.
Miscellaneous Conditions	
Congenital syphilis	If more than 1 day of treatment is missed in either of the following regimens, the entire course should be restarted.
Without central nervous system (CNS) involvement	IM procaine penicillin G (50,000 units/kg) daily for 10-14 days (follow-up Venereal Disease Research Laboratory [VDRL] test results should revert to negative if treatment is adequate by 1 year).
With CNS involvement	IV aqueous crystalline penicillin 50,000 units/kg/dose q 12 hr for the first 7 days of life and then q 8 hr for 10 days. Repeat lumbar puncture about every 6 months until results are normal.
Toxoplasmosis	PO sulfadiazine, 100 mg/kg/day divided q 12 hr and PO pyrimethamine, 2 mg/kg/day for 2 days then 1 mg/kg/day for 2-6 months, then 3 times weekly for up to 1 year. Dose is divided q 12 hr (supplemental folic acid, 1 mg/day, should be added). Ocular, CNS, or HIV involvement may require additional therapy.
Herpes simplex infections	IV acyclovir, 20 mg/kg/dose q 8 hr for 14 days if skin or mucous membrane involvement; 21 days if CNS involvement. If eye involvement, add trifluridine 1% ophthalmic or ganciclovir 0.15% ophthalmic.
Conjunctivitis	
Chlamydia species	PO erythromycin for 10 days (topical may be ineffective) or azithromycin for 5 days
• Gonococcus species	IM, IV ceftriaxone 25-50 mg/kg as a single dose and azithromycin for 5 days (cefotaxime if hyperbilirubinemia present)
Otitis Media	
• In otherwise normal neonate	PO amoxicillin/clavulanic acid (Augmentin), 40 mg/kg divided q 8 hr for 10 days.
• In neonate with nosocomial infection	PO or IV ampicillin and IV gentamicin (if there is no response to treatment, consider diagnostic tympanocentesis; *Staphylococcus aureus* and coliform species may be present).

CNS, central nervous system; *HIV,* human immunodeficiency virus; *hr,* hour; *IM,* intramuscular; *IV,* intravenous; *PO,* oral.

Data from Bradley JS, Nelson JD, eds. *Nelson's Pediatric Antimicrobial Therapy.* 24th ed. Elk Grove Village, IL: American Academy of Pediatrics and Redbook; 2018.

and dengue fever) or through sexual transmission. First identified in 1947 in Rhesus monkeys in the Zika forest of Uganda, Zika infection was reported in Brazil in 2015 and has spread rapidly.[62,127] The virus generally occurs close to sea levels and has been identified in Central/South America, Central Africa, Southeast Asia, the Pacific Islands, the Caribbean, Puerto Rico, New York, and in the gulf coast region of the United States.[14,156]

Signs and Symptoms. A careful maternal history is important. Zika may be asymptomatic or result in a subtle flulike illness.[62,156] Maternal symptoms may include fever, rash, pruritis, lymphadenopathy, edema of extremities, myalgia, arthralgia, headache, vertigo, retro-orbital pain, vomiting, diarrhea, or mucous ulcers.[127,156]

Infants may have a number of neurologic symptoms including microcephaly (if present on prenatal ultrasonography, testing is recommended). Encephalomyelitis, cerebral calcifications, ventriculomegaly and lissencephaly, mild cardiac defects (ASD, PDA, and VSD), ocular defects (colobomatous chorioretinal atrophy of the macula and pigmentary changes), arthrogryposis, and talipes have all been reported.[62,108,157]

Laboratory Data. **Viral particles have been detected by reverse-transcriptase polymerase chain reaction (RT-PCR) in blood, urine, amniotic fluid, semen, saliva, and in neuronal tissue.** Serologic testing with IgM, ELISA, or immunofluorescence assay may detect Zika virus in acute infections.[84,127] A plaque reduction neutralization test can help eliminate cross-reactivity to other *Flaviviridae* viruses in serology.

Treatment. Vaccine development is in progress using both DNA and inactivated viruses.[14]

Parent Teaching. **Parents should be aware of the need for developmental follow-up,** as microcephaly may result in developmental delay. Eye abnormalities may result in visual impairment. Progressive sensorineural hearing loss may be detected by serial hearing screens.[157]

Perinatal Acquisition During Labor and Delivery

CHLAMYDIA TRACHOMATIS INFECTION

Prevention. **Eye prophylaxis with erythromycin (preferred) or tetracycline ophthalmic ointment minimizes the development of conjunctivitis but has no effect on the subsequent development of pneumonitis.**[79,109]

Data Collection

History. A mother with a *Chlamydia trachomatis* infection is usually asymptomatic during her pregnancy.[9,109]

Signs and Symptoms. **Conjunctivitis may be manifested as congestion and edema of the conjunctiva, with minimal discharge developing 1 to 2 weeks after birth** and lasting several weeks with recurrences, particularly after topical therapy. **Infants with pneumonitis usually do not have a fever but have a prolonged staccato cough,** tachypnea, mild hypoxemia, and eosinophilia. Otitis media and bronchiolitis also may occur.[79,109]

Laboratory Data. Definitive diagnosis is made by isolating the organism in tissue culture and by nucleic acid amplification tests (NAATs) (e.g., PCR). Direct fluorescent antibody method or enzyme immunoassay is less sensitive and specific. **To enhance the likelihood of obtaining an adequate sample, scrape the lower conjunctiva (for conjunctivitis), or obtain deep tracheal secretions or a nasopharyngeal aspirate (for pneumonia).** NAATs are not recommended for nasopharyngeal aspirates unless the laboratory is Clinical Laboratory Improvement Amendments (CLIA) certified to perform the test. Scraping conjunctival epithelial cells and demonstrating characteristic intracytoplasmic inclusion bodies by a Giemsa stain is diagnostic. **Although serologic tests for conjunctivitis are unreliable, a significant titer rise in IgM-specific antibody may be reliable in cases of pneumonia. Eosinophilia (greater than 300 eosinophils/mm3) may suggest chlamydial pneumonia**. Cell culture and nonculture methods, such as DFA, can be used to diagnose neonatal chlamydial ophthalmia and neonatal chlamydial pneumonia although with less sensitivity and specificity than culture.[79,109]

Treatment. Table 22.1 **outlines the treatment of chlamydia.**

Parent Teaching. The mother and any sexual partners should be treated. The infant should be observed for emesis as hypertrophic pyloric stenosis has occurred in infants receiving oral erythromycin and azithromycin.[79]

ENTEROVIRUS (COXSACKIEVIRUS A, COXSACKIEVIRUS B, ECHOVIRUS, AND POLIOMYELITIS) INFECTIONS

Enterovirus infections are the most commonly diagnosed viral infections in the NICU, and coxsackievirus B1 was the most common in 2007 by the National Enterovirus Surveillance System.[31,77]

Prevention. To prevent poliomyelitis, it is essential to maintain poliomyelitis immunity with active immunization before conception. Passive protection with pooled human serum globulin may help in selected exposures (0.2 mL/kg body weight, given intramuscularly). **Routine nursery infection control procedures must be observed. It is recommended that only inactivated poliovirus vaccine (IPV) be used in the nursery.** The IPV is administered intramuscularly and contains no live virus, whereas oral poliovirus vaccine (OPV) (no longer available in the United States) is administered orally and contains live but attenuated virus, which has been reported to cause infection in immunocompromised patients.[79]

Data Collection

History. Infection may occur year-round but is more prevalent from June to December in temperate climates. Most enterovirus infections are asymptomatic. Poliomyelitis is rare because of a high level of vaccine-induced immunity in most of the world.[79]

Signs and Symptoms. Mothers with enteroviral infections are usually mildly ill, with fever or diarrhea. **Infants may be asymptomatic or have fever or diarrhea. Infants who acquire the infection without maternal antibody have severe disease and high mortality rates.** Fever, irritability, lethargy, and rash are common. Severe disease with sepsis, meningoencephalitis, myocarditis, pneumonia, hepatitis, or coagulopathy may occur.[2] Prematurity, early onset of illness (less than 7 days), maternal history of illness, high white blood cell count (15,000/mm^3 or greater), and low hemoglobin (less than 10.7 g/dL) have been shown to be risk factors of severe infection.[87]

Laboratory Data. The virus may be isolated from the throat, rectum, or CSF. Isolating coxsackie virus A may require suckling mouse inoculation. Serologic screening is impractical because of the large number of serotypes. PCR assay for enterovirus RNA in CSF and other specimens is available and is more sensitive than viral isolation.[79]

Treatment. **A randomized, double-blind, placebo-controlled trial of the antiviral agent *pleconaril* in 61 newborns with enteroviral sepsis characterized by hepatitis, coagulopathy, or myocarditis suggests that pleconaril decreases duration of culture and PCR positivity and increases survival. Further development and evaluation of pleconaril therapy for neonates is warranted.**[3] Pleconaril prevents viral attachment and entry into the host cells and seems to be well tolerated in neonates.[2,67] Hand hygiene is paramount to control spread of enteroviral infections.[79] Intravenous immunoglobulin may be effective in severe enteroviral infection.[3]

GROUP B STREPTOCOCCUS INFECTION

Prevention. **Group B *Streptococcus* (GBS) sepsis is associated with significant morbidity and mortality risks. A recent worldwide systematic review and meta-analysis found the risk of early onset GBS infection in neonates of colonized mothers to be 1% to 2%.**[132]

In 2019 the American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG) reaffirmed universal antenatal culture screening for the detection of GBS colonization and intrapartum antibiotic prophylaxis in colonized women to prevent early onset sepsis.[22, 122] Implementation of this strategy has decreased the incidence of early onset GBS in the United States form 1.8 cases/1000 live births in 1990 to 0.23 cases/1000 live births in 2015.[102]

Pregnant women who are GBS positive are treated with penicillin or ampicillin during labor or treated with cefazolin if they are allergic to penicillin. **Intrapartum prophylactic antibiotics are also indicated if the GBS status of the mother is unknown and one or more intrapartum risk factors exist (see History in the next section).**

Treatment with antibiotics for less than 4 hours is inadequate to prevent the transmission of GBS.[122] Use of these guidelines results in an 80% reduction in the number of neonates affected by early-onset GBS sepsis.[9,79,132]

Data Collection

History. **Maternal history of any risk factors that include (1) gestation less than 37 weeks, (2) rupture of membranes for 18 hours or longer, (3) a maternal temperature of 38°C (100.4°F) or higher, (4) a history of GBS bacteriuria during the current**

TABLE 22.2 MATERNAL AND INFANT CLINICAL CHARACTERISTICS OF EARLY-ONSET GBS DISEASE

GBS STATUS	ROM >18 HR	ANY FEVER	FEVER >100.4° C	INTRAPARTUM ANTIBIOTICS	TERM	PRETERM	ILL-APPEARING	ABNORMAL WBC COUNT	CRITICALLY ILL/DIED
Negative (*n* = 16)	7 (44)	8 (50)	3 (19)	2 (12)	14 (88)	2 (12)	11 (69)	12 (75)	5 (31)
Positive (*n* = 5)	3 (60)	2 (40)	1 (20)	2 (40)	2 (40)	3 (60)	4 (80)	2 (40)	2 (40)
Unknown (*n* = 4)	0 (0)	2 (50)	1 (25)	0 (0)	1 (25)	3 (75)	4 (100)	4 (100)	4 (100)
			5 (20)	4 (16)	17 (68)	8 (32)	19 (76)	18 (72)	11 (44)

Numbers in parentheses indicate percentage of total for each category (GBS negative, positive, or unknown and total cases). ROM indicates rupture of membranes; abnormal WBC count. *GBS,* Group B *Streptococcus; ROM,* rupture of membranes; *WBC,* white blood cell.
Modified from Puopolo KM, Madoff LC, Eichenwald EC. Early-onset group B streptococcal disease in the era of maternal screening. *Pediatrics* 2005;115(5):1240.

pregnancy, or (5) a previous infant with GBS infection warrants intrapartum antibiotics.[12,122]

Signs and Symptoms. Symptoms of early-onset GBS are seen within the first 24 hours of life. Table 22.2 depicts clinical and laboratory findings of early-onset GBS infection.

Laboratory Data. New screening tests have been developed and validated for rapid identification of GBS, including pigmented enrichment broths, chromogenic agars, DNA probes, and NAATs, such as PCR. A survey of antepartal and intrapartal use of NAATs found that only 18.7% of laboratories offered NAATS for rapid GBS screening.[52] Another study of the impact of rapid PCR to test for GBS in women at term with ruptured membranes found a clinically significant reduction in the use of prophylactic antibiotics.[57]

A full sepsis evaluation, including a lumbar puncture (LP), is indicated for any newborn who demonstrates signs of infection.

Treatment. Table 22.1 outlines the antibiotic treatment of GBS infection.

As outlines in the current guidelines there are three strategies for risk assessment of infant greater than or equal to 35 weeks' gestation: 1 categorical risk assessment (see Figure 22.1A), use of the Neonatal Early Onset Sepsis Calculator (see Figure 22.4 and 3) enhanced observation (see Figure 22.1B) For Infants less than or equal to 34 weeks' gestation the early onset risk assessment is outlined in Figure 22.2.

Use of the updated treatment algorithms have reduced the number of early onset sepsis evaluations ans antibiotic exposure without increasing the rate of GBS infection.[4, 23, 79, 144]

Complications. Although GBS prophylaxis has been shown to be effective for early onset sepsis, neonatal GBS disease remains a significant health problem.[135,140,144] Concerns for antibiotic resistance exist and the incidence of late onset GBS has not declined, but in fact is now more common than early onset GBS.[44,102] GBS contaminated breast milk may be a source of late onset GBS sepsis.[17, 168]

Parent Teaching. See Early Onset Bacterial Disease, Parent Teaching on p. 24 and Parent Teaching on p. 31.

HEPATITIS B

Prevention. Prenatal screening of women for hepatitis B surface antigen (HBsAg) is indicated and is cost-effective. **Use of active and passive immunization in infants born to HBsAg-positive mothers is recommended by the Advisory Committee on Immunization Practices[134]** (Tables 22.3 and 22.4). **Within 24 hours of birth, universal vaccination of medically stable newborns weighing greater than or equal to 2000 g born to HBsAg-negative women is recommended.[134]** Additionally, the new recommendations also include: (1) testing of HBsAg-positive pregnant women for

hepatitis B virus DNA, (2) postvaccination serologic testing for infants whose mother's HBaAg status is indefinitely unknown (when a parent relinquishes a newborn), (3) single-dose revaccination for infants born to HBsAg-positive mothers who are not responding to the initial dose, and (4) removal of permissive language for delaying the birth dose until after hospital discharge.[134] HepB vaccine or HBIG given together or alone are 75% and 71% effective, respectively, in preventing perinatal transmission of HBV. Combined, their efficacy is 94%. Vaccination produces seroprotection in 98% of healthy term neonates, with a better vaccine response in infants less than 2000 g birth weight at 1 month of age.[134]

Data Collection

History. **Mothers who are HBsAg positive because of the chronic carrier state or acute disease before delivery may pass the infection to their infants at delivery.**[9] Women at high risk include those of Asian, Pacific Islander, or Alaskan Eskimo descent; women born in Haiti or sub-Saharan Africa; and those with a history of liver disease, IV drug abuse, or frequent exposure to blood in a medical-dental setting.

Signs and Symptoms. **A neonate with hepatitis B is usually asymptomatic.** Occasionally, infected infants demonstrate elevated liver enzymes or acute fulminating hepatitis.[79] **Neonatal infection with subsequent chronic carriage has been implicated in the development of primary hepatocellular carcinoma later in life.**

Laboratory Data. Most infants at risk for acquiring hepatitis from their mother are HBsAg negative at birth. Many untreated infants become HBsAg positive 4 to 12 weeks after birth and become lifelong asymptomatic carriers or develop hepatitis B.[79]

Treatment. **Infants born to mothers who are Hepatitis B positive or are of unknown status should receive Hepatitis B vaccine and HBIG within 12 hours of life. In general, all stable newborns weighing 2000 g and over should receive Hepatitis B vaccine in the first 24 hours of life. Infants weighing less than 2000 grams should be immunized at 1 month of age or before hospital discharge.** Only single-antigen hepatitis B vaccine should be used for newborns. If inflammatory liver disease is present, referral to a hepatologist is advised.[79,134]

Parent Teaching. **Risk of chronic hepatitis B infection is increased in infants exposed prenatally or in the first year of life.** Up to 25% of infants who acquire chronic hepatitis B infection will develop HBV hepatocellular cancer or cirrhosis.[79] **Stable premature infants should get Hepatitis B immunizations at the same chronologic age and in the same dose as term infants throughout the complete series. Serologic testing for immunity is recommended** for infants born to HBsAG-positive women and to women with unknown status.[79,134]

HEPATITIS C

Prevention. **Neonates acquire hepatitis C virus (HCV) infection mostly through vertical transmission from the mother** and rarely through transfusion of hepatitis C–contaminated blood products. **Vertical transmission rates from the mother to the infant vary (approximately 5%), and risk factors associated with increased transmission are HCV viral load, coinfection with HIV, rupture of membranes more than 6 hours, and internal fetal monitoring.**[47,110,118] Reducing viral load by maternal antiviral therapy, especially in HIV-coinfected women, and avoiding internal fetal monitoring are interventions that can reduce transmission but have not been evaluated. **Breastfeeding is not associated with increased rates of transmission and is not contraindicated.**[79,118] Screening of blood products for HCV is mandatory for prevention of transfusion-related HCV infection.

Data Collection

History. **Approximately 1% to 2% of pregnant women in the United States are seropositive for HCV, but vertical transmission occurs only if the mother is HCV RNA positive at the time of delivery.**[79] HCV RNA titers rise many weeks after birth in infants, indicating a perinatal acquisition rather than an intrauterine transmission.[118]

Signs and Symptoms. **Neonates with perinatal acquisition of HCV infection are usually asymptomatic** without jaundice and with normal or only mildly elevated liver transaminase levels.[79] **Progression to chronic hepatitis is common and occurs in approximately 80% of infected infants. Liver biopsies in infants with perinatally acquired HCV during follow-up show evidence of chronic inflammation.** A small percentage (20%) of infants may spontaneously resolve their infection.[49]

Laboratory Data. **The essential diagnostic feature is HCV RNA positivity on at least two occasions by PCR.** Sensitivity of the PCR is 22% in infants younger than 1 month of age and 97% after 1 month of age.[45] Maternal antibodies may persist in the infant for 13 to 18 months and are not useful for

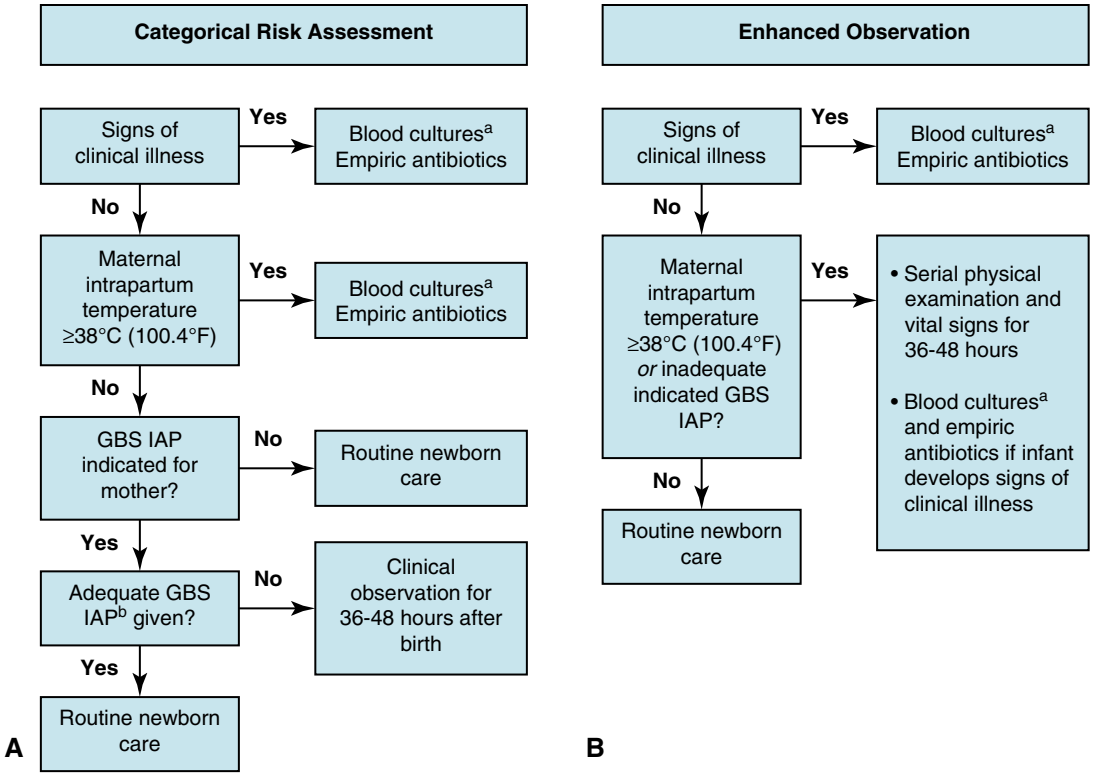


FIGURE 22.1 Options for EOS risk assessment among infants born ≥35 weeks' gestation. A, categorical risk assessment. B, Enhanced observation.[a] Consider lumbar puncture and CSF culture before initiation of empiric antibiotics for infants who are at the highest risk of infection, especially those with critical illness. Lumbar puncture should not be performed if the infant's clinical condition would be compromised, and antibiotics should be administered promptly and not deferred because of procedure delays.[b] Adequate GBS IAP is defined as the administration of penicillin G, ampicillin, or cefazolin ≥4 hours before delivery.

diagnosis. Following liver transaminase levels may help monitor the course of hepatic inflammation.

Treatment. Ribavirin and interferon alfa are used in the treatment of adults. A systematic review and meta-analysis of ribavirin and interferon for the treatment of chronic hepatitis C in children found that the combination therapy is both safe and effective.[43] One study found a 98% sustained viral response in children 1 to 5 years of age treated with interferon and ribavirin for chronic hepatitis C.[167] A 5-year follow-up of ribavirin/pegylated interferon found significant impairment in height; within the next 5 to 10 years, interferon-free regimens may become available.[65]

Parent Teaching. Transmission among family contacts is rare unless there is direct or mucosal exposure to blood. **Breastfeeding is safe as long as the mother's nipples are not cracked or bleeding.** Children with hepatitis C generally do not need to be excluded from child care settings.[79]

HERPES SIMPLEX (TYPES 1 AND 2) INFECTION

Prevention. The key to preventing herpes simplex is avoiding exposure. In the third trimester, use of maternal prophylaxis with antiviral agents for herpes decreases recurrence of maternal lesions and decreases the incidence of cesarean delivery. However, there is insufficient evidence that this strategy prevents neonatal herpes.[68] **Mothers with active lesions or in prodrome should have a cesarean delivery preferably within 4 to 6 hours of membrane rupture. Treatment with acyclovir should begin at the first sign of neonatal disease or when infants have been exposed to an active lesion.[9,79]**

Communication is necessary between obstetric and neonatal staff to determine the status of a family

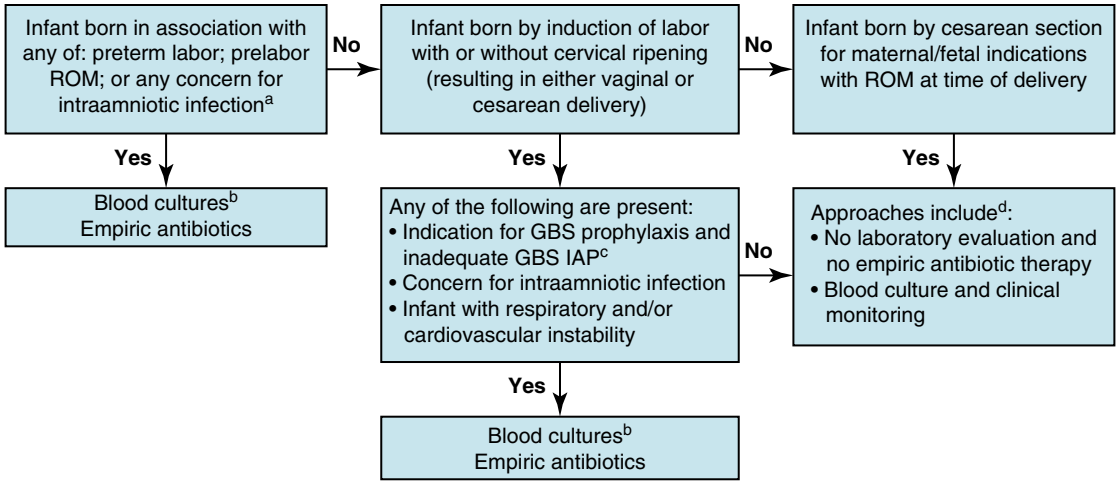


FIGURE 22.2 EOS risk assessment among infants born ≤34 week's gestation.[a] Intraamniotic infection should be considered when a pregnant woman presents with unexplained decreased fetal movement and/or there is sudden and unexplained poor fetal testing.[b] Lumbar puncture and CSF culture should be performed before initiation of empiric antibiotics for infants who are at the highest risk of infection unless the procedure would compromise the infant's clinical condition. Antibiotics should be administered promptly and not deferred because of procedural delays.[c] Adequate GBS IAP is defined as the administration of penicillin G, ampicillin, or cefazolin ≥4 hours before delivery.[d] For infants who do not improve after initial stabilization and/or those who have severe systemic instability, the administration of empiric antibiotics may be reasonable but is not mandatory.

TABLE 22.3 ACCEPTABLE METHODS OF PASSIVE IMMUNIZATION IN NEWBORNS

DISEASE	INDICATIONS	WHEN TO USE	PRODUCT	DOSE
Hepatitis A	Active infection in mother or close family contacts	As soon as possible	IGIM	0.02–0.04 mL/kg body weight given IM
Hepatitis B	Mothers with acute type B infection or who are antigen (+)	As soon as possible (within 12 hours)	HBIG*	0.5 mL IM
Tetanus	Inadequately immunized mothers with contaminated infant (e.g., dirty cord)	As soon as possible	TIG	250 units given IM (optimal dose not established)
Varicella	Administer as soon as possible to infant born to a mother who develops lesions <5 days before delivery, within 7 days after delivery, or when/if infant is exposed to varicella-zoster virus any time during the initial hospitalization.	Within 10 days	VariZIG	125 units/10 kg body weight up to a maximum of 625 units (62.5 units if ≤2 kg)

*Should be used in conjunction with active immunization with hepatitis B virus (HBV) vaccine (see Table 22.4).
HBIG, Hepatitis B immune globulin; *IGIM*, immune globulin for intramuscular injection; *IM*, intramuscularly; *TIG*, tetanus immune globulin (human); *VariZIG*, varicella zoster immune globulin.
Modified from Wilson C, Nizet V, Maldonado Y, Remington J, Klein J, eds. *Remington and Klein's Infectious Diseases of the Fetus and the Newborn Infant.* 8th ed. Philadelphia, PA: Elsevier Saunders; 2016; with addition from Updated recommendations for use of VariZIG—United States, 2013. *MMWR* 2013;62(28):574–576.

with a history of herpes. **Unnecessary restrictions should not be placed on postpartum mothers who are not actively infected.**[9] Health professionals should employ all family-centered strategies used in their institutions with families unless such strategies are precluded by the need for the infant's treatment.

Data Collection

History. Disease caused by type 1 herpes simplex usually is spread by the oral route, whereas disease caused by type 2 herpes simplex is usually spread by the genital route.[79] **Many mothers who transmit herpes simplex to their newborn infants are**

TABLE 22.4 ACCEPTABLE METHODS OF ACTIVE IMMUNIZATION IN NEWBORNS

DISEASE	INDICATION	WHEN TO USE	PRODUCT	DOSE
Hepatitis B	HBsAg positive or HBsAg negative	3 separate doses: at birth*; at 1 month; and at 6 months	Recombivax HB	0.5 mL given IM
			Engerix-B	0.5 mL given IM
Pertussis	To control outbreak in nursery	As soon as possible	TDaP†	0.5 mL given SC
Tuberculosis	Selected infants at risk for contracting tuberculosis	As soon as possible	BCG	0.1 mL or 0.2-0.3 mL of half-strength dilution given intradermally as a single dose

*As soon as possible (within first 24 hours of life).
†Pregnant mothers may provide passive immunity against pertussis if they receive TDaP between the 27th and 36th weeks of pregnancy.
BCG, Bacillus Calmette and Guérin; *HBsAg*, hepatitis B surface antigen; *IM*, intramuscularly; *SC*, subcutaneously; *TDaP*, tetanus, diphtheria, and pertussis vaccine.

asymptomatic.[71] The risk to the infant from recurrent lesions is minimal.[79]

Signs and Symptoms. Infants with herpes simplex have a spectrum of illnesses ranging from localized skin lesions (i.e., vesicular rash) to generalized infections involving the liver, lungs, and CNS (i.e., seizure).[38,159] A recent study found that 84% of infants presented with seizure, vesicular rash, or critical illness, and a subset (16%) lacked classic signs at admission but manifested HSV signs within 24 hours of admission.[38] Disseminated HSV has high morbidity and mortality rates.[71,79,159]

Laboratory Data. A cytologic examination of the base of skin vesicles with a Giemsa stain (Tzanck test) may reveal characteristic but nonspecific giant cells and eosinophilic intranuclear inclusions. The virus may be readily identified on a tissue culture within 48 hours from the respiratory and genital tracts, blood, urine, and CSF.[79] Rapid viral diagnosis by direct fluorescent antibody tests is widely available.[79] Detection of virus in CSF by PCR assay is preferred, if available.[28] Although tests of paired serology such as complement fixation (CF) test, ELISA, and neutralization are available, they are of little value in an acute clinical situation.[79] Elevated liver transaminases and thrombocytopenia may indicate herpes infection.[24]

Treatment. Table 22.1 outlines the treatment of herpes simplex infection.

Parent Teaching. Families with herpes simplex require consistent and detailed teaching about prevention of transmission of herpes to the infant. Breastfeeding mothers can be reassured that they may continue to breastfeed as long as no lesions are on their breasts. Emphasis should be placed on the need for breastfeeding mothers to check their breasts for lesions.[9]

Parents with active herpes simplex should employ good handwashing technique while caring for their infants. Parents with oral herpes should avoid kissing their infants while lesions are open and draining.[79]

LISTERIA MONOCYTOGENES INFECTION

Prevention. Pregnant women should avoid unpasteurized dairy products (i.e., milk and cheese) to prevent Listeria monocytogenes infection.[89]

Data Collection. See Laboratory Data on p. 20.

Treatment. Table 22.1 outlines the treatment of *L. monocytogenes* infection.

Parent Teaching. See Early Onset Bacterial Disease, Parent Teaching on p. 24 and Parent Teaching on p. 31.

MYCOBACTERIUM TUBERCULOSIS INFECTION

Prevention. Mothers at risk for Mycobacterium tuberculosis infection may be identified with a tuberculin test during pregnancy. If the mother is a tuberculin converter (has had a positive skin test result within the past 2 years), a radiographic examination of the chest and lungs should be performed. If the mother has active tuberculosis, she should be treated with isoniazid plus rifampin and ethambutol for at least 9 months. Safety of pyrazinamide in

pregnancy is not well established, and this drug is not used routinely in pregnant women. **Pyridoxine (vitamin B6) always should be given with isoniazid during pregnancy and breastfeeding because of the increased requirements for this vitamin.** If the mother does not have active tuberculosis, household contacts should be screened. **If the disease is identified in the mother or household contacts, the infant is at high risk for developing tuberculosis.**[79]

Separate infants of mothers with active disease from the mother until the mother is not contagious (usually negative sputum). Treat high-risk infants with isoniazid (10 mg/kg/day) or a tuberculosis vaccine (BCG) (see Table 22.4).[9,79]

Data Collection

History. **A strong history of maternal contact with tuberculosis favors the diagnosis.** This is especially true in high-risk populations (Southeast Asians, American Indians, and families with a known cavitary disease). **Mothers with HIV infection are at an increased risk for developing active tuberculosis.**[79] Mothers infected with tuberculosis have an 80% greater risk of pregnancy complications than noninfected mothers.[40]

Signs and Symptoms. Mothers may be relatively asymptomatic or have signs and symptoms that are generalized (fever and weight loss) or localized to the respiratory tract.[79] **A congenital infection is extremely rare.**[9] **Nonspecific signs and symptoms such as failure to thrive and unexplained hypothermia or hyperthermia are the most common manifestations in the neonatal period.**

Laboratory Data. **Acid-fast organisms found on smears of gastric aspirates, sputum, CSF, or infected tissues strongly suggest tuberculosis in the neonate.** Isolating *M. tuberculosis* by culture is diagnostic and should be sought aggressively. The tuberculin skin test result usually is positive (greater than 10-mm induration) in active tuberculosis. However, a positive skin test result requires 3 to 12 weeks after infection to manifest itself, and the test result is usually negative in a neonate. A chest radiograph examination also usually yields a negative result in a neonate.[79]

Treatment. Because congenital tuberculosis is such a rare condition, optimal therapy has not been established. However, most recommendations suggest four-drug therapy: isoniazid, rifampin, pyrazinamide, and ethambutol or an aminoglycoside (streptomycin or kanamycin).[79]

Parent Teaching. **Infants who are treated with isoniazid or breastfed infants whose mothers are treated with isoniazid should receive pyridoxine supplementation.**[79]

NEISSERIA GONORRHOEAE INFECTION

Prevention. Screening high-risk mothers before delivery may identify asymptomatic gonorrhea. Treating positive mothers before delivery or exposed infants at delivery is necessary.[79]

Administering silver nitrate, erythromycin, or tetracycline in the eyes is mandatory in all vaginal deliveries.[79,99]

Data Collection

History. Mothers with previous venereal disease are a high-risk group, because 80% of the infected women may be asymptomatic.

Signs and Symptoms. The predominant manifestation of gonorrhea is *ophthalmia neonatorum,* although a systemic bloodborne infection may rarely occur involving the joints, lungs, endocardium, and CNS. **Conjunctivitis usually begins 2 to 5 days after birth. Eye prophylaxis minimizes but does not guarantee freedom from infection. Scalp abscess resulting from fetal monitoring has been reported.**[79]

Laboratory Data. **A Gram stain of purulent eye discharge revealing gram-negative intracellular diplococci is diagnostic.** Culture confirmation using fermentation or fluorescence establishes the diagnosis of gonorrhea. The organism is labile, so specimens for culture should be taken to the laboratory and plated immediately. When gonorrhea is diagnosed, other sexually transmitted diseases may be present concomitantly (especially chlamydial infection).[79]

Treatment. Table 22.1 outlines the treatment of *Neisseria gonorrhoeae* infection.

Parent Teaching. Eye prophylaxis should be provided within 1 hour of birth.[79,99]

VARICELLA

Prevention. Tables 22.3 and 22.4 outline prevention of infection.[79]

Data Collection

History. A history of varicella in the mother before conception virtually excludes the diagnosis. Varicella manifests in the mother with a fever, respiratory symptoms, and characteristic vesicular rash primarily on the trunk. **If this occurs within 5 days of**

delivery, the newborn is at risk for infection.[79] Preventive measures should be instituted as soon as possible.[9] **Acute perinatal varicella is frequently a devastating systemic disease.** Nosocomial acquired transmission of varicella is a potentially significant problem for high-risk infants: premature infants born to susceptible mothers; infants who are severely premature regardless of maternal status; and immunocompromised patients of all ages (Table 22.5).

Signs and Symptoms. **Congenital varicella is rare but has followed maternal varicella in the first trimester of pregnancy. Congenital manifestations include limb atrophy, skin scars, and CNS and eye abnormalities.**[7,79]

Laboratory Data. Varicella can be identified from a scab or vesicular fluid using PCR. Viral culture and DFA are less sensitive.[79]

The demonstration of multinucleated giant cells containing intranuclear inclusions in skin scrapings on Giemsa stain is nonspecific but helpful. Virus can be isolated from scrapings of vesicle base during the first 3 to 4 days of the eruption by direct fluorescent antibody test or isolation of virus in tissue culture.[30,32] Isolating the virus from the respiratory tract is difficult. A number of serologic tests such as the fluorescent antibody to membrane antigen test, immune adherence hemagglutination test, ELISA, and neutralization test are available but are not helpful in the acute clinical situation. CF serologic tests are relatively insensitive.[79]

Treatment

Parent Teaching. **Contact and airborne precautions are needed to prevent the spread of varicella to susceptible individuals. The infant must remain separated from exposed individuals for 8 to 10 days** and separated from the mother until the mother's vesicles have dried. **VariZIG can be given to decrease the possibility of infection of the infant, however the infant needs to remain isolated from susceptible individuals for 28 days, and the pediatrician's office should be notified of the risk before any visits.** Expressed breast milk can be provided by the mother with varicella if there are no lesions on the breast.[79]

EARLY-ONSET BACTERIAL DISEASE

Prevention. For GBS only, see p. 10.

Data Collection

History. Early-onset disease is almost always acquired perinatally and is discussed here. Late-onset disease is discussed in the Postnatal Acquisition Late-Onset Bacterial Disease section later in this chapter. **Early-onset disease presents as a fulminant multisystem illness during the first days of life (less than 72 hours of age). Significant risk factors for early-onset disease include prematurity, low birth weight, premature onset of labor, rupture of membranes for 18 hours or more, maternal intrapartum temperature higher than 38°C (100.4°F), and chorioamnionitis.**[,79] Bacteria responsible for early-onset disease are acquired from the birth canal before or during delivery and are listed in Box 22.2. Although the advent of intrapartum antibiotic prophylaxis for **GBS infections has generally reduced early-onset disease of this pathogen, it has not been universally eliminated, and black preterm infants remain at considerably greater risk than do white preterm infants and both black term infants and white term infants.**

Also, **since the practice of intrapartum prophylaxis began, a predominance of gram-negative organisms has been noted in infants weighing less than 1500 g at birth,** and concern for this continued trend remains.[,135] **Gram-negative infections now account for more than one-half of the instances of early-onset sepsis.**[,135,140,143,144] Data from the National Institute of Child Health and Human Development (NICHD) Neonatal Research Network, which comprises 16 major neonatal units, showed an increase in *Escherichia coli* infections in very-low-birth-weight (VLBW) infants from 1998 to 2000 compared with 1991 to 1993 that persisted during the 2002 to 2003 period.[143] A more recent study of the epidemiology of early-onset sepsis found that from 2005 to 2014, GBS prevention with intrapartum antibiotics has not increased the incidence of early-onset *E. coli* infections.[135] Data from the Norwegian National Cohort demonstrated that **in infants born at less than 28 weeks' gestational age and with birth weight less than 1000 g, *E. coli* was the most common organism isolated on the first day of life.**[130] **Early-onset bacterial disease is associated with a high (11%) mortality rate and significant morbidity (6.3% with sequelae at discharge).**[135,140,144]

Signs and Symptoms. **Neonatal bacterial sepsis is characterized by systemic signs of infection associated with bacteremia. Meningitis in a neonate can be a sequela of bacteremia or can occur in 15% to 38% of neonates with negative blood culture.**[79,128] In addition, bloodborne bacteria may localize in other tissues, causing focal disease. Both

TABLE 22.5 INFECTION CONTROL MEASURES AND ISOLATION TECHNIQUES FOR SPECIFIC DISEASES

DISEASE/ ORGANISMS	RECOMMENDED PRECAUTIONS							
	WASH HANDS	PRIVATE ROOM OR COHORT	MASK	GOWN	GLOVE	INFECTIVE MATERIAL	DURATION OF ISOLATION/ PRECAUTION	COMMENTS
AIDS/HIV	X	D	No	(X)	(X)	Blood and body fluids	Duration of illness	Utmost care needed to avoid needle sticks
Adenovirus	X	X	No	(X)	(X)	Respiratory secretions and feces	Duration of hospitalization	During outbreaks, cohort patients suspected of having adenovirus infection
Conjunctivitis								
Gonococcal (ophthalmia neonatorum)	X	X	No	No	(X)	Purulent exudates	Until 24 hours after initiation of effective therapy	
Chlamydia	X	No	No	No	(X)	Purulent exudates	Duration of illness	
Coxsackievirus	X	D	No	(X)	(X)	Feces and respiratory secretions	For 7 days after onset of illness	
Cytomegalovirus	X	No	No	No	(X)	Urine and respiratory secretions	Counsel pregnant personnel	
Diarrhea	X	D	No	(X)	(X)	Feces	Duration of illness	Identify colonized or infected infants by culture; institute cohorting
Echovirus	X	D	No	(X)	(X)	Feces and respiratory secretions	For 7 days after onset of illness	
Gastroenteritis	X	X	No	(X)	(X)	Feces	Duration of illness	
Hepatitis A	X	D	No	(X)	(X)	Feces	For 7 days after onset of illness	Most contagious before symptoms
Hepatitis B	X	No	No	(X)	(X)	Blood and body fluids	Duration of positivity	Avoid needle sticks
Herpes simplex	X	X	No	(X)	(X)	Lesions, secretions, urine, and stool	Duration of illness	
Influenza A or B	X	X	No	(X)	(X)	Respiratory secretions	Duration of illness	Cohort patients suspected of having influenza during outbreak; staff should receive yearly influenza vaccine

Continued

TABLE 22.5 INFECTION CONTROL MEASURES AND ISOLATION TECHNIQUES FOR SPECIFIC DISEASES—CONT'D

	RECOMMENDED PRECAUTIONS							
DISEASE/ ORGANISMS	WASH HANDS	PRIVATE ROOM OR COHORT	MASK	GOWN	GLOVE	INFECTIVE MATERIAL	DURATION OF ISOLATION/ PRECAUTION	COMMENTS
Meningitis								
Aseptic	X	D	No	(X)	(X)	Feces	Duration of illness	Cohort colonized or infected infants during a nursery outbreak
Bacterial	X	No	No	No	No			
Necrotizing enterocolitis	X	No	No	(X)	(X)	(?) Feces	Duration of illness	Cohort ill infants
Respiratory syncytial virus	X	X	X	(X)	(X)	Respiratory secretions	Duration of illness	Cohort suspected infants, especially premature infants, during outbreaks
Rubella	X	X	X	No	No	Respiratory secretions	Duration of hospitalization	Infants may shed virus for as long as 2 years; seronegative women should avoid contact
Staphylococcal disease *(Staphylococcus aureus)*	X	D	No	(X)	(X)	Purulent exudate	Duration of illness	
Streptococcal disease								
Group A	X	D	No	(X)	(X)	Respiratory secretions	24 hours after initiation of effective therapy	
Group B	X	D	No	(X)	(X)	Respiratory and genital secretions	Cohort ill and colonized infants during a nursery outbreak	
Syphilis	X	No	No	No	(X)	Lesion secretions and blood	24 hours after initiation of effective therapy	
Toxoplasmosis	X	No	No	No	No	None		
Varicella	X	X	X	X	X	Respiratory and lesion secretions	Until lesions are crusted	Neonates born to mothers with active chickenpox should be placed in isolation precautions at birth; persons who are not susceptible do not need to mask
Vancomycin-resistant organisms	X	X	No	X	X	Secretions	Duration of illness	

AIDS, Acquired immunodeficiency syndrome; *D,* desirable but optional; *HIV,* human immunodeficiency virus; *X,* recommended at all times; *(X),* recommended if soiling is likely or if touching infective materials.

BOX 22.2 CRITICAL FINDINGS
ORGANISMS CAUSING EARLY-ONSET BACTERIAL SEPSIS

Common Organisms
Group B Streptococcus
Escherichia coli
Coagulase-negative *Staphylococcus*

Unusual Organisms
Staphylococcus aureus
Neisseria meningitidis
Streptococcus pneumoniae
Haemophilus influenzae (type B and nontypable)

Rare Organisms
Klebsiella pneumoniae
Pseudomonas aeruginosa
Enterobacter species
Serratia marcescens
Group A *Streptococcus*
Anaerobic species
Listeria monocytogenes

patterns of bacterial disease, early onset and late onset, have been associated with systemic infections during the neonatal period.[79,128]

In general, signs, particularly in early-onset disease, are nonspecific and nonlocalizing.[79] Signs and symptoms may include temperature instability (hypothermia or hyperthermia), respiratory distress (apnea, cyanosis, and tachypnea), lethargy, feeding abnormalities (vomiting, increased residuals, and abdominal distention), jaundice (particularly increased direct fraction), seizures, or purpura (Fig. 22.3).[128]

Quantification of risk of early-onset neonatal sepsis using maternal risk factors and neonatal clinical examination may significantly decrease antibiotic use in neonates early after birth.[48,121] From this initial research, the Kaiser Newborn Sepsis Calculator was developed (Fig. 22.4). **National and international, single-center studies to evaluate the safety and efficacy of the calculator have been conducted with their outcomes listed in** Box 22.3. Additionally, potential benefits of the calculator's use include a reduction in health care costs, fewer painful procedures,

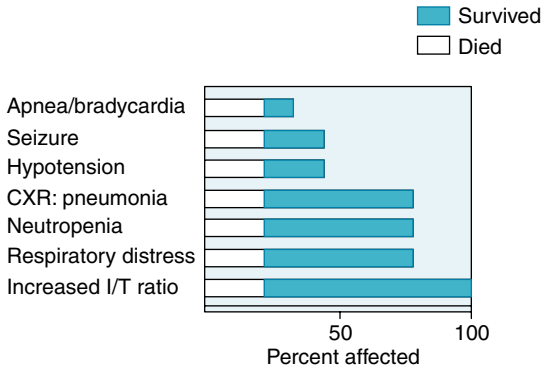
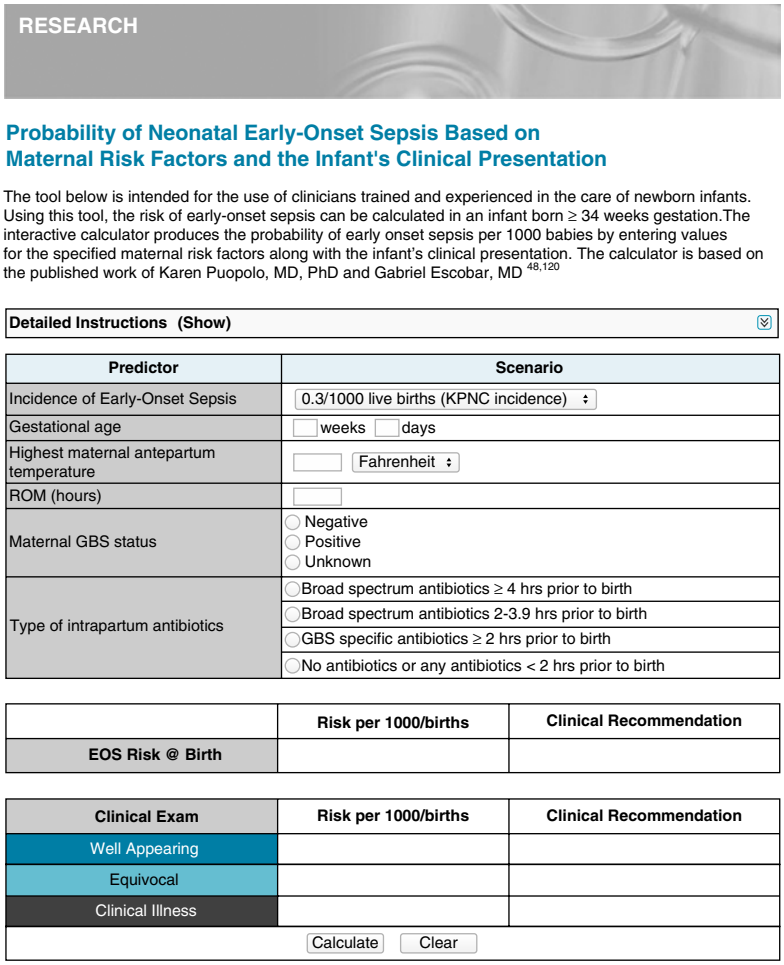


FIGURE 22.3 Clinical and laboratory findings in nine infants with signs and symptoms of early-onset group B streptococcal disease. *CXR,* Chest x-ray; *I/T,* ratio of immature to total neutrophils. (From Nelson SN, Merenstein GB, Pierce JR. Early onset group B streptococcal disease. *J Perinatol.* 1986;6:234.)

promotion of breastfeeding by avoiding unnecessary separation of mother and baby, and a strategy for promotion of antibiotic stewardship.[54,160] **Continuous, competent, clinical observation must accompany use of the calculator** because in one study some neonates with culture-proven early-onset sepsis would have been missed using the calculator alone,[23] and in another study some neonates with initial low sepsis scores deteriorated after 12 hours of life.[76] Multicenter multinational RCTs to evaluate the systematic use of the sepsis calculator and the effects on clinical practice and outcomes are warrented.[4,23,54,76,83,98,160]

Laboratory Data. **Isolating bacteria from a nonpermissive site (blood, CSF, urine, closed body space) is the most valid method of establishing the diagnosis of bacterial sepsis.[162]** Surface cultures (including ear and gastric aspirates) do not establish the presence of active systemic infection but merely indicate colonization. Bacterial antigens or endotoxins may be demonstrated in sera, CSF, urine, or body fluids by a variety of methods (counterimmunoelectrophoresis, latex agglutination, and limulus lysate tests). Such a demonstration is not totally definitive, nor does it allow the determination of the antibiotic sensitivity of the offending organism.[128] False-positive reactions may be caused by skin surface contamination or gastrointestinal absorption of antigen.[13] Because the sensitivity of blood cultures is very low (i.e., high false-negative results),[58,95] other laboratory methods to identify bacterial sepsis in neonatal blood are being researched. Methods such as rapid PCR testing[146] and amplification/analysis of ribosomal DNA in bacterial



RESEARCH

Probability of Neonatal Early-Onset Sepsis Based on Maternal Risk Factors and the Infant's Clinical Presentation

The tool below is intended for the use of clinicians trained and experienced in the care of newborn infants. Using this tool, the risk of early-onset sepsis can be calculated in an infant born ≥ 34 weeks gestation.The interactive calculator produces the probability of early onset sepsis per 1000 babies by entering values for the specified maternal risk factors along with the infant's clinical presentation. The calculator is based on the published work of Karen Puopolo, MD, PhD and Gabriel Escobar, MD [48,120]

Detailed Instructions (Show)

Predictor	Scenario
Incidence of Early-Onset Sepsis	0.3/1000 live births (KPNC incidence)
Gestational age	weeks days
Highest maternal antepartum temperature	Fahrenheit
ROM (hours)	
Maternal GBS status	Negative Positive Unknown
Type of intrapartum antibiotics	Broad spectrum antibiotics ≥ 4 hrs prior to birth Broad spectrum antibiotics 2-3.9 hrs prior to birth GBS specific antibiotics ≥ 2 hrs prior to birth No antibiotics or any antibiotics < 2 hrs prior to birth

	Risk per 1000/births	Clinical Recommendation
EOS Risk @ Birth		

Clinical Exam	Risk per 1000/births	Clinical Recommendation
Well Appearing		
Equivocal		
Clinical Illness		

Calculate Clear

FIGURE 22.4 Kaiser newborn sepsis calculator: probability of neonatal early-onset sepsis based on maternal risk factors and the infant's clinical presentation. (From Kaiser Permanente Division of Research. Available at: https://neonatalsepsiscalculator.kaiserpermanente.org. ©2019 Kaiser Permanente Division of Research. Accessed March 9, 2019.)

genes and electrophoresis[58,145] show promise in rapid identification of the organism and diagnostic accuracy.

The CSF is examined in most infants suspected of sepsis, because meningitis is a frequent manifestation of sepsis in neonates, especially in symptomatic infants and infants with GBS sepsis and with late-onset disease (Table 22.6).[81,128] Low yield and potential adverse effects from LP have resulted in examination of CSF being deferred in asymptomatic infants being evaluated for maternal risk factors or respiratory distress.[128] **Meningitis is difficult to exclude without an LP, and its diagnosis affects therapy and follow-up in the neonate.[81,128,135] In VLBW preterm infants with late-onset sepsis, 1.4% of all VLBW and 5% of those who had LP had meningitis.[142] One-third of the VLBW preterm infants with meningitis had negative blood cultures. In VLBW infants, meningitis was associated with lower gestational age, prior sepsis, longer mechanical ventilation, longer length of stay, seizures, and death.[142]** More recent research into early and late onset neonatal sepsis shows variation in the use of LP: (1) low use for late-onset sepsis (21% in a single-center study),[166] (2) variable use from country to country (higher in Denmark than in Sweden) for early-onset sepsis,[42]

Classification of Infant's Clinical Presentation (Hide)

Clinical Exam	Description
Clinical Illness	1. Persistent need for NCPAP / HFNC / mechanical ventilation (outside of the delivery room) 2. Hemodynamic instability requiring vasoactive drugs 3. Neonatal encephalopathy /Perinatal depression ▪ Seizure ▪ Apgar Score @ 5 minutes < 5 4. Need for supplemental O_2 ≥ 2 hours to maintain oxygen saturations > 90% (outside of the delivery room)
Equivocal	1. Persistent physiologic abnormality ≥ 4 hrs ▪ Tachycardia (HR ≥ 160) ▪ Tachypnea (RR ≥ 60) ▪ Temperature instability (≥ 100.4°F or <97.5°F) ▪ Respiratory distress (grunting, flaring, or retracting) not requiring supplemental O_2 2. Two or more physiologic abnormalities lasting for ≥ 2 hrs ▪ Tachycardia (HR ≥ 160) ▪ Tachypnea (RR ≥ 60) ▪ Temperature instability (≥ 100.4°F or <97.5°F) ▪ Respiratory distress (grunting, flaring, or retracting) not requiring supplemental O_2 Note: abnormality can be intermittent
Well Appearing	No persistent physiologic abnormalities

FIGURE 22.4, cont'd

and (3) neither C-reactive protein (CRP) or IT ratio are predictive in identifying neonates with confirmed or suspected meninigitis.[59,147] These researchers recommend that the **decision to perform an LP be focused on the individual presentation of the infant and a positive blood culture.**[59,147]

Several laboratory aids are used in assessing neonatal sepsis, but it must be realized that these tests are not sensitive or specific enough to influence clinical decisions on their own.[34,46,79] *Leukocyte indices* predict sepsis with sensitivities ranging from 17% to 90% and specificities from 31% to 100%.[34] **CRP is an acute-phase reactant synthesized in the liver in the first 6 to 8 hours of the infective process with a low sensitivity (60%) early in sepsis. However, serial CRP measurements at 24 and 48 hours improve sensitivity to 82% and 84%, and specificity and positive predictive values range from 83% to 100%.**[103] Negative predictive values for CRP are extremely high. **Serial CRP patterns have been found to be useful to follow resolution of infection and guide antibiotic therapy.**[70,95,136] **CRP levels do not seem to be affected by gestational age and have better sensitivity and negative predictive values compared with leukocyte indices.**[39] CRP response has been found to be better in gram-negative infections compared with infections with coagulase-negative *Staphylococcus*. The use of CRP in neonatal sepsis has recently been reviewed.[69,95,136]

Procalcitonin, **another acute-phase reactant, which rises within 4 hours of exposure to**

bacterial endotoxin, has a sensitivity and specificity ranging from 83% to 100%. The serum profile of procalcitonin has been claimed to be superior to that of CRP in the diagnosis of sepsis, after resolution of infection, and may differentiate between sepsis and other inflammatory processes (e.g., trauma).[113] Procalcitonin may have sufficient diagnostic accuracy in differentiating invasive fungal infections from bacterial infections and uninfected individuals.[41] Recent systematic reviews found that procalcitonin has moderate accuracy in diagnosing neonatal sepsis, is more accurate than CRP, and should be used within the context of other clinical parameters and relevant investigations.[123,165] **Another meta-analysis and systematic review found that a combination of CRP and procalcitonin improves the accuracy of the diagnosis of neonatal sepsis.**[131]

Serial measurements may be more useful, as is a combination of tests.[95,103,104,131] Radiographic examination of the chest and other specific areas indicated by clinical concerns may also be helpful.[128]

Several other nonspecific laboratory abnormalities may accompany neonatal sepsis, including hyperglycemia, hypoglycemia, and unexplained metabolic acidosis. Molecular techniques for diagnosis of infection are fast and reliable and may be very useful, especially in infants whose mothers have received intrapartum antibiotics.

Treatment. **Antibiotics are the cornerstone of treatment for presumed or confirmed infections in neonates. However, the indiscriminate or inappropriate use of systemic antibiotics may cause undesirable side effects[82,150] (increased risk of NEC, ROP, BPD and mortality, especially in VLBW premature infants),[21,22,37,150] favor the emergence of resistant strains of bacteria, and alter the microbiome of the newborn.**[29] Antibiotic stewardship for appropriate therapy and duration of therapy is

BOX 22.3 USE OF THE KAISER NEWBORN SEPSIS CALCULATOR: RESEARCH EVIDENCE

- Fewer sepsis workups
  - 14.5% (before calculator use) versus 4.9% (after calculator use)[83]
- Reduction in empirical antibiotics
  - 5% (before calculator use) versus 2.6% (after calculator use)[83]
  - 4.8% to 2.7% (prospective use of calculator with existing protocols)[4] resulting in a 44% reduction without delay or prolongation of therapy
  - 92% (using CDC 2010 guidelines) versus 23% (use of sepsis calculator)[160]
  - 50% reduction in antibiotic use[76]
  - 99% (in neonates whose mothers had chorioamnionitis before use of calculator) versus 2.5% (after calculator use)[98]
  - Fewer days of antibiotics (2.08 days to 0.05 days)[98]
- Reduction in invasive, costly laboratory testing[160]
- Improved antibiotic stewardship[160]
- No increase in adverse effects (i.e., readmission, meningitis, or death)[83]

TABLE 22.6 NORMAL CEREBROSPINAL FLUID VALUES IN NEONATES

	WHITE BLOOD CELLS	POLYMORPHONUCLEAR NEUTROPHILS	PROTEIN (mg/dL)	GLUCOSE (mg/dL)
Premature Infants				
Reported means	2–27		75–150	79–83
Reported ranges	0–112		31–292	64–106
Term Infants				
Reported means	3–5	2–3	47–67	51–55
Reported ranges	0–90	0–70	17–240	32–78

Modified from Wilson C, Nizet V, Maldonado Y, Remington J, Klein J, eds. *Remington and Klein's Infectious Diseases of the Fetus and the Newborn Infant.* 8th ed. Philadelphia, PA: Elsevier Saunders; 2016; Mhanna MJ, Alessah H, Gori A, et al. Cerebrospinal fluid values in very low birth weight infants with suspected sepsis at different ages. *Pediatr Crit Care Med.* 2008;9:294.

of paramount importance in improving neonatal outcomes.[21,94,98,115,124,158]

Adequate and appropriate specimens for culture should be obtained before antibiotic therapy is initiated. Emergence of antibiotic resistance in gram-negative organisms is a major clinical concern.[18] In the data from the NICHD Neonatal Research Network, 85% and 75% of early-onset *E. coli* infections were ampicillin resistant in the 1998 to 2000 and the 2002 to 2003 cohorts, respectively.[140,143] Plasmid-mediated extended-spectrum beta-lactamases (produced by *Klebsiella* spp., *E. coli,* and *Serratia*) that confer resistance to a variety of β-lactam agents (penicillins and cephalosporins) and chromosomally mediated AmP-C–type beta-lactamase (*Enterobacter* and *Citrobacter* spp.)–producing gram-negative organisms have been isolated from the NICU.[63,64,116] **Exposure to third-generation cephalosporins (e.g., cefotaxime) and being a VLBW infant are noted risk factors for the acquisition of resistant organisms.**

Broad-spectrum antibiotic coverage, usually with ampicillin and an aminoglycoside for early-onset sepsis, is commonly initiated pending culture and sensitivity results. Once causative organisms are identified and antibiotic sensitivities are established, **the most appropriate and least toxic antibiotic or antibiotic combination should be continued for an appropriate period by a suitable route.** If adequate cultures are negative after a reasonable period (24 to 48 hours), antibiotic therapy may be discontinued in most situations.

Antibiotics are not the entire solution to treating the infected newborn. Meticulous attention to the treatment of associated conditions, such as shock, hypoxemia, thermal abnormalities, electrolyte or acid-base imbalance, inadequate nutrition, anemia, or presence of pus or foreign bodies, may be as important as choosing the proper antibiotic. IV immunoglobulins are not recommended because they do not reduce the length of stay, mortality, or major disability at 2 years of age in infants with suspected or proven neonatal infection.[107] Table 22.1 **provides guidelines for choosing the proper antibiotic for indicated conditions;** Table 22.7 **gives the proper dose, route, and frequency of administration of commonly used antibiotics in the newborn nursery.** Table 22.8 **describes the passage of antibiotics across the placenta, and** Table 22.9 **describes their passage into breast milk.**

Parent Teaching. Transplacental infection often results in fetal abnormality or death. Newborns who survive may have long-term sequelae such as developmental, neurologic, motor, sensory, growth, and physical abnormalities.

Before antibiotic use, the mortality rate from bacterial sepsis was 95% to 100%, but antibiotics and supportive care have reduced the mortality rate to less than 50%; however, survival is highly variable and depends on the organism and underlying or associated conditions. **Debilitated infants (preterm and sick neonates) are at greater risk and have a higher incidence of morbidity and mortality than term healthy neonates. The most common complications of bacterial sepsis are meningitis and septic shock.** The outcome is influenced by early recognition and vigorous treatment with appropriate antibiotics and supportive care.

POSTNATAL ACQUISITION LATE-ONSET BACTERIAL DISEASE

Prevention. The CDC defines *nosocomial* as **all neonatal infections acquired in the intrapartum period or during hospitalization. Infants requiring the specialized care of NICUs are highly susceptible to infection.** Prematurity, stress, immature immune systems, and complicated medical and surgical problems contribute to their increased susceptibility. In addition, most **infants in the NICU require a variety of invasive diagnostic, therapeutic, and monitoring procedures; many of these procedures bypass natural physical barriers, which may allow colonization to occur and a nosocomial (late-onset) infection to develop.[56]**

A recent *Cochrane* review states that lactoferrin supplementation to enteral feedings (either with or without probiotics) decreases late-onset sepsis and severe NEC in preterm infants without adverse effects (see Chapter 17).[112] Although current evidence is of low quality, when ongoing trials of >6000 preterm infants are completed, new data may enhance the quality of evidence.

Central line–associated bloodstream infections (CLABSIs), also called catheter-related bloodstream infections, are the most frequent hospital-acquired infections and are of particular concern in the NICU because of the prevalence of indwelling catheter lines needed for fluids, nutrition, and medications. Infection occurs via the insertion site with migration of microorganisms along the

TABLE 22.7 ANTIBIOTIC, ANTIVIRAL, AND ANTIFUNGAL AGENTS: DOSAGES FOR NEONATES

ANTIBIOTIC, ANTIVIRAL, OR ANTIFUNGAL	ROUTE	DAILY DOSAGES AND INTERVALS	
		0–7 DAYS OF AGE	MORE THAN 7 DAYS OF AGE
Acyclovir†	IV	20 mg/kg/dose q 8–12 hr depending on weight and age	Same
Amikacin sulfate	IV, IM	15 mg/kg/dose q 24–48 hr depending on gestation and age	15–17.5 mg/kg/dose q 24 hr
Amoxicillin	PO	15 mg/kg every 12 hr	Same
Amoxicillin/clavulanic acid	PO	Not recommended	25–45 mg/kg/day divided q 12 hr
Ampicillin			
• Meningitis	IV	100–150 mg/kg/day divided q 8–12 hr For GBS 200–300 mg/kg/day divided q 8 hr	150–200 mg/kg/day divided q 6–8 hr For GBS, 300 mg/kg/day divided q 6 hr
• Other indications	IV, IM, PO	50 mg/kg/day divided q 12 hr	75 mg/kg/day divided q 8 hr
Azithromycin	IV, PO	10 mg/kg/day q 24 hr	Same
Cefazolin*	IV, IM	50 mg/kg/day divided q 12 hr	75 mg/kg/day divided q 8–12 hr
Cefotaxime	IV, IM	100 mg/kg/day divided q 12 hr	150 mg/kg/day divided q 8 hr
Ceftazidime*	IV	100 mg/kg/day divided q 12 hr	150 mg/kg/day divided q 8 hr
Ceftriaxone	IV, IM	25–50 mg/kg q 24 hr	Same
Clindamycin	IV, PO	15–21 mg/kg/day divided q 8 hr	15–27 mg/kg/day divided q 8 hr
Erythromycin ethyl succinate (EES)	PO	40 mg/kg/day divided q 6 hr	40 mg/kg/day divided q 6 hr
Ganciclovir†	IV	6 mg/kg/dose q 12–24 hr	Same
Gentamicin	IV, IM	4–5 mg/kg/dose q 24–48 hr depending on gestation and age	4–5 mg/kg/dose q 24–36 hr depending on gestation and age
Meropenem*	IV	40–60 mg/kg/day divided q 8–12 hr depending on gestational age and weight	60 –90 mg/kg/day divided q 8 hr (higher doses may be needed in meningitis)
Metronidazole	IV, PO	15–22.5 mg/kg/day divided q 8–12 hr	15–30 mg/kg/day divided q 8–12 hr
Nafcillin	IV	50–75 mg/kg/day divided q 8–12 hr	75–150 mg/kg/day divided q 6–8 hr
Nystatin‡	PO	400,000 units divided q 6 hr	Same
Penicillin G			
• GBS Meningitis	IV	250,000 to 450,000 units/kg/day divided q 8 hr	450,000–500,000 units/kg/day divided q 6 hr
• Other indications	IV	100,000 units/kg/day divided q 12 hr	150,000–200,000 units/kg/day divided q 6–8 hr
Penicillin G, benzathine	IM	50,000 units/kg (1 dose only)	Same
Penicillin G, procaine	IM	50,000 units/kg/day once daily	Same
Pentamidine isethionate*	IV	4 mg/kg/day for 14 days	Same
Piperacillin/tazobactam	IV	300 mg/kg/day divided q 8 hr	320 mg/kg/day divided q 6 hr
Rifampin	IV, PO	10 mg/kg/day q 24 hr	Same
Ticarcillin	IV	150 mg/kg/day divided q 12 hr	150 mg/kg/day divided q 8–12 hr

Continued

TABLE 22.7 ANTIBIOTIC, ANTIVIRAL, AND ANTIFUNGAL AGENTS: DOSAGES FOR NEONATES—cont'd

ANTIBIOTIC, ANTIVIRAL, OR ANTIFUNGAL	ROUTE	DAILY DOSAGES AND INTERVALS	
		0–7 DAYS OF AGE	MORE THAN 7 DAYS OF AGE
Tobramycin	IV, IM	4–5 mg/kg/dose q 24–48 hr depending on gestation and age	5 mg/kg/dose q 24–36 hr
Trimethoprim/sulfamethoxazole (TMP/SMX)	PO IV	Not recommended	8–10 mg/kg/day divided q 12 hr For PCP treatment, 15–20 mg/kg divided in 3 doses Infants >2 months of age
Vancomycin	IV	10–15 mg/kg/dose q 12–48 hr depending on gestation and serum creatinine	10–20 mg/kg/dose q 12–48 hr depending on gestation and serum creatinine
Zidovudine†	IV	3–6 mg/kg/day divided q 12 hr depending on gestation and age	Same
	PO	4–8 mg/kg/day q 12 hr depending on gestation and age	Same

*Pharmacokinetics in newborns not well characterized. These drugs should be used with extra caution in neonates (pediatric infectious disease consultation recommended).
†Antiviral agent.
‡Antifungal agent.
CDC, Centers for Disease Control and Prevention; *hr,* hour; *IM,* intramuscularly; *IV,* intravenously; *PO,* orally.

TABLE 22.8 PASSAGE OF ANTIBIOTICS ACROSS THE PLACENTA*

PERCENTAGE OF ANTIBIOTIC IN INDICATED CATEGORY	ANTIBIOTIC
Equal to serum concentration	Amoxicillin Ampicillin Carbenicillin Chloramphenicol Methicillin Nitrofurantoin Penicillin G Sulfonamides
50% of serum concentration	Aminoglycosides
10%–15% of serum concentration	Amikacin Cephalosporins Clindamycin Nafcillin Tobramycin
Negligible (<10% of serum concentration)	Dicloxacillin Erythromycin

*Several factors determine the degree of transfer of antibiotics across the placenta, including lipid solubility, degree of ionization, molecular weight, protein binding, placental maturation, and placental and fetal blood flow.

TABLE 22.9 PASSAGE OF ANTIBIOTICS INTO BREAST MILK*

PERCENTAGE OF ANTIBIOTIC IN INDICATED CATEGORY	ANTIBIOTIC
Equal to serum concentration	Isoniazid Metronidazole Sulfonamides Trimethoprim
50% of serum concentration	Chloramphenicol Erythromycin Tetracyclines
<25% of serum concentration	Cefazolin Kanamycin Nitrofurantoin Oxacillin Penicillin G Penicillin V

*Data on concentrations of antibiotics in human breast milk are sparse. Because most antibiotics are present in breast milk in microgram amounts, they are normally not ingested by the infant in therapeutic amounts.

catheter/catheter hub, seeding from another site of infection, and infusion of contaminated fluids.

Longer dwell times for catheters are also associated with increased CLABSIs. Rates of infection increase over the first 2 weeks and then remain elevated for the duration of the line. In the first 40 days from placement, coagulase-negative staphylococci are the most prevalent organisms. After 50 days, the risk of gram-negative infection is increased.[16,96,106,137]

A systematic and multidisciplinary approach to reducing CLABSIs should be included in the infection control policies of every NICU. Evidence-based guidelines or "bundles" (of specific evidence-based interventions) are packaged together to reduce variability in insertion and catheter maintenance and have been shown to reduce CLABSIs. "Bundles" can be developed by individual NICUs or obtained through collaborative practice organizations.[117,163] **Strategies to prevent CLABSIs generally include (1) education for all health care providers, (2) need for adequate nurse staffing, (3) meticulous hand hygiene, (4) strict aseptic technique, (5) limitation of line manipulations, and (6) limitation on dwell time.** For line placement, use of maximum sterile barriers (i.e., hat, mask, sterile gown and gloves) and a full sterile body drape is recommended. Other strategies include the use of ultrasonography to limit placement attempts, avoiding the femoral vein for percutaneous placement, and proper disinfection of hubs, connectors, and injection ports.

Dressings should be changed every 7 days and/or when the dressing is loose, damp, or visibly soiled. Lines should be removed immediately when signs of infection or phlebitis are present. The need for line continuation should be evaluated daily and the line removed as soon as possible. A process for tracking CLABSIs is essential so that causes are identified and intervention quickly occurs when rates increase.*

Infection control principles and practices for the prevention of these nosocomial infections are outlined in Table 22.10. **Table 22.5 outlines infection control measures and isolation techniques for specific diseases.**[19,79,137]

Data Collection

History. Late-onset disease may occur as early as 3 days of age but is more common after the first week of life. Affected infants may have a history of obstetric complications, but they are less common than obstetric complications in early-onset disease. Bacteria responsible for late-onset sepsis and meningitis include those acquired from the maternal genital tract and organisms acquired after birth from human contact or from contaminated equipment or material (Box 22.4).[9] **Gram-positive organisms predominate in late-onset sepsis, and gram-negative organisms account for about one-third of late-onset cases of sepsis in VLBW infants.**[141] **Although prematurity remains the most significant factor, invasive procedures performed on a neonate, such as intubation, catheterization, and surgery, also increase the risk for bacterial infection.**[78,111,141]

Signs and Symptoms. Similar to those of early-onset sepsis, signs and symptoms are nonspecific. Heart rate variability, the acceleration and deceleration of heart rate that occurs as a result of activity and neonatal states, has been researched as a sign of sepsis. **Decreased heart rate variability (from baseline) and transient decelerations have been noted to occur up to 24 hours before symptoms of sepsis occur.**[61,100] **Therefore decreased heart rate variability is an early sign of late-onset sepsis.**

Decreased baseline variability also occurs in systemic inflammatory response syndrome, necrotizing enterocolitis, intraventricular hemorrhage, and chronic lung disease. Medications also affect variability. Paralytics, anesthetics, and anticholinergics decrease variability, whereas dexamethasone improves variability.

As noninvasive screening tools for late-onset sepsis, algorithms that highlight changes in baseline heart rate variability have been developed. These algorithms are adjuncts to clinical assessment/observation and laboratory data in decision making regarding sepsis evaluation and need for empirical antibiotics. The most recent research into alterations of heart and respiratory rates and oxygen saturations before overt signs of late-onset sepsis have found: (1) trending of heart rate (bradycardia) and oxygen saturations (desaturations) in preterm infants with developing infection[101] and (2) VLBW premature infants in two NICUs showed a high correlation of heart rate and oxygen saturations in relation to respiratory rate (i.e., periodic breathing or apnea that resulted in bradycardia and desaturation) in the 24 hours before overt sepsis symptoms.[50] Translating metrics

*References 16, 53, 96, 97, 106, 137, 163

TABLE 22.10 INFECTION CONTROL PRINCIPLES AND PRACTICES TO PREVENT NOSOCOMIAL INFECTION

PRINCIPLE	PRACTICE
Handwashing	
Handwashing is the most important procedure for controlling infection in the NICU.	1. Before each shift, wash hands, wrists, forearms, and elbows with antiseptic. Scrub hands with a brush or pad for 2–3 minutes, and rinse thoroughly. Chlorhexidine, hexachlorophene, and iodophors are the preferred products. 2. Wash hands for 10–15 seconds between infant contacts. Soap and water are adequate unless the infant is infected or contaminated objects have been handled. 3. Use an antiseptic for handwashing before surgical or similar invasive procedures. 4. Alcohol-based disinfectants are effective when used before and after patient contact.
Cell Phone	
Cell phones and other handheld electronic devices are a potential vector for bacteria.[15,80] Bacteria may be transmitted from phone to hands.	1. Clean phones with a hospital-approved wipe. 2. Clean hands after using a cell phone.
Patient Placement	
Overcrowding in the NICU increases the risk for cross-contamination.	1. Provide 4- to 6-foot intervals between infants.
SKIN AND CORD CARE	
The skin, its secretions, and its normal flora are natural defense mechanisms that protect against invading pathogens (see Chapter 19). No single method of cord care has been identified to prevent colonization or limit disease.	1. The American Academy of Pediatrics suggests using a dry technique: a. Delay initial cleansing until temperature is stable. Manipulating an infant's skin must be minimized. b. Use sterile cotton sponges and sterile water or mild soap to remove blood from face and perineal area. c. Do not touch other areas unless they are grossly soiled. 2. Local application of alcohol, triple dye, and various antimicrobials may be used in areas where the risk of omphalitis is high.
MEDICAL DEVICES	
Medical devices facilitate infections by the following: 1. Bypassing normal defense mechanisms, providing direct access to blood and deep tissues 2. Supporting growth of microorganisms and becoming reservoirs from which bacteria can be transmitted with the device to another patient 3. Providing a "protected site" when placed in deeper tissue, so phagocytosis or defense mechanisms cannot eradicate the organisms 4. Using sterile medical devices that are occasionally contaminated from the manufacturer or central supply	1. IV infusion devices predispose infants to phlebitis and bacteremia. Preventive measures include preparing the site with tincture of iodine (2% iodine in 70% alcohol), an iodophor, or 70% alcohol, or 2% chlorhexidine in infants with mature skin,[78] anchoring the IV securely; performing frequent site assessment, rotating the IV site when clinically indicated;[161] changing the IV administration set every 48–96 hours on IVs that do not contain lipids or blood products;[153] and discontinuing the IV at the first sign of complication. 2. Central lines are common in the NICU and are a common locus of infection. Central lines should be placed under sterile conditions.[111] The use of evidence-based CLABSI bundles that include sterile tubing changes and continuous monitoring is necessary to prevent infection. 3. Arterial lines predispose infants to bacteremia. Preventive measures include aseptically inserting the catheter using gloves, inspecting the site and performing site care every 24 hours, treating the catheter and stopcocks as sterile fields, and minimizing manipulation by drawing all blood specimens at the same time. 4. Intravascular pressure–monitoring systems predispose infants to septicemia. Preventive measures include replacing the flush solution every 24 hours and replacing the pressure transducer according to manufacturer's recommendations and hospital policy. 5. Respiratory therapy devices increase the risk for contamination. Preventive measures include using aseptic technique during suctioning; dating opened solution for irrigation, humidification, and nebulization, and discarding after 24 hours; ensuring routine replacement and cleaning of all respiratory equipment, including Ambu bags, cascade nebulizers, endotracheal tube adaptors, and tubing.

TABLE 22.10 INFECTION CONTROL PRINCIPLES AND PRACTICES TO PREVENT NOSOCOMIAL INFECTION—cont'd

Specimen Collection	
Improperly collected specimens cause infection at the site of collection or erroneous diagnosis, leading to the administration of the wrong antibiotic or delayed administration of the appropriate antibiotic.	1. Wash hands before collecting specimen. 2. Observe aseptic technique to reduce risk for infection and to avoid contamination of specimen. 3. Deliver specimens to the laboratory immediately. 4. Do not use femoral sticks.
Nursery Attire	
Personal clothing and unscrubbed skin areas of personnel should not touch infants.	1. Short-sleeved scrub gowns accommodate washing elbows. 2. Long-sleeved gowns should be worn and changed between handling of infected or potentially infected infants. 3. Sterile gowns are necessary for sterile procedures.
Employee Health	
Transmission of disease among patients and employees can occur bidirectionally. Each NICU must establish reasonable guidelines for restriction of assignments based on the employee's potential to transmit disease and the potential risk for acquiring disease.	1. Conditions that commonly restrict personnel from patient care in the NICU are skin lesions and draining wounds, acute respiratory infections, fever, gastroenteritis, active herpes simplex (oral, genital, or paronychial), and herpes zoster. 2. Conditions that are transmitted from infants to personnel are the following: a. Rubella: Obtain rubella titers from women of childbearing age; if a protective level is not present, they should be vaccinated. b. Cytomegalovirus is a potential threat to pregnant women. Adherence to good infection control practices may reduce this threat. c. Hepatitis B is usually not a major problem in the NICU, because host vaccine is available and may be considered for high-risk individuals (see Tables 22.3 and 22.4). d. Use of gloves with body fluid contact will decrease the risk for transmission of hepatitis B virus and human immunodeficiency virus.
Cohorting	
Cohorting is an important infection control measure used primarily during outbreaks or epidemics in the NICU. The object of cohorting is to limit the number of contacts of one infant with other infants and personnel.	1. Group together infants born within the same time frame (usually 24–48 hours) or who are colonized or infected with the same pathogen. These infants should remain together until discharged. 2. Provide nursing care by personnel who do not care for other infants. 3. After all infants in cohort are discharged, clean the room before admittance of a new group of infants.

IV, Intravenous; *NICU,* neonatal intensive care unit.

Modified from Siegel JD, Rhinehart E, Jackson M, et al; the Healthcare Infection Control Practices Advisory Committee. 2007 Guideline for Isolation Precautions. Preventing Transmission of Infectious Agents in Healthcare Settings. Available at: https://www.cdc.gov/infectioncontrol/guidelines/isolation/. Accessed February 27, 2019.

into real-time bedside displays and conducting randomized clinical trials to determine their efficacy in clinical care and impact on outcomes are the next research directions.[50]

Laboratory Data. **A complete set of culture specimens should be obtained,** but limitations are similar to those in early-onset infection.

Treatment. **Broad-spectrum antibiotic coverage, usually vancomycin and an aminoglycoside or a third-generation cephalosporin, is commonly initiated pending culture and sensitivity results. However, vancomycin resistance remains a potential problem in the care of sick neonates.**[29,36,90] To minimize the development of these

BOX 22.4 CRITICAL FINDINGS
ORGANISMS CAUSING LATE-ONSET BACTERIAL SEPSIS

- Coagulase-negative *Staphylococcus*
- *Escherichia coli*
- *Klebsiella* species
- *Enterobacter* species
- *Candida* species
- *Malassezia furfur*
- Other enteric organisms
- Group B *Streptococcus*
- Methicillin-resistant *Staphylococcus aureus*

resistant organisms, the CDC has recommended prudent vancomycin use, education of medical personnel about the problem of vancomycin resistance, early detection and prompt reporting of organisms, and immediate implementation of appropriate infection control measures (see Table 22.10).

Complications. CLABSIs increase morbidity and mortality rates, length of stay, and cost of care.

Parent Teaching. Parents should be taught to wash their hands on entering the nursery and before touching their infant and between siblings. Parents should also be told that it is acceptable to remind others to wash their hands before touching their infant.

FUNGAL INFECTION

Fungal infections have been a significant cause of neonatal morbidity and mortality.[33,88] Fungal infections are the third most common infection after 72 hours of life in infants weighing less than 1500 g.[33,88,141] Prevalence rates vary from 33% in the NICHD cohort[141] to 35% in a more recent 15 year retrospective Italian study.[88] Candida species are the most common in Europe and America[20] (44% in a recent Italian epidemiologic study),[88] and other species predominate in Asia.[20] Of the 4% to 8% of ELBW infants who develop candidemia, there is a 30% mortality rate.[148] Both the incidence and mortality rate of invasive fungal infection is inversely related to birth weight and gestational age.[75] Survivors of invasive fungal disease have long-term neurodevelopmental impairments.[5,14]

In addition, fungal infections are usually seen in infants with congenital anomalies requiring surgery or infants who require multiple or prolonged vascular catheterization.

Prevention. Because these infants are often colonized at birth, strict adherence to aseptic technique when dealing with central catheters is essential. Use of broad-spectrum antibiotics (e.g., cephalosporins), administration of histamine$_2$ (H2) receptor blockers, and use of corticosteroids are significant risk factors, and their use should be minimized.[33,75,133]

One study of 322 NICUs found the incidence of invasive fungal infections decreased from 3.6 episodes/1000 infants in 1997 to 1.4 episodes/1000 infants in 2010.[8] This reduction is attributed to reduced use of broad-spectrum antibiotics, fluconazole prophylaxis, fewer CLABSIs, and empirical antifungal therapy.[8,75]

Intravenous fluconazole prophylaxis reduces the incidence of invasive fungal infection in very preterm or VLBW neonates; however the meta-analysis does not show a statistically significant effect on mortality.[35] Antifungal prophylaxis should be used for preterm infants < less than 27 weeks' gestational age and less than 1000 g birth weight because intravenous fluconazole (at 3 mg/kg twice a week) and nystatin are effective in the prevention of invasive candida sepsis, improving survival and neurodevelopmental outcomes.[74,114,129] The lowest dose of fluconazole is recommended as higher dosing does not increase efficacy and increases the risk of toxicity and costs.[85]

A recent systematic review and meta-analysis of RCTs showed that the use of enteral probiotics is associated with a lower risk of candida colonization.[69] When one of the seven studies was removed from meta-analysis because of high baseline fungal infections, only limited data showed that probiotic supplementation prevented invasive fungal infection in preterm neonates.[69]

Data Collection

History. Prematurity (less than 32 weeks' gestational age), Apgar score less than 5 at 5 minutes, shock, antibiotic therapy, parenteral nutrition for longer than 5 days, use of lipids for longer than 7 days, presence of a central catheter, length of hospital stay longer than 7 days, use of H2 blockers, and intubation are risk factors for fungal infections.[33,88,72,133]

TABLE 22.11 ANTIFUNGAL THERAPY

DRUG	DOSAGE	COMMENTS
Amphotericin B	1 mg/kg/day IV	Nephrotoxicity
Amphotericin B lipid complex	5 mg/kg/day IV over 2 hr	Thrombocytopenia Anemia Hypokalemia
5-Fluorocytosine (5-FC)	100 mg/kg/day PO divided q 6–8 hr	Hepatotoxicity Bone marrow suppression
Fluconazole	3–6 mg/kg/day IV, PO divided q 6 hr	Liver toxicity Adjust for renal function

hr, Hour; *IV,* intravenously; *PO,* orally.

Signs and Symptoms. **Signs and symptoms may be nonspecific, nonlocalizing, and difficult to differentiate from those of bacterial sepsis. Skin and oral infections in high-risk infants, especially in VLBW infants, can become invasive and should be treated.**

Laboratory Data. Routine laboratory data, as may be collected based on clinical signs and symptoms, are rarely helpful in differentiating fungal from bacterial infection. **A positive culture result from urine, blood, CSF, or a skin biopsy indicates systemic infection.** A recent study comparing platelet counts in fungal and bacterial infections found: (1) a significant decrease in platelet count and a higher CRP level in the early stage of fungal infection when compared with bacterial infection and (2) no difference in platelet and CRP counts in the acute stage of fungal and bacterial infections.[164] These researchers found **a high accuracy in the early diagnosis of fungal infection when the platelet count was less than 157.0 × 10^9/L and an effective predictor of invasive fungal infections in preterm infants.**[164]

Urine for analysis and culture, ophthalmologic examination, imaging of the brain by computed tomography scan or magnetic resonance imaging, echocardiogram for endocarditis, and renal ultrasonography for fungal mycetomas are mandatory in disseminated fungal infections.[105]

Treatment. **Supportive care and removal of foci of infection (i.e., infected catheters or fungal mycetomas) are important. Antifungal therapy with amphotericin B is the mainstay of treatment for invasive fungal infections in the neonate.**[114,79] For CNS candidiasis using monotherapy with amphotericin B, if the CSF does not become sterile within a few days or the neonate becomes more ill, 5-fluorocytosine (5-FC) is added. 5-FC has excellent CSF penetration and is reserved for use in combination with amphotericin B in neonates with CNS candidiasis[51] (Table 22.11).

Lipid formulations of amphotericin are available that are less toxic and may be the choice in infants who cannot tolerate standard amphotericin.[6] A recent drug utilization review of liposomal amphotericin B use in neonates cited the weakness of the studies and recommended additional RCTs to determine the true benefits of the drug.[138] **Fluconazole therapy may have efficacy similar to amphotericin but without the toxicity.**[60]

PARENT TEACHING

Parents who have an infant with viral or bacterial infection require support and information about their infant's condition. Questions arise about treatment and prognosis, as well as about possible long-range effects of the infection. Parents experience significant guilt feelings based on misperceptions about what role they had in causing the infection. Health care professionals should remain sensitive to the crisis that parents are experiencing and address the issues of etiology as well as treatment and prognosis. Valid and factual

data, as well as information about complications and long-term effects, should be shared with parents in a timely manner.

Controlling infection in the nursery is of prime importance but does not exclude parents from caring for their sick infant. Everyone must adhere to proper handwashing, gowning, and isolation techniques.[137] Educating the parents and siblings about the **importance of these procedures, along with appropriate reminders, ensures cooperation. With proper precautions, there is no evidence of increased incidence of infection with parent and sibling visits.**

All those entering the nursery must be screened for the presence of illness. Anyone (including staff) with a fever, respiratory symptoms (cough, runny nose, sore throat), gastrointestinal symptoms (nausea, vomiting, diarrhea), or skin lesions should not come in contact with the infant. People with communicable disease (e.g., varicella) or recent exposure to a communicable disease also should not come in contact with the sick neonate.[19,137] Daily cord care should be demonstrated, and a demonstration by the parents should be observed before discharging the infant. ***Every* parent should be taught the signs and symptoms of neonatal illness, because early recognition of signs and symptoms expedites prompt treatment. Parents must be taught to take axillary temperatures and to read a thermometer. They should be aware that both hypothermia and hyperthermia may be signs of neonatal illness.**[19,137]

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23 RESPIRATORY DISEASES

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Despite the marked improvement over the past years in the survival of premature newborns with respiratory distress, significant mortality and high morbidity rates persist. Much of the improvement in neonatal mortality has been the result of successful treatment and management of respiratory diseases in the neonate.

This chapter presents an overview of some of the common respiratory diseases and their treatments and outcomes. General principles and concepts related to respiratory physiology, etiologic factors, and symptomatology are presented, followed by specific disease processes and their management.

GENERAL PHYSIOLOGY

Any discussion of general respiratory physiology must include some elements of anatomy and embryology and their significance to the clinician (Table 23.1).

Surface-active compounds such as phosphatidylcholine and phosphatidylglycerol stabilize the alveoli. Surface tension forces act on air-fluid interfaces, causing a water droplet to "bead up." The surface-active compound (e.g., soap added to a water droplet) reduces the surface tension and allows the droplet to spread out in a thin film. **In the lung, surface tension forces tend to cause alveoli to collapse. A compound such as surfactant reduces surface tension and allows the alveoli to remain open.**

However, the situation is more complicated than just described. Laplace detailed the magnitude of the pressure (p) exerted at the surface of an air-liquid interface as equaling twice the surface tension (st) divided by the radius (r) of curvature of the surface ($p = 2\ st \div r$). In the absence of surfactant, an alveolus with a small radius of curvature has a greater magnitude of pressure at its surface (tending to collapse it) than does an alveolus with a larger radius of curvature. **Therefore smaller alveoli tend to collapse and empty contained gas into larger alveoli.**

Surfactant modifies surface tension by decreasing surface tension when the radius of curvature is small and increasing surface tension when the radius of curvature is greater. An alveolus with a larger radius of curvature has a greater-than-expected pressure (tending to reduce its volume), and an alveolus with a smaller radius of curvature has less-than-expected pressure. Therefore the alveoli are stabilized at a uniform radius of curvature (uniform volume).

Surfactant provides a number of useful properties in addition to reducing surface tension, which increases lung compliance, provides alveolar stability, and decreases opening pressure. It also enhances alveolar fluid clearance, decreases precapillary tone, and plays a protective role for the epithelial cell surface. **Surfactant is constantly being formed, stored, secreted, and recycled. Conditions that interfere with surfactant metabolism include acidemia, hypoxia, shock, overinflation, underinflation,**

BLUE type highlights content that is particularly applicable to clinical settings.

TABLE 23.1 LUNG DEVELOPMENT

STAGE AND MAJOR EVENTS	SIGNIFICANCE
Embryonic (Up to 5 Weeks)	
Single ventral outpocketing quickly divided into two lung buds.	Airways begin to differentiate.
Mesenchyme surrounds endodermal lung buds, which continue to divide and extend into the mesenchyme.	
Branching of the airways begins.	Branching anomalies (e.g., pulmonary agenesis and sequestered lobe) occur early in fetal life.
Pulmonary arteries invade lung tissue following the airways and divide as the airways divide. Pulmonary veins arise independently from the lung parenchyma and return to the left atrium, thus completing the pulmonary circuit.	
Pseudoglandular (5-16 Weeks)	
Progressive airway branching begins; bronchi and terminal bronchioles form.	All subdivisions that will form airways are complete by the sixteenth week.
Muscle fibers, elastic tissue, and early cartilage formation can be seen along the tracheobronchial tree. Mucous glands are found at 12 weeks and increase in number until 25-26 weeks, when cilia begin to develop.	
Diaphragm develops.	Herniation of the diaphragm occurs.
Canalicular (13-25 Weeks)	
Airway changes from glandular to tubular and increases in length and diameter.	Air-conducting portion (bronchi and terminal bronchioli) continues luminal development.
20 Weeks	
Fetal airways end in blind pouches lined with cuboid epithelium; a relatively large amount of interstitial mesenchyme is present; few pulmonary capillaries are present, and they are not closely associated with the respiratory epithelium.	
22-24 Weeks	
Rapid proliferation of the pulmonary capillary bed, an increase of the surface area of the respiratory epithelium, and formation of alveolar ducts and sacculi occur.	Development of gas exchange portion (the respiratory bronchi and alveolar ducts) begins; pulmonary vasculature develops most rapidly.
Respiratory epithelium contains cells that become differentiated into type I and type II pneumocytes.	
Type I pneumocytes produce an extremely thin squamous epithelial layer that lines the alveoli and fuses to the underlying capillary endothelial cells.	By the late fetal period, the resulting membrane between the alveoli and capillaries allows sufficient gas exchange to support independent life.
Type II pneumocytes (cuboid cells) are the site of surfactant synthesis and storage.	At 22 weeks, surface-active phospholipids (lecithin) can first be detected.
Terminal (24-40 Weeks)	
Lung differentiation: proliferation of the pulmonary vascular bed, creation of new respiratory units (alveolar ducts and alveoli), decrease in amount of mesenchyme, and fusion of the gas-exchange epithelium to the pulmonary capillary epithelium occur.	Before this time, the fetal lungs are incapable of supporting adequate gas exchange because of insufficient alveolar surface area and inadequate pulmonary vasculatur.

TABLE 23.1 LUNG DEVELOPMENT—CONT'D

STAGE AND MAJOR EVENTS	SIGNIFICANCE
34-36 Weeks	
Phosphatidylglycerol appears, and a dramatic increase in the principal surfactant compound phosphatidylcholine occurs.	Adequate amounts of surface-active material protect against the development of respiratory distress syndrome.
Alveolar (Postnatal Lung Development: Late Fetal Life to 8-10 Years of Age)	
At term, the number of airways is complete; there is sufficient respiratory surface for gaseous exchange, and the pulmonary capillary bed is sufficient to carry the gases that have been exchanged.	Although the infant is capable of sustaining respiratory effort and the lung is able to provide oxygenation and ventilation at birth, lung development is still incomplete.
Alveoli continue to increase in number, size, and shape; they enlarge and become deeper to maximize the exposed surface area for gas exchange.	Ongoing lung development implies that infants who have suffered severe lung disease at birth need not have lifelong pulmonary compromise.

pulmonary edema, mechanical ventilation, and hypercapnia. Surfactant production is delayed in infants of diabetic mothers (IDMs) of classes A, B, and C; infants with erythroblastosis fetalis; and infants who are the smaller of twins. Surfactant production is accelerated in the following:

- IDMs of classes D, F, and R
- Infants of heroin-addicted mothers
- Premature rupture of membranes of greater than 48 hours' duration
- Infants of mothers with hypertension
- Infants subjected to maternal infection
- Infants suffering from placental insufficiency
- Infants affected by administration of corticosteroids
- Infants affected by abruptio placentae

The fetal lung is filled with a volume of liquid (20 to 30 mL/kg) equal to the functional residual capacity. This fluid is not amniotic fluid but rather a liquid that has been produced in the lung and discharged through the larynx and mouth into the amniotic fluid. **Lung fluid is continuously produced at a rate of approximately 2 to 4 mL/kg/hr.**

The movement of lung fluid and its components (notably lecithin) into amniotic fluid has become a notable clinical tool as the lecithin-sphingomyelin (L/S) ratio. Noting a sharp increase in the L/S ratio, Gluck and Kulovich[185] found they could predict which infants were at risk for respiratory distress syndrome (RDS). In general, **L/S ratios of more than 2:1 are not associated with RDS, whereas ratios of less than 2:1 are associated with it.** Phosphatidylglycerol (PG), the second most common phospholipid in surfactant, appears at about 36 weeks' gestation and increases until term. **The presence of PG is associated with a very low risk for RDS, whereas its absence is associated with the development of RDS.** Unlike the L/S ratio, **PG determination is valid in the presence of blood-contaminated amniotic fluid.**

During vaginal delivery, approximately one third of the lung fluid may be removed during the thoracic "squeeze" as the infant passes through the birth canal; the remainder of the fluid is removed mainly by the pulmonary lymphatics, although pulmonary capillaries may play a role. After a cesarean section, all of the lung fluid will be removed by the pulmonary lymphatic system, capillaries, and reversal of the sodium and chloride pumps.

The *first breath of life,* a response to tactile, thermal, chemical, and mechanical stimuli, initiates respiratory effort. The fluid-filled lungs, surface forces, and tissue-sensitive forces are obstacles to the first breath. At birth, gas is substituted for liquid to expand the alveoli. Lung ultrasounds at the **first breath(s) of life in neonates born (by vaginal and C-section) at 35 or more weeks' gestation found 89% fluid clearance at the 1 to 10 minute examination and complete fluid clearance at the 11 to 20 minute examination in all the infants.**[57] After the alveoli are "opened" during the first few breaths, a film of surfactant-active material stabilizes the alveoli.

The first breath of life requires an opening pressure of 60 to 80 cm H_2O to overcome the effects of the surface tension of the air-liquid interface, particularly the small airways and alveoli. Thus on each subsequent breath, less pressure is necessary to allow for a similar increase in air volume in the lung. The effort of breathing is lessened with subsequent breaths.

GENERAL ETIOLOGIC FACTORS

Respiratory disease **may be defined as a progressive impairment of the lungs to exchange gas at the alveolar level.** Although the pathologic process causing respiratory distress in the neonate may occur in any portion of the respiratory system, **the final common pathway in respiratory disease is impairment of gas exchange.**

Prematurity is the single most common factor in the occurrence of RDS. Its incidence is inversely proportional to gestational age (GA) and occurs most frequently in infants of less than 1200 g and 30 weeks' gestation. **RDS occurs in male infants twice as frequently as in female infants (2:1). The principal factor operating in the development of RDS in very premature infants is surfactant deficiency.**

Multiple gestations increase the risk for respiratory disease related to lung maturity in the second, third, or more siblings. The second and subsequent infants may experience perinatal asphyxia, malpresentation, or mode of delivery (e.g., cesarean section) that contributes to respiratory disease. Grand multiparity is associated with increased risk for respiratory disease, particularly when other siblings have had RDS.

Prenatal maternal complications increase the risk for respiratory disease in the infant. Maternal illnesses such as cardiorespiratory disease, hypoxia, hemorrhage, shock, hypotension, or hypertension result in decreased uterine blood flow with subsequent hypoxia or ischemia at the placental level. Severe maternal anemia causes fetal cardiac depression and respiratory depression. Maternal diabetes may result in preterm delivery because of fetal and maternal indications. There is also a greater incidence of false-positive L/S ratios in diabetic populations. There has been a propensity of IDMs to develop RDS despite documentation of L/S ratios greater than 2:1. (A combination of an L/S ratio of 2:1 or greater and the presence of PG confirms fetal lung maturity.) Abnormal placental conditions (compressed umbilical cord caused by prolapse or breech delivery, placental disease such as infarcts or syphilis, or hemorrhage as a result of placenta previa or abruption placentae) affect oxygen transfer from mother to fetus and result in asphyxial insult to the developing fetal lung. Premature rupture of the membranes predisposes the fetus or newborn to the development of infections such as pneumonia, sepsis, or meningitis. **Premature or prolonged rupture of the membranes not associated with neonatal infection accelerates fetal lung development and thereby lessens the incidence of RDS.** Maternal toxemia and maternal drug addiction also hasten fetal lung maturation. **Antenatal administration of glucocorticoids[372] results in less severe RDS and fewer doses of surfactant, fewer cases of patent ductus arteriosus (PDA) and intraventricular hemorrhage (IVH), and lower mortality rates.**

Factors affecting the fetus during the birth process may lead to respiratory distress. Depression of the respiratory center can occur as a result of maternal medications that cross the placenta. An infant delivered shortly after analgesics, anesthetics, or magnesium sulfate is administered to the mother may have only minimal respiratory efforts at birth. Excessive uterine activity, usually as a result of oxytocin induction or augmentation of labor, may result in decreased uterine blood flow, late fetal heart deceleration, and respiratory depression in the infant at birth. Respiratory distress may be the result of direct trauma to the respiratory center or a cerebral hemorrhage in proximity to it. Fetal shock caused by difficult labor or dystocia, tight nuchal cord, cerebral hemorrhage, or hemorrhage from the fetal side of the placenta results in central nervous system (CNS) depression and hypoxia. Bleeding results in a generalized hypovolemic condition characterized by decreased oxygen-carrying capacity. Fetal or neonatal asphyxia and blood loss lead to progressive respiratory distress. After cesarean birth, retention and slower absorption of lung fluid through circulatory and lymphatic channels contributes to a higher incidence of transient tachypnea of the newborn.

The timing of cesarean section influences the incidence of RDS. Recent studies noting the increased risk of late-preterm infants and RDS in elective cesarean sections are cited in Chapter 5.

Obstruction of the airway caused by aspiration of meconium or amniotic fluid occurs before

birth, spontaneously at birth, or during resuscitative efforts. Although the lungs initially fill with air, subsequent atelectasis occurs as airway obstruction prevents further entrance of air. Conversely, a "ball-valve" or "air-trapping" effect may occur as air is allowed in but is unable to escape because of intermittent obstruction. The presence of amniotic debris, vernix, lanugo, and meconium in the respiratory tract increases the incidence and severity of pulmonary infection. Diaphragmatic paralysis occurs after phrenic nerve injury during birth (usually in a large-for-gestational-age [LGA] infant) and is often associated with brachial plexus injuries. The paradoxic movement of the paralyzed diaphragm during inspiration and expiration results in inadequate tidal volume and impaired gaseous exchange.

Existing neonatal conditions increase the risk for respiratory distress. Congenital defects that prevent transmission of the stimulus to or from the respiratory center, prevent normal respiratory effort, reduce gas-exchange surface area, or hamper the delivery of oxygen to the site of exchange will predispose the infant to respiratory compromise. Such defects include heart or great vessel anomalies, diaphragmatic hernia and hypoplastic lung, respiratory tract anomalies (e.g., choanal atresia or tracheoesophageal fistula), chest wall deformities, and CNS defects.

Diseases of the infant also can lead to respiratory distress. Hemolytic disease, such as ABO and Rh incompatibility, results in anemia and, if severe, in hypovolemic shock. Blood incompatibilities may cause respiratory distress by decreasing the oxygen-carrying capacity of the blood. Infections stress the body's systems, increase oxygen requirements, and contribute to an impairment of surfactant production. Chronic lung disease in the form of bronchopulmonary dysplasia (BPD) occurs as a result of therapies used to treat respiratory disease. Prolonged treatment of RDS may be necessitated by the severity of the disease but may increase the risk for developing chronic lung disease.

GENERAL PREVENTION

Antepartum

Prevention of respiratory disease begins with prevention of the conditions that predispose to respiratory distress. These conditions that constitute "reproductive risks" have been identified and can be categorized as psychosocial, genetic, biophysical, or economic in nature. Once an individual is identified as being in a high-risk category, comprehensive prenatal care with immediate attention given to maternal complications that arise is crucial (see Chapter 2).

Intrapartum

Fetal well-being is assessed by use of electronic monitoring of uterine activity, fetal heart rate, and fetal scalp blood sampling. Electronic fetal heart rate monitoring enables instantaneous fetal heart rate tracings that provide coincident correlation between uterine contractions and fetal response. These tools enable the practitioner to evaluate how well the fetus withstands the stresses of labor and to make decisions about the laboring course.

Fetal cardiac response to stress is unlike an older child's or adult's response to hypoxia, hypercapnia, and acidosis with tachycardia from sympathetic nervous system discharge. A fetus responds to these same stresses with an initial increase in heart rate that is quickly followed by bradycardia from parasympathetic stimulation when the hypoxia, hypercapnia, and acidosis persist (see Chapter 2).

Postpartum

After delivery, an infant should be maintained in an environment that minimizes stress and thereby minimizes oxygen requirement. All infants, but particularly at-risk infants, should be maintained within the narrow parameter of physiologic homeostasis (as outlined in Unit Two, Support of the Neonate).

GENERAL DATA COLLECTION

Because the clinical manifestations of many neonatal illnesses include respiratory symptoms (cardiac, metabolic, neurologic, and hematologic), a systematic and thorough approach to data collection is essential in evaluating an infant in respiratory distress.

History

The perinatal history (antepartum, intrapartum, and postpartum) should be reviewed for risk factors (see Chapter 2).

Signs and Symptoms

Vital signs such as temperature, pulse, respiration, and blood pressure should be evaluated. Hypothermia and hyperthermia increase oxygen requirements by altering the basal metabolic rate. Hypotension is often associated with respiratory distress.

RESPIRATORY EXAMINATION

Respiratory effort is normally irregular in rate and depth and is chiefly abdominal, rather than thoracic, with a **rate of 30 to 60 breaths/min.** A recent study of the respiratory rates of healthy term infants at 2 hours of age found: (1) median rates of 46 breaths/min, (2) at the 95th percentile, rates of 65 breaths/min, and (3) at the 5th percentile rates of 30 to 32 breaths/min.[531] In this study, respiratory rates increased with being awake, being a boy, and being born after heavy meconium-stained amniotic fluid. There was **no difference in respiratory rates between vaginal and cesarean births.**

Bradypnea is characterized by a rate below 30 breaths/min that is regular (as opposed to periodic or apneic) and may be caused by an insult to the respiratory center of the CNS. **Tachypnea, a rate of 60 breaths/min or greater after the first hour of life, is the earliest sign of respiratory (and often other) diseases.** As a compensatory mechanism, tachypnea attempts to maintain alveolar ventilation and gaseous exchange. As a decompensatory mechanism, tachypnea increases oxygen demand, energy output, and the "work" of breathing.

Periodic respirations are cyclic respirations of apnea (5 to 10 seconds) and ventilation (10 to 15 seconds). The average respiratory rate is 30 to 40 breaths/min. Periodic breathing is a common occurrence in small preterm infants as a result of an immature CNS. **Apnea is a nonbreathing episode lasting longer than 20 seconds and accompanied by physiologic alterations.** The syndrome of apnea is discussed under Apnea later in this chapter.

Use of accessory muscles of respiration is indicative of a marked increase in the work of breathing. Retractions reflect the inward pull of the thin chest wall on inspiration. Retracting is best observed in relation to the sternum (substernal and suprasternal) and the intercostal, supracostal, and subcostal spaces. The increased negative intrathoracic pressure necessary to ventilate the stiff, noncompliant lung causes the chest wall to retract. This further compromises the lung's expansion. **The degree of retraction is directly proportional to the severity of the disease.**

Nasal flaring is a compensatory mechanism that attempts to take in more oxygen by increasing the size of the nares and thus decreasing the resistance (by as much as 40%) of the narrow airways. **Grunting is forced expiration through a partially closed glottis.** The audible grunt may be heard with or without the aid of a stethoscope. **As a compensatory mechanism, grunting stabilizes the alveoli by increasing transpulmonary pressure and increases gaseous exchange by delaying expiration.**[212]

Color is normally pink within the first 10 minutes of life. *Acrocyanosis,* **which is peripheral cyanosis of the hands and feet in the first 24 hours of life, is normal. Pallor** with poor peripheral circulation may indicate systemic hypotension. **Ruddy, plethoric skin color** may indicate hyperviscosity, polycythemia, or both as the cause of respiratory symptoms. However, the lack of a deep-red coloring does not rule out polycythemia or hyperviscosity.

Cyanosis, a late and serious sign, is a blue discoloration of the skin, nail beds, and mucous membranes. Differentiation between **peripheral cyanosis** (of hands and feet) and **central cyanosis** (of mucous membranes of mouth and generalized body cyanosis) is essential. **Because a large decrease in PaO_2 may be tolerated without detectable cyanosis, the lack of cyanosis does not ensure a healthy infant.** When hypoxemia reaches a level that produces frank cyanosis, the insufficiency is usually in advanced stages (see Chapter 8). Therefore cyanosis or its lack is not a reliable sign in neonates.

Symmetry of the newborn chest is characterized by a relatively round or barrel shape, because the anteroposterior diameter equals the transverse diameter. With prolonged respiratory distress, there is an increase in the anteroposterior diameter, so the neonate becomes *pigeon-chested.*

Auscultation of a newborn's chest includes comparing and contrasting one side with the other and noting the quality of breath sounds and the presence or absence of rales, rhonchi, or other abnormal sounds. Because of the relatively small size of the newborn's chest, it is hyperresonant, so breath sounds are widely transmitted. **Therefore one cannot always rely on auscultation to detect**

pathologic conditions (e.g., pneumothorax). Percussion of the chest to determine the presence of air, fluid, or solids may not be useful in the neonate because of small chest size and hyperresonance. Palpation of the neonatal chest wall while the infant is crying may detect gross changes in sound transmission through the chest. **Palpation of crepitus in the neck, around the clavicles, or on the chest wall suggests the complication of air leak.**

NONRESPIRATORY EXAMINATION

Hypotonia is characterized by a froglike positioning and a lax, open mouth. Progressing from flexion to flaccidity indicates progression of hypoxia and exhaustion from the work of breathing. Cardiac and related findings such as a murmur, absence of pulses, bounding pulses, palmar or calf pulses, weight gain, hepatosplenomegaly, cyanosis, edema, bradycardia, or tachycardia indicate congestive heart failure or congenital heart defects. **A scaphoid abdomen indicates a diaphragmatic hernia.**

Laboratory Data

Because the clinical presentation of many respiratory and nonrespiratory diseases is the same, a **chest x-ray examination** may be the only way to differentiate cause and establish the proper diagnosis. X-ray evaluation helps eliminate congenital anomalies (e.g., diaphragmatic hernia with lung hypoplasia, masses, and obstruction) as the cause when acquired respiratory disease (e.g., RDS, transient tachypnea of the newborn, and pneumonia) is the cause of the distress. X-ray films confirm the presence of pneumothorax or other pulmonary air leaks.

Measurement of arterial blood gases is used to demonstrate alterations in oxygenation and acid-base balance and to differentiate between respiratory and metabolic components. Initial baseline values are followed by serial observations at least every 15 to 30 minutes after any change in therapy during the acute phase of illness. **Pulse oximetry enables immediate evaluation of oxygenation status and is an adjunct to arterial blood gas sampling.**[15] **A *shunt study* may differentiate between lung origin and cardiac origin of respiratory distress.** The symptoms of pulmonary disease (cyanosis and low PaO_2) are often alleviated with crying, increased FiO_2, or continuous positive airway pressure. If the same symptoms are cardiac in origin, they remain unchanged or worsen with these interventions. Administration of 100% FiO_2 for 10 minutes or longer may result in an increased PaO_2 (greater than 100 mm Hg), whereas in cardiac disease caused by right-to-left shunting, there is no change in PaO_2 after 100% FiO_2 administration.

CAUTION: In the presence of severe lung disease with significant right-to-left shunting, cyanosis and PaO_2 may not be changed with 100% FiO_2.

The **hematocrit value is used to rule out anemia or polycythemia** as the cause of the respiratory distress. In anemia, inadequate oxygen content promotes tissue hypoxia. In polycythemia, increased viscosity and sludging of blood flow adversely affect tissue oxygenation.

The white blood cell count, differential, and C-reactive protein (CRP) (see Chapter 22) aid in diagnosing sepsis as the cause of distress. A blood culture is an invaluable aid when infection is suspected and should be obtained before antibiotic therapy is initiated. **Blood glucose** determination to rule out hypoglycemia as a cause is particularly important in IDMs, small-for-gestational-age (SGA) infants, LGA infants, and preterm appropriate-for-gestational-age (AGA) and late-preterm infants. An **electrocardiogram (ECG), echocardiogram, and cardiac catheterization** are used to rule out cardiac abnormalities.

An electroencephalogram (EEG) and ultrasonographic examination of the brain help rule out CNS abnormalities. **Serum electrolytes** (calcium, sodium, and potassium) aid in eliminating metabolic aberration as the cause of the distress.

GENERAL TREATMENT STRATEGIES

Treatment of any condition should be directed at correction of its underlying cause. In meconium aspiration syndrome, the presence of meconium damages the neonatal lung. No therapeutic measure is available at present to augment the healing process. Therapy is thus directed at preventing or alleviating the consequences of neonatal lung diseases, such as hypoxemia and acidemia, allowing healing to take place and reducing the potential for iatrogenic complications.

Respiratory support is the hallmark of treatment of neonatal respiratory disease. Respiratory support involves increasing inspired oxygen tensions and providing ventilation, if necessary.

Supplemental Oxygen

Oxygen is a *drug*, the most commonly used drug in neonatal care. Historically, the policy of unrestricted and unmonitored oxygen therapy was accompanied by potential harm (e.g., RDS, chronic lung disease [BPD/CLD], retinopathy of prematurity [ROP] [discussed in Chapter 31], PDA [see Patent Ductus Arteriosus later in this chapter], necrotizing enterocolitis [NEC] [discussed in Chapter 28], and IVH/periventricular leukomalacia, hypoxic-ischemic encephalopathy [PVL, HIE] [discussed in Chapter 26]) from oxygen free radicals without clear benefits).

Free radicals are continuously produced in all cells as a byproduct of cell metabolism. Free radicals have positive effects in normal physiologic processes as follows: (1) biologic defense against bacteria, viruses, and cancer cells; (2) vasodilation; (3) neurotransmission; and (4) the up-regulation of some genes.[28] However, free radicals may also have harmful effects. **Free radicals, highly reactive atomic molecules with unpaired electrons, regain their stability by quickly reacting with other molecules in proximity to obtain the molecules they need. Reaction with free radicals causes damage to these close molecules by changing their structure and function.** To maintain homeostasis, the human body either uses or counters free radical activity with endogenous and exogenous antioxidants. Neonates, especially preterms, have maturational deficiencies in endogenous antioxidant systems, nutritional issues altering exogenous dietary intake of antioxidants, and diseases/conditions requiring interventions that preclude control of free radical–generating stimuli in their environment.[28] **Therefore the neonatal period is an especially vulnerable time for free radical damage and injury.[526] Neonates, especially preterms and sick term infants, depend on care providers to use strategies that emphasize the prudent use of oxygen therapy (e.g., use of the minimum amount of oxygen to provide the desired therapeutic effect),[28,193,526] because the proper concentration of supplemental oxygen, especially for extremely preterm infants, remains to be established.[20,61,503]** Neonatal animal modeling of hyperoxia lung injury shows a direct relationship between oxygen concentration and severity of alveolar simplification.[369]

When the neonate cannot maintain adequate oxygenation, supplemental oxygen must be provided. Because oxygen is a drug, it must be treated as such and given only for specific indications (Box 23.1). Institutional protocols for ordering, delivering, monitoring, and documenting oxygen therapy are recommended.[15]

BOX 23.1 CRITERIA THAT INDICATE A NEED FOR SUPPLEMENTAL OXYGEN

Biochemical

Hypoxemia: PaO_2 <60 mm Hg

Asphyxia: progressive hypoxemia, hypercarbia, and acidosis

Clinical

Respiratory distress: Tachypnea
- Grunting
- Flaring
- Retractions
- Apnea

Activity: decreased/no response to painful stimuli; lack of spontaneous activity

Hypotonia and saturation: PO <90%

Hypoperfusion: low blood pressure and/or prolonged CRT >3 seconds

Central cyanosis: perioral, mucous membranes of gums/lips, skin, periorbital

CRT, Capillary refill time; *PO*, pulse oximetry.

Regardless of the mode of delivery (hood, nasal cannula or prongs, endotracheal tube [ETT], bag, or mask), safe and effective oxygen administration follows certain principles outlined in Table 23.2.

OXYGEN TARGETING FOR THE VERY-LOW-BIRTH-WEIGHT PRETERM INFANT

Because an infant who is hyperoxic (PaO_2 greater than 80 mm Hg) clinically looks no different from an infant whose PaO_2 is normal, **monitoring of oxygen saturations and partial pressure of oxygen with arterial blood gases is mandatory whenever oxygen is administered.** Because PO gives immediate and continuous data, fewer PaO_2 values are obtained, so interpretation of PO readings and their relationship to PaO_2 values is critical. **Because PO saturations higher than 92% can often be associated with hyperoxia (e.g., PaO_2 greater than 80 mm Hg),** cohort[540] studies demonstrated a significant reduction in the incidence of ROP and BPD/CLD in preterms when their oxygen saturations were maintained in the lower (SpO_2 89% to 94%) rather than the higher range (SpO_2 96% to 99%).

TABLE 23.2 PRINCIPLES OF OXYGEN ADMINISTRATION

PRINCIPLE	RATIONALE
No concentration of oxygen has been proved to be "safe."	A concentration (e.g., 30%, 50%, 80%, 100%) that is therapeutic for one infant may be toxic for another.
Oxygen blenders must be available wherever oxygen is being administered (e.g., delivery room, transition nursery, level I, II, III, IV nursery).	Enables the delivery of different amounts of inspired oxygen concentrations[28,193]
Oxygen must be titrated to the individual needs of each newborn so that the infant is maintained in a normoxic state, avoiding both hypoxemia and hyperoxemia.[276] Acutely ill neonates requiring supplemental oxygen therapy also should have blood pH and $PaCO_2$ measured.[15]	Maintaining normoxia results in effective pulmonary vasodilation, thus preventing PPHN.[292] Normoxia is measured preductally by: Arterial PaO_2 levels between 60 and 80 mm Hg Pulse oximetry levels between 92% and 94% or as high as 90% -97%[292] (see section on oxygen targeting: 90%-95%) If a newborn has a *diagnosed* cyanotic congenital heart defect, a PO level below 90% or a PaO_2 level below 60 mm Hg is "tolerated" because the shunting in the heart and the admixture of oxygenated and unoxygenated blood prohibit a higher PO or PaO_2 level.
Titrate inspired oxygen concentrations to the individual neonate's need by continuous noninvasive pulse oximetry wherever oxygen is being administered (e.g., delivery room, transition nursery, level I, II, III, IV nursery).	**Oxygen administration without some form of continuous monitoring of the individual infant's oxygenation level is dangerous and not recommended.**[15]
Evaluation of the color of a neonate (e.g., pink or cyanotic) as an indicator for the need for or lack of need for oxygen was used prior to the development of modern monitoring devices. The practice of "eyeballing oxygen"—administering oxygen in concentrations just sufficient to abolish cyanosis—was used to titrate oxygen between blood gases in facilities without blood gas capability and prior to pulse oximetry.	**Because of the presence of fetal hemoglobin, the neonate's color is a poor indicator of oxygenation status: cyanosis is a *late* sign of hypoxemia and being pink in color does not mean that a newborn is well oxygenated.** **Central cyanosis of the mucous membranes of the mouth, around the eyes (periorbital cyanosis), and generalized cyanosis (blue discoloration of the skin and nailbeds) is pathologic and must be distinguished from peripheral cyanosis (acrocyanosis of the hands and feet).** **Central cyanosis is a *late* and serious sign because a large decrease in PaO_2 may be tolerated by the neonate (with fetal hemoglobin) without detectable cyanosis. When hypoxemia reaches a level that produces frank cyanosis, the insufficiency of oxygen is at an advanced stage.** For example: a neonate with a PaO_2 of 35 mm Hg will have an oxygen saturation of only 80% and be pink, even though he or she is hypoxic and in need of supplemental oxygen. (See The 30-60-90 rule in Chapter 8.) Lack of cyanosis or the presence of pink skin is not a reliable sign in neonates and does not ensure a healthy, well-oxygenated neonate. **Oxygen administration without some form of continuous monitoring of the infant's oxygenation (e.g., arterial blood gases or pulse oximetry) is dangerous and not recommended.**[15]
Delivered oxygen should be humidified (30% to 40%).	Dry gases are irritating to mucous membranes of the neonatal airway; humidity decreases insensible water loss. To prevent respiratory therapy equipment from becoming a source of infection, humidifiers and tubing should be replaced per institutional and product protocols.
Oxygen should be warmed (31-34° C; 87.8-93.2° F]) so that the temperature at the delivery site is the same as the incubator temperature. **Oxygen delivered by ETT should be warmed to core temperature (i.e., 36.5-37° C [97.7-98.6° F]).**[193]	Warming oxygen prevents cold stress and increased oxygen consumption from blowing cold air in the infant's face or down the ETT.[496] A recent integrative review of the literature of mechanical ventilation in premature infants found that recommended levels of heat and humidification were not maintained.[420]

Continued

TABLE 23.2 PRINCIPLES OF OXYGEN ADMINISTRATION—CONT'D

PRINCIPLE	RATIONALE
The oxygen concentration delivered to the neonate must be monitored by continuous or intermittent sampling (at least every hour) and recorded. Additionally, hourly documentation of the following parameters should also be recorded: • PO saturation values • Mode of oxygen delivery (e.g., hood, nasal cannula, CPAP, CMV HFV) • Amount of oxygen being delivered (e.g., FiO_2, liter flow/minute)[14]	The concentration of the drug, oxygen, its mode of delivery, and PO saturations are documented interventions.
Oxygen monitors and analyzers should be calibrated according to the manufacturer's recommendations.[15]	Assure accuracy of readings from devices.
Wean cautiously from supplemental oxygen.[496] Adjust FiO_2 in small increments (2%-5%) to avoid hypoxemia and/or hyperoxemia. Adjustment of supplemental oxygen, particularly lowering the oxygen, must be done slowly to avoid the *flip-flop phenomenon.*	*For every 1% decrease in FiO_2 there is a 10 mm Hg decrease in PaO_2.* See Chapter 8 for a discussion of the "rule of seven" which states that the estimated percentage change in inspired oxygen is equal to the desired change in PaO_2 divided by 7. A stable concentration of oxygen is necessary to maintain PaO_2 and PO levels within the desired normal limits. The neonate responds to changes in supplemental oxygen with a *flip-flop phenomenon*—a sudden increase or decrease in oxygen concentration may result in a disproportionate increase or decrease in PaO_2 or PO value caused by vasodilation (increased oxygen) or vasoconstriction (decreased oxygen) in response to oxygen.[496] The closer to term gestation the more developed the musculature around the pulmonary vessels, and the more labile these infants are to deceases in supplemental oxygen and/or receiving oxygen that keeps their PO below 90%.[537] When more mature infants are not given enough oxygen to keep their pulmonary vasculature dilated or have a sudden drop in their oxygenation level—handling, bathing, weighing, discontinuing oxygen to take baby from delivery room to nursery, examinations—a hypoxic insult occurs. Any hypoxic insult may result in: • Pulmonary vasoconstriction, which causes hypoperfusion and increased pulmonary vascular resistance • Opening of the ductus arteriosis • Right-to-left shunting at the DA and the FO • Hypoxemia, hypercarbia, and acidosis • Essentially these changes represent the reversion to fetal circulation—without the presence of the placenta as the organ of gaseous exchange. This persistence or reversion to fetal circulation is the pathophysiology of PPHN. In this population of sick neonates (late-preterm/early term/term), the risk of developing PPHN is higher than the risk of ROP, so that the PO saturation ranges from at least 92%-94% (or 90%-97%)[292] should be maintained to prevent PPHN.
Observe and document color, respiratory effort, activity, and circulatory response in addition to PO saturations and PaO_2 values	Clinical response aids in determining the need for oxygen therapy and for appropriate adjustments.
Clinical observations, FiO_2 concentrations, and time of adjustments must be described, documented, and reported.	Oxygen concentrations should be returned to previous levels if clinical observations of distress and inability to tolerate decreased levels of oxygen occur.

TABLE 23.2 PRINCIPLES OF OXYGEN ADMINISTRATION—CONT'D

PRINCIPLE	RATIONALE
Prone positioning with the head of the bed elevated to a 45 degree angle promotes oxygenation Prone positioning skin-to-skin care with mother/father	See Chapter 13; Box 13.11: Effects of prone positioning on page ***. Gravity assists the abdominal organs to be dependent and not pushing upwards and compromising respiratory excursion. Improves gaseous exchange, especially in preterm infants <1000 g (see Chapter 13)
Place cardiorespiratory monitor and/or pulse oximeter.	PO required for every baby on oxygen and prone positioning requires monitoring device(s) for safety.
Minimize internal stress:	
Maintain in neutral thermal environment and in thermal neutrality to minimize oxygen consumption and oxygen demand.	Hypothermia increases oxygen demand and oxygen consumption in an already stressed neonate needing oxygen.
Maintain adequate blood glucose levels.	Hypoglycemia causes respiratory distress that increases the need for oxygen.
Handle gently and minimally (DO NOT BATHE) to prevent iatrogenic hypoxic episodes that can precipitate PPHN (see PPHN section in this chapter).	Handling a sick neonate for any reason causes a fall in PaO_2 and PO saturations. With handling the PaO_2 variations in the neonate are:[113,161] • At rest ±15 mm Hg variation • Crying: decrease in PaO_2 by as much as 50 mm Hg • Routine care: decrease in PaO_2 by as much as 30 mm Hg
Minimize external stress:	
Minimize painful procedures.	Pain increases heart and respiratory rates and blood pressure and decreases PaO_2 and PO.
Use nonpharmacologic (comfort) interventions for painful procedures that are necessary.	See Chapter 12: Nonpharmacologic (comfort) interventions on page *** for neonatal pain.

C, Centigrade; *CMV,* conventional mechanical ventilation; *CPAP,* continuous positive airway pressure; *DA,* ductus arteriosus; *ETT,* endotracheal tube; *F,* Fahrenheit; *FiO_2,* fraction of inspired oxygen; *FO,* foramen ovale; *HFV,* high frequency ventilation; *PO,* pulse oximetry; *PPHN,* persistent pulmonary hypertension of the newborn; *ROP,* retinopathy of the newborn.

A systematic review and meta-analysis in 2011 found a 50% reduction in severe ROP and a 20% to 25% reduction in BPD/chronic lung disease when the lower rather than higher oxygen saturation range was used.[453] Two studies (STOP-ROP[519] and BOOST[21]) that randomized preterm infants (several weeks after birth) to a lower or higher saturation range also found that **higher saturations resulted in (1) more BPD/CLD, (2) no difference in the progression to threshold ROP, (3) more days on oxygen supplementation, and (4) a higher use of health care resources**.

Five multicenter, multinational trials (SUPPORT,[503] three BOOST II trials,[61] and the COT trial[459]) randomized a total of 4965 premature infants of less than 28 weeks of gestation to low (Spo_2 85% to 89%) or high (Spo_2 91% to 95%) ranges. Outcomes at 2 years corrected age (CA) of preterm infants included in the BOOST-II trial who were randomized to the *lower* saturation group included: (1) nonsignificantly higher rates of death or disability in each trial analyzed separately and (2) a significantly higher rate of death or disability and death alone when both trials were analyzed together.[61] Results of all five trials have recently been systematically reviewed and a final meta-analysis (the NeOProM) performed to determine optimal oxygen saturation targets for preterm infants (mean GA of 26 weeks; mean birth weights of 820 to 850 g).[20] **At 18 to 24 months CA, there was no significant difference between the lower and higher saturation groups in mortality or major disability.**[20] Secondary analysis of the data found **that the *lower* saturation group had: (1) more death prior to 36 weeks' postmenstrual age (PMA), before discharge from the neonatal intensive care unit (NICU) and before reaching 18 to 24 months' CA, (2) a significantly higher risk of severe NEC, and (3) a significantly higher risk of PDA requiring ligation. Preterm infants randomized to the *higher* saturation group had a significantly higher risk of BPD and ROP requiring treatment but no increase in blindness.**[20]

Based on these studies, a survey of 193 NICUs in 27 European countries[234] and the NeOProM systematic review,[20] guidelines for oxygen targeting in preterm infants less than 28 weeks' GA recommend[112,260,454,506]:

- **Target Spo2 between 90% and 95%**

Maintaining ranges between 90% and 95% to avoid hypoxemia/hyperoxemia is an enormous challenge to care providers, especially neonatal nurses. A recent systematic review found that the proportion of time that preterm infants spent outside of designated ranges varied from 8.2% to 22.4%.[331] The narrower target range (90%–95%) is associated with an increase in median SpO_2 and a right shift in the distribution,[542] but there was no change in the time spent between 90% and 95%.

Maintaining oxygen saturations within narrow ranges is labor intensive, with one study finding that **the fraction of inspired oxygen (FiO_2) concentration was adjusted between 16 and 41 times per day, with an average of one adjustment every hour. These researchers noted an increased frequency of prolonged hyperoxia when nurses were each caring for more than one neonate.**[318] Factors influencing clinical decision making about oxygen titration include poor staffing, nursing shortage, and lack of knowledge about oxygen use.[251] A recent study evaluated the incidence of hypoxemia episodes (SpO_2 <75) in 24 mechanically ventilated premature infants to compare the difference between day and night frequency and severity.[241] During the nighttime hours (2100 to 0500), the frequency of mild hypoxemia (SpO_2 <85) and severe and prolonged hypoxemia was less when compared to daytime hours (0900 to 1700). Frequency of severe hyperoxemia (SpO_2 >95%) was greater during the nighttime hours, whereas the mean FiO_2 did not vary between the day and night hours. The researchers concluded that fewer hypoxemia episodes were due to less handling and sensory stimulation at night.

New mechanical devices such as a closed-loop automatic control (CLAC) reduce nursing workload, improve oxygen administration, and automatically control FiO_2 to preterm infants receiving CPAP or mechanical ventilation.[206] **In ventilated preterm infants, automated control of inspired oxygen reduced episodes of hypoxemia and hyperoxemia while maintaining better oxygen saturation ranges.**[296]

Fluctuations of PaO_2 (e.g., hypoxemia and hyperoxemia episodes) in the very-low-birth-weight (VLBW) preterm may be a more significant risk factor than hyperoxia alone for the development of threshold ROP.[587] These episodes of hyperoxia and/or hypoxia may result from the underlying respiratory pathology or the result of care providers' interventions (e.g., positioning; suction; "chasing desaturations by increasing FiO_2"; surfactant administration).

DELIVERY METHODS

For instructions on the bag-and-mask resuscitation method, see Chapter 4. **An oxygen hood is a clear plastic hood that fits over the infant's head to deliver a constant concentration of oxygen.** If the infant has sufficient ventilation to maintain a normal arterial carbon dioxide tension, oxygenation by increased inspired oxygen tensions through an oxygen hood may be the only respiratory support that is necessary. This degree of support is particularly applicable in cases of mild RDS, transient tachypnea of the newborn (TTN), meconium aspiration, or neonatal pneumonia.

A **blender system** is the most reliable way to administer a fixed oxygen concentration via a hood. An appropriate-size hood should be used. If it is too large, the infant may slip out of the hood and FiO_2 may be diluted by leaks; if it is too small, pressure points may develop, especially around the neck. **Another source of oxygen must be provided when the infant's head is removed from the hood because of feeding, being held, or suctioning.** This secondary source may be set up from the blender source so that the infant's PaO_2 remains constant during suctioning or feedings. The infant may need increased FiO_2 from the secondary source. This can be adjusted easily according to assessments made with pulse oximetry, and these changes should be recorded.

For both home and hospital use, a **nasal cannula** (NC) is used to administer oxygen to the dependent infant who is developing social and motor skills:

- **Choose the appropriate-size cannula for the infant**—a cannula that is too large obstructs the nares, prevents air leak thus enabling an increase in CPAP, irritates the nasal mucosa, and is uncomfortable for the baby.[283]
- **Position the cannula across the infant's upper lip.** Secure it to the infant's face by first applying hydrocolloid barrier or transparent dressings directly to the infant's cheeks and taping the cannula to it to prevent skin irritation.

- Oxygen tubing should be long enough to provide opportunities for social and gross motor skill development.

CAUTION: Neonates are obligatory nasal breathers, so nasal obstruction (mucus or milk) will decrease the amount of oxygen actually received. Therefore nares should be suctioned as needed. **Because the exact concentrations of oxygen delivered by cannula cannot be measured, flow rates are titrated by monitoring PaO_2 or pulse oximetry readings and by evaluating the clinical course.**

Two thirds of neonatal centers in the United States, Australia, and New Zealand have adopted **heated, humidified, high-flow (greater than 1 L/min) nasal cannula (HHHFNC) therapy** as **primary respiratory therapy for preterms with RDS, apnea of prematurity, and postextubation respiratory care, including weaning from nasal continuous positive airway pressure (NCPAP).**[154,283,332,430,570] Use of NCs with oxygen rates above 0.5 L/min may result in inadvertent administration of continuous distending (positive) pressure.[326] **HHHFNC generates CPAP to the preterm airway that may be excessive** given the conditions of (1) closed mouth, (2) tightly fitting NC, (3) rate of flow, and (4) infant size (less than 1500 g).[283]

Commercial HHHFNC devices currently in use can achieve flow rates of 4 to 8 L/min.[167] Unlike CPAP devices that are equipped with a pressure gauge and a pop-off safety valve, **HHHFNC devices do not have a direct measure of the pressure applied to the infant's airway** or a pop-off valve to prevent the accumulation of excessive pressure; **flow rates as high as 6 L/min have been used without measurement of the level of CPAP delivered.**[167] **CPAP generated with HHHFNC depends on flow rate and weight; the smallest infants with the highest flow rates and a completely closed mouth may achieve clinically significant and unpredictable levels of CPAP.**[283,571] Several more recent studies have compared HHHFNC and NCPAP by examining the breathing patterns, work of breathing, lung mechanics, gas exchange, pulse oximetry saturations and thoracoabdominal synchrony in a total of 40 preterm infants (27–31 weeks' gestation) and found no significant differences.[305,471]

Improved ventilation and oxygenation with HHHFNC (at flow rates above 2 L/min) with comparable efficacy to use of NCPAP in preterms with RDS have been demonstrated in several observational and retrospective studies.[332,451,475] **Newer studies of the use of HHHFNC versus NCPAP for primary respiratory support in preterm infants with mild to moderate RDS show conflicting results in** Box 23.2. Because of the conflicting research, **a consensus panel issued a report about high-flow nasal therapy use, found in** Box 23.3.

As primary therapy for RDS, HHHFNC has also been compared to nasal intermittent positive-pressure ventilation (NIPPV) in preterms (<35 weeks' gestation and >1000 g birth weight). There was no significant difference in the need for endotracheal intubation/ventilation or the rate of morbidities (i.e., pneumothorax, BPD, IVH, NEC, PDA, or nasal trauma) between the preterms randomized to the HHHFNC or the NIPPV treatment groups.[285] This randomized pilot study also found a longer duration of respiratory support when compared to NIPPV.

NOTE: The use of HHHFNC for postextubation care is discussed under the heading Weaning from the Ventilator later in this chapter.

Continuous Distending Pressure

Continuous distending pressure (CDP) is used for the prevention and treatment of RDS, apnea of prematurity, and weaning from intermittent positive-pressure ventilation. CDP results in less respiratory failure and mortality but an increased rate of pneumothorax.[225] Application of a continuous distending pressure (CDP) to the lungs increases functional residual capacity and PaO_2. Oxygenation is improved by decreasing intrapulmonary shunting and by improving the match of ventilation and perfusion. The application of CDP improves compliance of the lung and lessens the work of breathing.[194] **Early application of CDP in preterms with RDS reduces the subsequent use of intermittent positive-pressure ventilation (IPPV) with its accompanying adverse effects.**

In RDS, in which the functional residual capacity is reduced, increased respiratory oxygen tensions through an oxygen hood (oxyhood) may not be sufficient to maintain an adequate arterial oxygen tension. More invasive techniques may be necessary.

CPAP and continuous negative pressure (CNP) are two methods of delivery of CDP. If the infant cannot maintain a PaO_2 of 60 mm

BOX 23.2 USE OF HEATED, HUMIDIFIED HIGH-FLOW NASAL CANNULA (HHHFNC) AS PRIMARY RESPIRATORY SUPPORT FOR PRETERM INFANTS: RESEARCH EVIDENCE

Advantages

- For preterm infants >28 weeks' gestation, there is no difference in treatment failure (i.e., need for intubation and mechanical ventilation) and no difference in secondary outcomes (i.e., duration of respiratory support, need for surfactant, incidence of pneumothorax or BPD/CLD)[304,593]
- Less nasal trauma and damage[217,337,430,593]
- Stable preterm infants with mild respiratory dysfunction have comparable diaphragm thickness and chest excursion with NCPAP and HHHFNC[157]
- HHHFNC is a safe and efficacious alternative to NCPAP for primary respiratory support for mild to moderate RDS,[216,217,304,593] in treatment of apnea of prematurity,[448] for weaning from CPAP,[485] and for post-extubation failure[484]
- Systematic reviews of the evidence for use of HHHFNC in preterm infants agree that there is no difference in death or BPD/CLD and other morbidities except a need for longer therapy[173,332,570]
- No difference in achieving full oral feedings among VLBW (<1500 g) randomized to HHHFNC or NCPAP[184]

Disadvantages

- Inability to measure pressure of HHHFNC with possibility of air leak and lung injury[337]
- Few studies of HHHFNC use in ELBW infants[337]
- Less effective than NCPAP overall, but effective for the majority of preterms of at least 28 weeks' gestation without surfactant therapy. The HIPSTER trial was halted because of treatment failure (25.5% HHHFNC vs. 13.3% NCPAP failure) that was significant in preterm infants <32 weeks and >32 weeks gestation. There was longer duration of use (4 days vs. 3 days) and more use of supplemental oxygen with HHHFNC.[430]
- Longer use, longer exposure to positive pressure and oxygen[216,227]
- More treatment failures (need for intubation/mechanical ventilation) as a result of more hypoxia among preterm infants (30–35 weeks' gestation) randomized to HHHFNC compared to NCPAP. No difference in respiratory or clinical outcomes and complications between groups.[472]
- Significantly higher treatment failure (need for higher level of respiratory support) among preterm infants with both moderate and severe respiratory distress in the HHHFNC (26.3%) compared to the NCPAP group (7.9%) when used as primary respiratory support[362]
- Case report of tension pneumocephalus as a complication of HHHFNC use[235]
- Chart review of pre and post use of HHHFNC: higher rates of ROP and a trend toward higher rates of BPD/CLD; delayed oral feedings and fewer infants orally feeding at discharge, higher use of intermediate care and longer length of stay among those who used HHHFNC[227]
- Lack of adequately powered RCTs: (1) comparing HHHFNC to other forms of primary respiratory support, (2) for weaning from other forms of noninvasive support, and (3) use varying populations (i.e., ELBW; mildly preterm) populations.[570]
- Lack of evidence that HHHFNC is superior to NCPAP and that it is cost effective[173]
- Lack of large prospective RCTs so that "HHHFNC should not be a routine or first choice of neonatal respiratory support for RDS."[81] (The HUNTER trial in Australia and New Zealand may provide answers because it will be a multicenter [eight non-tertiary centers] RCT of the use of HHHFNC versus NCPAP for primary respiratory support in preterm infants ≥31 weeks' gestation to evaluate safety, efficacy, and cost-effectiveness.[335])

BPD/CLD, Bronchopulmonary dysplasia/chronic lung disease; *CPAP,* continuous positive airway pressure; *ELBW,* extremely low-birth-weight; *HHHFNC,* humidified, high-flow nasal cannula; *NCPAP,* nasal CPAP; *RCT,* randomized controlled trial; *RDS,* respiratory distress syndrome; *ROP,* retinopathy of prematurity; *VLBW,* very-low-birth-weight.

Hg in 0.6 FiO_2, a trial of CPAP through the nasal route is indicated. Initial levels of CPAP should be in the range of 4 to 5 cm H_2O. CPAP should be increased to 8 to 10 cm H_2O by 1 to 2 cm increments if necessary to raise the infant's PaO_2 (as measured by arterial blood gas determinations, noninvasive monitoring, or both).

Not all CPAP application techniques are equal. Neonates receiving "bubble" CPAP experience chest wall vibrations (similar to those seen in high-frequency ventilation [HFV]) that contribute to gaseous exchange. Two studies of the mechanics of bubble CPAP are important for information about maintenance of an adequately functioning system. **Lung volume recruitment and breathing efficiency during bubble CPAP are influenced by the size and depth of submergence of the expiratory limb of a CPAP circuit, the diameter of the bubble generator bottle, and lung compliance.[578] Condensation in the exhalation limb of a patient circuit during bubble CPAP accumulates at the rate of 3.8 mL/hr.[588] When this condensation reaches volumes greater than 10 mL, the oscillating fluid increases airway pressure and results in significant increases in mean tracheal pressure.** These researchers recommend **frequent (i.e., every 2 to 3 hours) emptying of the exhalation tube, continuous monitoring of**

BOX 23.3 CONSENSUS BY CLINICIANS ABOUT ASPECTS OF HHHFNC USE[434,586]

- Adequate heating (37° C)[78] and humidification (100% relative humidity)[82]
- Prevention of nasal occlusion (a nasal prong-to-nares ratio of 50% to 80%)[82]
- Initial flow rates in the range of 4 to 6 L/min with a minimal flow rate of 2 L/min[82] and a maximum flow rate of 8 L/min
- Criteria for escalation or weaning of therapy includes work of breathing and assessment of amount of supplemental oxygen
- Equivalence of high-flow nasal cannula with NCPAP for noninvasive respiratory therapy for preterm infants >28 weeks' gestation with RDS (both initial therapy and resolving RDS)
- Equivalence of high-flow nasal cannula for noninvasive support of stable infants on NCPAP
- No consensus on discontinuation of high-flow therapy

HHHFNC, Humidified, high-flow nasal cannula; *NCPAP,* nasal continuous positive airway pressure; *RDS,* respiratory distress syndrome.

pressure at the nasal airway interface, and using an adjustable pressure-relief valve in the circuit (set to 5 cm H_2O pressure above the desired mean pressure).[588]

***Bubble CPAP* compared with ventilator-derived nasal CPAP (NCPAP) in VLBW infants with moderate RDS has comparable failure rates (need for intubation) with no difference in complication rates (i.e., IVH and mortality).**[4] When 170 preterm infants (<34 weeks' gestation) were randomized to jet CPAP or bubble CPAP, failure rates at 72 hours were similar between the two groups.[56] Another comparison of bubble and jet CPAP in preterm infants under 34 weeks' GA found that those using bubble CPAP had more nasal injury.[268] Bubble CPAP is a low-cost device for developing countries that decreases neonatal mortality.[258,339,363,444]

High-amplitude bubble NCPAP (called Seattle PAP) provides different support from conventional bubble CPAP by changing the angle of the exhalation limb and decreasing the work of breathing.[563,564] The esophageal pressures of 40 preterm infants under 32 weeks' gestation were measured after 2 hours of conventional bubble NCPAP and then after 2 hours of Seattle PAP. Use of the high-amplitude Seattle PAP resulted in a lowered effort of breathing with no adverse effects (pneumothoraces or nasal trauma).[564] Whether a lowered effort of breathing translates to less morbidity and mortality awaits further study.

In one center, use of bubble CPAP from birth in 401 to 1000 g preterms has resulted in (1) fewer delivery room intubations, (2) fewer days on mechanical ventilation, (3) less use of postnatal steroids, (4) better weight gain, and (5) no increase in complications, including the incidence of CLD/BPD.[367] In a randomized controlled trial (RCT), larger preterms (mean GA of 36 weeks; mean birth weight of 2900 g) with respiratory distress were treated with either supplemental oxygen in an oxygen hood or with bubble CPAP through nasal prongs.[70] Only 23% of the larger preterms who were treated with CPAP were transported to a higher-level NICU compared with 40% of the preterms who were treated with oxygen in a hood. Also, cost savings were realized and there was no increase in oxygen use or mortality rate. However, there was a clinically—not statistically—significant increase in the incidence of pneumothorax in the CPAP group; the **24-hour presence of a neonatal nurse practitioner or physician to relieve air leaks is mandatory with the use of CPAP.**

More recent studies of bubble CPAP continue to demonstrate cost effectiveness and better outcomes of preterms with RDS, including extremely low-birth-weight (ELBW) and VLBW preterms.[258,339,363,444] A 7-year retrospective review of respiratory outcomes in 633 VLBW infants found a significant reduction in BPD/CLD (43% lower chance), less mechanical ventilation, and fewer discharged with diuretics and supplemental oxygen after use of bubble CPAP.[174] A subset analysis of the outcomes of ELBW preterms receiving bubble CPAP found a faster extubation rate, fewer days of mechanical ventilation (more ELBW off mechanical ventilation at 1 week of age), less ROP, fewer PDA ligations and deaths, and an increase in low-grade IVHs.[174] Another study found a 27% improvement in survival in a developing country with the use of bubble CPAP, especially in VLBW preterms, those with RDS, or those with sepsis.[258] A small trial (n = 18) of bubble NCPAP verus ventilator NCPAP found no differences in short-term outcomes (vital signs, oxygen saturation) and a nonsignificant difference in decreasing respiratory rate and cerebral fractional oxygen extraction while on bubble NCPAP.[196] A meta-analysis of seven RCTs of nasal bubble CPAP found a reduced failure rate and length of stay.[555] A systematic review of the

use of CPAP in low-and middle-income countries showed that it was safe and effective, and that it reduced mortality, the need for invasive mechanical ventilation, and transfer to a higher level facility, but higher quality evidence and the need for larger studies was recommended.[523]

Large, multicenter RCTs of NCPAP starting at birth include the COIN trial,[355] the SUPPORT trial,[497,503] the VON Delivery Room Management trial,[146] the CURPAP,[448] Colombian Network,[436] and South American Neocosur Network[511] trials. The COIN trial[355] compared NCPAP with intubation and ventilation of 25 to 28 weeks' gestation preterms breathing spontaneously by 5 minutes of age with respiratory distress. Within the first 5 days of life, 46% of those randomized to NCPAP were intubated, at a median of 6.6 hours of life. Outcomes at 36 weeks were no different for either group in the combined outcome of death or oxygen dependence. A nonsignificant trend toward less CLD/BPD occurred in the more mature preterms, whereas there was a trend toward increased mortality rates in the less mature preterms randomized to NCPAP. Unlike other studies, only 77% of the infants randomized to intubation received surfactant, and surfactant use was halved in the NCPAP group.[355] The SUPPORT trial compared immediate CPAP to intubation, surfactant, and mechanical ventilation in 24 to 27⅙ weeks gestation preterms and found fewer ventilator days, less postnatal steroid use, and no difference in air leaks, BPD/CLD, or death.[503] **In the SUPPORT trial, the most immature (24 to 25 weeks' gestation) preterms benefited the most from the early initiation of NCPAP**[503] and had less respiratory morbidity at 18 to 22 months' CA.[497] The CURPAP[448] and Colombian Network[436] trials demonstrated no difference in the rate of BPD/CLD with early CPAP versus prophylactic surfactant. **From these data the American Academy of Pediatrics (AAP) policy statement on respiratory support in preterm infants at birth recommends initiation of NCPAP at birth as an alternative to routine intubation and early surfactant therapy.**[14] **The AAP policy and the evidence-based recommendations of the EPICE group recommends combining early NCPAP with selective surfactant therapy in extremely preterm infants,** which results in lower BPD/CLD and death rates compared with early/prophylactic surfactant therapy.[14,590] (see also later section under Surfactant Replacement Therapy and Box 23.15). A more recent study shows that early NCPAP in preterm infants 32 weeks' gestation or under decreased the need for mechanical ventilation and surfactant use but had no significant effect on the development of BPD/CLD.[79]

Alternate methods of delivering continuous distending pressure in neonates include biphasic NCPAP and NIPPV. NIPPV use as the initial respiratory support for preterm infants (26 to 32 weeks' GA) has been shown to result in less need for surfactant or invasive ventilation in the first 72 hours of life, while reducing the incidence of moderate to severe BPD/CLD.[388,447]

However, a meta-analysis of the rates of death or BPD/CLD in preterm infants randomized to NIPPV with a conventional mechanical ventilator or bilevel device found no significant difference between the two in BPD/CLD or death.[347] Biphasic CPAP delivers two alternating levels of distending pressure at specific rates independent of the neonate's own respiratory rate. Biphasic is similar to CPAP but possibly better at maintaining an appropriate functional residual capacity (FRC). An RCT comparing biphasic CPAP and NCPAP of 540 preterm infants under 30 weeks' gestation and under 2 weeks of age found no significant difference in preventing extubation failure or in BPD/CLD, death, IVH, NEC requiring surgery, or pneumothorax.[549] Other trials have found that noninvasive ventilation strategies such as biphasic positive airway pressure (BiPAP) and nasal synchronized intermittent positive-pressure ventilation (NSIPPV) reduced the risk of failure in VLBW infants when compared to CPAP[447] and that Bi-NCPAP was superior to regular NCPAP for apnea of prematurity.[239] Even though biphasic CPAP delivery seems promising, specific volume drivers are required for its use, thus potentially limiting access.

Indications and complications in the use of CPAP are listed in Table 23.3. If the infant maintains ventilation as indicated by normal arterial carbon dioxide tension, no further respiratory support may be necessary. CPAP may be delivered by facemask, nasal pharyngeal tubes, nasal prongs, or ETT. Delivery of CPAP by nasal prongs is the most common method used; use of short binasal prongs is the most effective.[133] However, a more recent RCT and a systematic review both found that use of a mask for CPAP is as effective as nasal prongs, with less nasal trauma and pulmonary interstitial emphysema (PIE) and fewer CPAP failures.[186,243]

TABLE 23.3 CONTINUOUS POSITIVE AIRWAY PRESSURE

INDICATIONS	COMPLICATIONS
Premature infant who breathes spontaneously yet has mild to moderate respiratory distress syndrome; primary, initial respiratory support after birth	Respiratory difficulty secondary to narrowing of the nasal passage with prongs or of the trachea with the presence of an endotracheal tube
Very-low-birth-weight infant with primary or secondary apnea	Pneumothorax and other air leaks
Support during weaning from mechanical ventilation	Nasal and/or septal irritation, trauma, deformity, obstruction[488]; gastric and abdominal distention; perforation; infection (tracheal colonization on day 5 of nasal continuous positive airway pressure [NCPAP] use also associated with longer need for respiratory support)[12]

Advantages to the use of NCPAP include[174,193]:

- Less invasive than ETT
- Decreased incidence, duration, and complications of intubation and mechanical ventilation
- Earlier extubation
- Decreased incidence and morbidity of BPD/CLD
- Improved oxygenation and decreased work of breathing
- Decreased need for surfactant and second doses of surfactant
- Reduced mortality rate

Disadvantages include (1) gaseous distention of the bowel or gastrointestinal (GI) perforation[176] (both are rare occurrences),[532] (2) increased rate of pneumothorax,[70,355] (3) difficulties keeping prongs in the nose and maintaining patency, (4) infant agitation, and (5) alteration in appearance (dilation of the nares).[488] **The nutritional approach to neonates on noninvasive respiratory support must be individualized** so that pulmonary function and nutritional support are optimized without compromising either one.[64]

Nasal CPAP is labor intensive for the neonatal nurse.[172] Choosing the correct size of nasal prong is important to avoid movement and erosion of nasal tissue. A recent systematic review found an incidence of 20% to 100% for nasal trauma with the incidence highest in preterms under 30 weeks' gestation.[236] **The risk of nasal injury is also increased with longer duration of NCPAP, the type of device used, and longer NICU stay.[268,563]** Box 23.4 **lists important aspects of care of the neonate on NCPAP (or any other device using the nasal route) to optimize safety and efficacy.**

Criteria that indicate improvement on CPAP are listed in Box 23.5. Failure of CPAP is associated with (1) birth weight less than 1500 g, (2) GA 30 weeks or less, (3) "whiteout" chest x-ray, (4) FiO_2 50% or greater at 20 minutes of CPAP, and (5) positive end-expiratory pressure (PEEP) 5.5 cm H_2O or greater.[207,508] When the infant's PaO_2 is consistently over 70 mm Hg, inspired oxygen concentration or CDP may be lowered. Oxygen concentration is usually lowered in 5% to 10% increments to a level of 40% to 60%. CDP is lowered in increments of 1 cm H_2O to a level of 2 cm H_2O before discontinuation.[242] Results in weaning from NCPAP are seen when the pressure is lowered, then stopped, rather than removed for a number of hours during the day.[242] The infant may then be placed into an oxygen hood with the same FiO_2. Neonates should be monitored closely with pulse oximetry and arterial blood gases.

Pulmonary Hygiene

Pulmonary hygiene is normally maintained by ciliary activity, a covering of mucus, and narrowing and dilation of the bronchi with respiration and coughing. Anatomic and physiologic variations in the neonate alter these normal pulmonary mechanisms. **The small airway of the neonate has a diameter that is four times smaller than that of the normal adult.** Debris that causes only a moderate obstruction for the adult airway causes a disproportionately greater obstruction of the smaller airway of the neonate. Also, **a neonate normally has an underdeveloped cough reflex.** A sick neonate with insufficient respiratory effort and a weak or nonexistent cry has underventilated lungs. If a neonate who is attached to multiple life-support systems is cared for in the same position, secretions localize in the dependent pulmonary tree and predispose to hypostatic pneumonia.

BOX 23.4 CARE OF INFANTS RECEIVING NASAL THERAPIES* TO OPTIMIZE SAFETY AND EFFICACY

Prongs

- Nasal prongs should fill the entire nares without distending or causing blanching of the nares
- Presence of a small space (at least 2 mm) between the nares and prong base
- Lateral straps are used to secure the prongs by providing gentle, equal tension
- Assess prongs and NCPAP device at least every hour to ensure proper positioning and functioning
- Remove NCPAP device q 2–4 hr to assess skin integrity (e.g., color, perfusion, pressure, excoriation) and massage nasal septum
- Alternate use of nasal prongs with mask at least twice a day[77] to remove pressures on nares

Hat

- Use the appropriate size hat to avoid prong movement; change hat size with neonatal head growth
- Position just above the eyebrows, with the back of the hat extending to the base of the neck and completely covering the infant's ears
- Use ties on the hat to secure tubing, thus decreasing movement and/or upward pull of CPAP system

Nose

- Suction nares only PRN to maintain nasal patency
- Avoid deep nasal suctioning unless absolutely necessary for individual infant
- Use a hydrocolloid dressing[582] or silicone gel[198] over the nose and philtrum to provide a barrier layer for skin protection

Mouth

- Place orogastric tube for decompression of the stomach
- Encourage closed mouth by use of pacifier and/or prone positioning

Comfort Measures

- Positioning prone, swaddled, or contained (to promote flexion) (see Chapter 13) decreases movement and pulling/dragging of the device on the nares
- Minimal handling and position change q 2–4 hr and/or with infant agitation and developmental positioning
- Skin-to-skin care with parents (see Chapters 12 and 13)
- Pacifier, nonnutritive sucking, sucrose
- Environmental management—decrease light/noise (see Chapter 13)
- Use neonatal pain scale and administer pharmacologic sedation and/or pain relief (see Chapter 12)

*Noninvasive nasal therapies include *NBiPAP,* Nasal biphasic positive airway pressure; *NCPAP,* nasal continuous positive airway pressure; *NHFOV,* nasal high-frequency oscillator ventilation; *NIPPV,* nasal intermittent positive-pressure ventilation; *NSIPPV,* nasal synchronized intermittent positive-pressure ventilation.
CPAP, Continuous positive airway pressure; *NCPAP,* nasal CPAP; *PRN,* as needed.
Adapted from McCoskey L. Nursing care guidelines for prevention of nasal breakdown in neonates receiving nasal CPAP. *Adv Neonatal Care.* 2008;8(2):116; Squires AJ, Hyndman M. Prevention of nasal injuries secondary to NCPAP application in the ELBW infant. *Neonatal Netw.* 2009;28(1):13; Flanagan KA. Noninvasive ventilation in preterm neonates. *Adv Neonatal Care.* 2016;16(2):91.

Pulmonary hygiene consists of two major components: chest physiotherapy (CPT) and suctioning. The goals of pulmonary hygiene are:

- To maintain a patent airway by clearing secretions
- To promote optimal pulmonary oxygenation and ventilation
- To prevent pulmonary infection from accumulated secretions
- To facilitate removal of pulmonary debris by loosening and mobilizing secretions into the mainstem bronchi for suctioning

Pulmonary hygiene has been used as a treatment for intubated patients with conditions associated with atelectasis, increased secretions, and pulmonary debris (pneumonia, meconium aspiration, RDS, and BPD).

CHEST PHYSIOTHERAPY

CPT consists of positioning, percussion, and vibration. Postural changes use gravity to facilitate the movement of pulmonary debris from smaller to larger bronchi. Postural changes used with pediatric and adult respiratory patients have been used for neonatal CPT. **However, most ill neonates, especially VLBW and ELBW infants, do not tolerate multiple positioning and repositioning.** Periodic (every 2 to 4 hours with care) repositioning changes the ventilation-perfusion matching in dependent lung areas and improves oxygenation. Prone positioning improves lung mechanics and lung volumes and improves oxygenation (see Chapter 13).

Percussion of the chest wall creates a suction action that loosens secretions. Percussion should

BOX 23.5 CRITICAL FINDINGS

CRITERIA THAT INDICATE IMPROVEMENT ON CONTINUOUS POSITIVE AIRWAY PRESSURE

Blood Gases

- Decrease or stabilization of oxygen requirement FiO_2 ≤0.60 with PaO_2 >50 mm Hg or pulse oximetry >90%
- Maintenance of adequate ventilation
  - $PaCO_2$ ≤50 to 60 mm Hg
  - pH 7.25 to 7.45

Clinical

- Decreased work of breathing—decreased respiratory rate, grunting, flaring, and retracting
- Improved lung volumes and appearance on chest x-ray films
- Improved patient comfort

occur through gently tapping over the affected lung. **In infants with BPD, rib fractures have been documented that resulted from vigorous percussion[417] and vibrator use.[576]** Vibration of the neonate's chest may follow percussion. Even though vibration must be done on expiration to move secretions with the exhalation of air, this is very difficult to accomplish with the neonate's rapid, shallow breathing cycle.

Any manipulation of the sick neonate has the potential for decreasing oxygenation and precipitating hypoxia (see Chapter 13). During CPT, bradycardia, cyanosis, hypotonia, fighting, struggling, and alterations in oxygenation are signs of stress. There is also an increase in plasma epinephrine and norepinephrine levels with CPT and endotracheal suctioning; this stress response is decreased in sedated preterm infants.[195] CPT is no better than standard care for clearing secretions in ventilated neonates and is accompanied by hypoxia and increased oxygen requirements. Postextubation CPT has also shown no differences in preventing atelectasis, decreasing the number of apnea/bradycardia episodes, the need for reintubation, or the duration of supplemental oxygen.[30]

The most severe complications reportedly resulting from CPT are an increased risk for IVH (see Chapter 26) and cerebral encephalopathy. An increased incidence of severe intraventricular/periventricular hemorrhage has been reported in preterm infants treated with early CPT.[423] In 1992, a previously unrecognized and distinct pattern of severe, late-onset brain injury was reported in 15 neonates (24 to 32 weeks' GA; 600 to 1270 g birth weight). The pattern of brain injury was of extensive, dense, and cystic lesions involving the periphery of the brain bilaterally. This full-thickness cortical necrosis, called *encephaloclastic porencephaly,* resulted in 14 deaths and severe neurologic deficit in the only survivor.[111] This nursery changed its protocol to include holding the baby's head steady during CPT; no further cases of brain injury have occurred.[422]

Another study of 454 babies found 13 babies (24 to 27 weeks' GA; 680 to 1100 g birth weight) with lesions similar to the encephaloclastic porencephaly just described. The lesions in these infants were described as cystic with cortical and subcortical destruction and peripheral rather than periventricular; they occurred between 2 and 3 weeks of life. These hemorrhagic infarcts are consistent with the pathologic changes in older infants from *shaken baby syndrome.*[277,572] The extremely immature brain of the VLBW infant may be particularly vulnerable to the shaking movements of CPT. Five of these infants died; seven of the eight surviving infants had disabilities (e.g., mild hemiplegia to severe spastic quadriplegia; cognitive delay) at 6 to 16 months of age. For longer than 3 years, no VLBW infant in this NICU has received CPT in the first month of life; no further cases of this brain injury have occurred.[277,572]

The techniques, efficacy, complications, outcomes, safety, and frequency of CPT have not been studied sufficiently.[230] Given the lack of data, the lack of clear evidence of benefit, and the concerns of safety for VLBW infants, recommendations include[422,572,577]:

- Use CPT cautiously.
- Do not use CPT on VLBW infants in the first month of life.
- Keep the infant's head steady during CPT.
- CPT should be used only for definite indications when the infant is fit and able to tolerate the procedure.
- CPT should never be done "routinely," but should be applied on an individual basis after careful and thorough assessment.

- Percussion should be used only when secretions are not cleared by suction alone.
- Use of CPT in the delivery room lacks evidence-based research.
- CPT should not be included in pulmonary hygiene until research clearly substantiates its benefits.

SUCTIONING

Once secretions are loosened and mobilized, they must be removed through the nose, mouth, or trachea with suctioning.

Naso-oropharyngeal Suctioning. When an infant has no artificial airway, **suctioning the naso-oropharynx serves two purposes: removing secretions and initiating a cough reflex that mobilizes secretions**. With either a suction bulb or catheter, the infant is suctioned when secretions are produced. Providing an oxygen source during the procedure is necessary. **Because stimulation of the nares causes reflex inspiration with possible inhalation of oropharyngeal contents, first the *mouth* and then the *nose* should be suctioned.** The results should be documented.

CAUTION: Suctioning should be avoided for 30 minutes to 1 hour after feeding unless it is necessary to establish a patent airway. The catheter should be gently inserted upward and back into the nares, never forced. If the catheter is hard to pass or the nares seem blocked, this procedure should be abandoned to prevent swelling or trauma. **Frequent nasal suction creates trauma and edema. The catheter may initiate vasovagal stimulation with alterations in heart rate[37] and/or resultant bradycardia.**

Endotracheal Suctioning. An artificial airway prevents normal warming, humidifying, and cleansing of the air by the upper airway. The presence of the foreign body (the tube) also increases pulmonary secretions. **To maintain a patent airway, sterile endotracheal suction should be performed on an individual basis, *never* on a routine basis (e.g., on a schedule of every 2, 3, or 4 hours).**[17] A *Cochrane* review states that there is insufficient evidence to identify the ideal frequency of ETT suctioning in mechanically ventilated neonates.[68] **Individual assessment criteria to establish that the infant "needs" suction are listed in** Box 23.6. Knowledge of the infant's respiratory diagnosis suggests the need and the frequency of suction. The acute phase (first 72 hours) of RDS is a restrictive disease; few secretions are produced, so minimal suctioning (every 12 to 24 hours) is necessary. **Studies have found no increase in occluded tubes when suction frequency was changed from every 6 to every 12 hours (during the first 72 hours of RDS)[574] and from every 4 to every 8 hours.**[106] Disease processes noted for secretion production (e.g., the chronic phase of RDS, CLD/BPD, meconium aspiration syndrome, or pneumonia) may require early and frequent suctioning.

ETT suctioning is not an innocuous procedure. **ETT suction is associated with numerous physiologic alterations and complications** (Box 23.7). Hypoxia and changes in heart rate and blood pressure alter cerebral blood flow, increase intracranial

BOX 23.6 CRITICAL FINDINGS
INDIVIDUAL ASSESSMENT CRITERIA FOR SUCTION

Evidence of Secretions
- Visible secretions in tube
- Audible coarse, wet, or decreased breath sounds
- Palpation of wet, coarse vibrations through chest wall

Alterations in Vital Signs
- Changes in respiratory pattern:
  - Increased work of breathing (retractions, grunting, flaring)
  - Tachypnea or apnea
- Change in cardiac pattern; tachycardia or bradycardia

Alterations in Neonatal State
- Increased agitation, irritability, restlessness
- Hypertonic or hypotonic
- Listless, lethargic

Alterations in Oxygenation and Ventilation
- Desaturations (<90%) or labile saturations on pulse oximeter
- Skin color changes—pale, dusky, cyanotic
- Changes in arterial blood gas values—increased pCO_2, decreased PaO_2, respiratory acidosis
- Increased peak inspiratory pressure on mechanical ventilation and increased high-pressure alarms
- Decreased chest wall vibration with high-frequency ventilation (HFV)

BOX 23.7 PHYSIOLOGIC ALTERATIONS AND COMPLICATIONS ASSOCIATED WITH ENDOTRACHEAL TUBE SUCTION

- Hypoxia/hypoxemia[162,416]
  - Caused by disconnection from the ventilator and oxygen and presence of suction catheter and application of negative pressure, which partially occludes the airway; handling during the procedure; desaturations on the PO
- Alterations in heart rate[37,162,428]
  - Bradycardia, dysrhythmias, and asystole are precipitated by hypoxemia
- Alterations in blood pressure
  - Hypertension/hypotension
- Alterations in cerebral blood flow[403,428]
  - Changes in oxygenation, heart rate, and blood pressure increase cerebral blood flow, both during and after the procedure (late [6 minutes]/prolonged [25 minutes] elevations of CBF),[252] and intracranial pressure, which increase the risk for intraventricular hemorrhage
- Increase in plasma epinephrine and norepinephrine levels[195]
- Tissue damage
  - Granuloma formation within airways; increased severity of CLD/BPD associated with colonization of lungs with gram-negative bacilli; lobar emphysema and atelectasis; bronchial stenosis
- Atelectasis
  - Marked increase in opening (inflation) pressures of the lungs; adequate lung recruitment and PEEP may prevent lung collapse and deterioration in arterial oxygenation; atelectasis
- Pneumothorax
  - From aggressively ventilating neonate above baseline pressures
- Infection
  - Airway colonization with gram-positive cocci and gram-negative bacilli by 2 weeks of life despite the method of suction
- Unplanned extubation

CBF, Cerebral blood flow; *CLD/BPD,* chronic lung disease/bronchopulmonary dysplasia; *PEEP,* positive end-expiratory pressure; *PO,* pulse oximetry.

pressure, and predispose the preterm to an increased risk for IVH (see Chapter 26). **Pulse oximetry is a valuable tool in assessing oxygenation status during and after suctioning. The infant may be preoxygenated before suctioning, or if oxygen saturation falls (below 90%) during suctioning, the infant may be hyperventilated.** *Preoxygenation* is the increase of FiO_2 above baseline concentration before ETT suction to prevent/reduce hypoxemia.[17] **To avoid exposing the preterm to hyperoxic events that may predispose to ROP, the FiO_2 is increased by 10% to 20% above baseline when clinically indicated for an individual infant. For ELBW/VLBW infants, FiO_2 increases may be from 2% to 5%.** Using 100% oxygen only if it is clinically indicated for the individual infant prevents hyperoxia. *Hyperventilation* (e.g., increasing respiratory rate) with a bag or the manual breaths on the ventilator after each catheter pass minimizes hypoxia and contributes to shortened time of stabilization and recovery. More research is needed on the optimal timing of increasing the FiO_2 and the amount of oxygen to use.[416]

Administration of intermittent doses of morphine during endotracheal suctioning has not been shown to reduce pain scores in ventilated preterms. In this same RCT, multisensory stimulation after suctioning also was not associated with reduced pain scores.[93] **Comfort measures (e.g., nonnutritive sucking, expressed breast milk, sucrose, swaddling, facilitated tucking) are recommended during suction to provide pain relief[87,136] and to reduce bradycardia and desaturations (see Chapter 12).**

Most of the physiologic alterations and complications of ETT suction are the result of decreases in PEEP, lung volume, and oxygen during disconnection of the ETT from the ventilator for use of the open suction procedure. Use of closed suction systems (e.g., an adapter to suction without disconnection from the ventilator) decreases associated hypoxemia and bradycardia by enabling oxygenation and ventilation to continue during suction.[106,512] However, closed suction interferes with ventilator function (i.e., substantial negative intratracheal pressure during suction; the potential for higher airway pressures and tidal volumes after suctioning).[274] Closed suction is associated with smaller decreases in cerebral oxygenation, smaller variations in cerebral blood volume, and related hemodynamic changes, particularly in ventilated preterms.[253,357] Use of a four-handed closed suction technique was recently found to have no advantages in baseline heart rate, oxygen saturation, or salivary cortisol levels.[103] However, in this randomized crossover design, four-handed suction was associated with fewer stress-related and more self-regulatory behaviors.[103] A small study comparing the effects of open versus closed suction for mechanically (conventional and high-frequency) ventilated ELBW preterms ($n = 19$) found decreases in cerebral blood flow and heart rate during suction

and return to baseline after suctioning ceased; both of these changes were independent of the kind of ventilation and the type of suction used.[428] Two studies comparing open and closed suction had conflicting results: (1) no differences in an RCT of 39 neonates 34 weeks' GA or older[395] and (2) a significant decrease in hypoxemia and drop in Spo_2 with a higher Spo_2, mean arterial Po_2, and mean oxygenation ratio after closed versus open suction.[408] A more recent study comparing open and closed ETT suctioning found no significant difference in respiratory or heart rates, arterial PaO_2 values, or pain of the ventilated neonates between the two suction procedures.[73]

Closed suction removes secretions as effectively as open suction with no increase in the rate of bacterial airway colonization (with catheter change every 24 hours), suction frequency, reintubation, duration of mechanical ventilation, length of hospitalization, incidence of nosocomial pneumonia or sepsis, severity of BPD/CLD, or mortality rate in 175 low-birth-weight (LBW) infants.[105] Enclosure of the catheter in a clear sheath decreases the possibility of cross-contamination and environmental pollution of objects and personnel with bacterial and viral pathogens. Closed suction systems are easier to use, less time consuming, better tolerated by the neonate, cost effective, and well accepted by neonatal nurses.[106] **Closed suction improves short-term outcomes but needs more research to be recommended as the only method of ETT suction by *Cochrane* reviews,[512] but it is suggested for neonates by the American Association of Respiratory Care.[17]** Another study comparing open and closed suctioning found less time and staffing were necessary when closed suctioning was used and that there were fewer physiologic disturbances (e.g., less reduction in SpO_2, fewer heart rate and mean airway pressure increases).[163] **Closed ETT suction has been identified as "best practice" in reducing nosocomial sepsis in the NICU.[96]**

The actual procedures used in closed and open suction often are not supported by research data. Table 23.4 **outlines common suction techniques, research data, and recommendations to alter clinical practice.**

Procedure for Closed Suction

Equipment to Be Prepared.

- Inline suction catheter (changed daily)
- Sterile normal saline (without preservative)
- Suction canister and tubing (60 to 80 mm Hg negative pressure)

Procedure.

- Unlock the inline suction catheter. Press suction control valve and check suction pressure.
- Place saline solution syringe on the proximal port of the adapter to irrigate the catheter before suction, place normal saline syringe or bullet at the distal port or adapter, and squeeze saline solution into the port while applying suction.
- Slide the catheter through the plastic cover down the ETT to the predetermined distance.
- Apply suction while withdrawing the catheter tip to the catheter window (the plastic cover will inflate from ventilation if the catheter is pulled back too far; the catheter will completely or partially occlude the ventilatory circuit if not pulled back far enough). Only one suction attempt should be made before the infant is again ventilated. Assess tolerance of the procedure by observing pulse oximeter and infant's color, heart rate, tone, and activity. Hyperventilate the lungs with appropriate FiO_2 for 6 to 8 breaths or until adequate oxygenation has been established.
- To irrigate the catheter after suction, place a normal saline syringe at the distal port adapter and squeeze saline solution into the port while simultaneously applying suction. Remove the saline solution and close the port when the catheter has been rinsed thoroughly.
- Rotate and lock the suction control cap to discontinue suction.
- Suction the nasopharynx and oropharynx as needed with a suction bulb or separate suction catheter and tubing. Do *not* disconnect the closed suction catheter from its suction line—this contaminates the setup for ETT suction.
- Check respirator settings, including alarm system in "on" position. Check tube position to be sure the tracheal tube is not strained or bent.
- Note amount and type of secretions obtained.

Procedure for Open Suction

Equipment to Be Prepared.

- Sterile suction catheter of appropriate size (discard after each suctioning)
- Sterile gloves
- Sterile normal saline solution (without preservative)
- Stethoscope

TABLE 23.4 SUCTION PROCEDURE: RESEARCH BASIS AND RECOMMENDATIONS

COMMON TECHNIQUES	RECOMMENDATIONS	RESEARCH DATA
Instillation of 0.25–0.5 mL sterile NS before suction *Purpose:* Mobilize and thin secretions; aid in catheter passage	Mucus is not miscible with saline solution so bolus saline does not thin or liquefy secretions[17]; vaporized or nebulized NS thins secretions.[17] Bolus saline accumulates at the end of the ETT; <20% of the saline solution is retrieved with suction and remainder is absorbed by the body. Use of NS associated with increased hypoxia, deterioration of lung mechanics, and infection.[17] Maintenance of adequate humidification (100%) and warming oxygen to core temperature keep secretions loose and lubricate the ETT and the surrounding tissues. Routine use of NS instillation before suction should not be performed.[17]	*Closed suction:* Irrigate catheter before suction; place NS syringe at distal port adapter and squeeze saline solution into port while simultaneously applying suction. *Open suction:* Dip or moisten catheter tip in sterile NS or water-soluble jelly to facilitate sliding down the small-diameter ETT.
Head turned from side to side with suction *Purpose:* To advance catheter down contralateral bronchus	Suction causes fluctuations in cerebral blood flow, which increases ICP and the risk for intraventricular hemorrhage.[403] Sharply turning head to the side occludes the jugular vein and increases ICP, which is at its lowest when the head is in the midline or slightly elevated.[403]	*Turned head position:* Contraindicated because of data on increased ICP, jugular vein occlusion, and anatomic impossibility of passing catheter into bronchi using this strategy. Do not turn the infant's head during suction; keep head in midline for suction.
Catheter inserted until resistance (touching the carina) is met, withdrawn slightly; then suction applied	Application of negative pressure with suction and touching the bronchial mucosa with catheter cause irritation, tissue damage, and significant oxygen desaturations.[193]	Shallow suction does not touch the carina with the catheter tip[17,181]: Using the ETT markings and the length of the adapter, insert the catheter no more than 1 cm beyond the total distance (e.g., if the ETT is inserted 10 cm and the length of the adapter is 1.5 cm, the suction catheter should be inserted 11.5 cm to no farther than 12.5 cm).
Catheter is inserted and removed several times	One small study ($n = 16$) evaluated nurses' subjective reports of amount of secretions obtained with one and two suction passes; no difference was noted.	Limit number of catheter passes to the number needed to adequately remove secretions. Do not use up-and-down motion while removing the catheter because this decreases oxygenation and promotes hypoxia and tissue damage. Only one suction attempt should be made before the neonate is again ventilated; every catheter passage is considered a suction event; occlude ETT with catheter for no longer than 5–10 sec.
Use as large a suction catheter as will easily go down the lumen of the ETT	Use suction catheter that occludes less than 70% of the lumen of the ETT.[17]	Impedance to gas flow occurs in an ETT when more than 70% of the lumen is occluded.[17]
No use of developmental care adjustments during the stressful procedure of suction	Body containment significantly decreases the magnitude of the preterm's response (e.g., pain, desaturations and bradycardia) to suctioning.[162]	Use the developmental care technique of containment (swaddling or facilitated tucking), NNS, or sucrose during suction (see Chapters 12 and 13).

ETT, Endotracheal tube; *ICP,* intracranial pressure; *NNS,* nonnutritive sucking; *NS,* normal saline.

- Suction machine and tubing (60 to 80 mm Hg negative pressure)

Procedure.

- The sterile catheter and glove package are opened. Sterile normal saline solution (0.25 to 0.5 mL) is drawn up in a 1 mL syringe. The resuscitation bag is connected to oxygen, and the patency is checked so that if the neonate becomes apneic or bradycardic during the procedure, resuscitation equipment is immediately available. If the infant is on a ventilator equipped with a bag, this may be used for resuscitation if necessary.
- Disconnect and dip the suction catheter in or wet the tip of the suction catheter with the sterile normal saline.
- Put gloves on and attach sterile catheter to suction tubing. With nondominant hand, disconnect ETT from ventilator.
- Gently pass catheter down the ETT to premeasured length.
- Occlude suction hole in catheter and withdraw. Use continuous suction so that secretions are not "released" with intermittent suction. Only one suction attempt should be made before the infant is again ventilated. Assess tolerance of procedure by observing pulse oximeter and infant's color, heart rate, tone, and activity.
- Reconnect ETT to ventilator and hyperventilate with appropriate FiO_2 for 6 to 8 breaths or until adequate oxygenation has been established. Check ventilator settings including alarm system in "on" position. Check tube position to ensure that the tube is not bent or strained. Note amount and type of secretions obtained.

NOTE: When two persons are available for suction, one remains "sterile" and does the suctioning while the other detaches the ETT from the ventilator and hyperventilates the infant between suctionings.

Because ETT suctioning compromises the neonate's physiologic homeostasis, adequate recovery time is necessary after the procedure.[162] For ETT suction, an average of 4.4 minutes of recovery time is necessary (6 of 25 infants in one study never returned to baseline during the observation). Use of containment such as swaddling or facilitated tucking, expressed breastmilk, or oral sucrose has been shown to decrease pain response and improve oxygenation after suctioning.[136] **These infants may need a significant rest period after suctioning before other aspects of care such as feeding are attempted.**

Endotracheal Intubation

Endotracheal intubation may be accomplished by the orotracheal route or the nasotracheal route. An ETT diameter that approximates the diameter of the infant's fifth digit generally fits snugly into the trachea. **To measure for an ETT, the distance from the oral orifice to midway between the glottis and carina may be calculated by multiplying the crown–heel length by 0.2. In an emergency, the distance from the lips to midway between the glottis and carina may be approximated by the *7-8-9-10 rule.* The distance is 7 cm in a 1 kg infant, 8 cm in a 2 kg infant, 9 cm in a 3 kg infant, and 10 cm in a 4 kg infant.**

Premedication for intubation is recommended for any nonemergent intubation.[287] **Intubation is a painful procedure associated with unfavorable physiologic side effects such as bradycardia, desaturation, and increased blood pressure, intracranial pressure, and pulmonary pressure. Increases in intracranial pressure in the ELBW infant are of particular concern because this population already is predisposed to IVH.** Medications listed in Table 12.13 with rapid onset and short duration of action are ideal. The agitation and pain of intubation are relieved with analgesia and sedation; vagolytics and muscle relaxants reduce the cardiovascular side-effects of intubation. Premedication also decreases the number of attempts, the amount of airway trauma and significantly contributes to more rapid intubation, regardless of the experience of the intubating professional.[341] **The neonate should be pretreated for pain with a more rapid, short-acting opiate such as fentanyl or remifentanil rather than morphine because it has no more effect on the severity of hypoxemia or bradycardia at intubation than placebo.**[313] Benzodiazepines should not be used alone for intubation because of an increase in desaturations during the procedure and a need for cardiopulmonary resuscitation after intubation.[341] Midazolam may be used for additional sedation or to potentiate the effect of the opiate so smaller doses of each medication can be administered.

Table 23.5 **is a protocol for premedication for elective endotracheal intubation.** One study of 166 infants (24 to 44 weeks' GA) being premedicated

TABLE 23.5 PREMEDICATIONS FOR ELECTIVE ENDOTRACHEAL INTUBATION

DRUG	DOSAGE	COMMENTS
Analgesia: Remifentanil	2 mcg/kg IV: Dose with medication pump over 3 minutes to prevent chest wall rigidity from rapid administration Onset: 1 minute Half-life: 5.4 minutes	Excellent conditions for intubation (ease of laryngoscopy, vocal cord position, jaw relaxation, lack of limb movement and cough) and short procedure time when compared to morphine[401,565]
Sedation: Midazolam	0.1 mg/kg IV: Dose with medication pump over 2 minutes to prevent chest wall rigidity from rapid administration Onset: 1–2 minutes Half-life: 6.3 hours	Use for preterm infants ≥34 weeks' corrected GA Do *not* use for preterm infants <34 weeks' corrected GA because of systemic and cerebral hypotension with resulting brain injury with bolus doses[19]
Vagolytic: Atropine	0.02 mg/kg IV: Rapid IV push Onset: 1 minute 0.02 mg/kg IM Onset: 15–30 minutes	Blocks vagal response and bradycardia to placement of laryngoscope blade/ETT; minimizes oral secretions; increases heart rate
Muscle Relaxants*:	1 mg/kg IV push	
Rocuronium	Onset: 1–3 minutes Duration: 40–60 minutes Treat chest wall rigidity with: 1 mg/kg IV push.	Intermediate duration non-depolarizing neuromuscular blocking agent. Stable in IV solution—does not require reconstitution like vecuronium. Higher first attempt success rate of intubation when compared to no muscle relaxing agent used.[165]
Succinylcholine	2 mg/kg IV[40] Onset: 20–40 seconds[343] Duration: 6–8 minutes[343] 4 mg/kg IM Onset: 4–16 minutes	More rapid intubation and elimination of intracranial hypertension.[40] Associated with 50% fewer attempts at intubation and improved first attempt success (58% verus 18%).[311] Adverse effects: Use with caution in neonates with baseline hyperkalemia as medication may increase serum potassium levels. Extra caution in neonates receiving medications that may cause hyperkalemia: B-adrenergic blockers and angiotensin-converting enzyme inhibitors. May trigger malignant hyperthermia.

*Only ordered by NICU attending or fellow. Neonate must be supportable by bag/mask ventilation before paralytic administration.
Adapted from McPherson C. Premedication for endotracheal intubation in the neonate. *Neonatal Network*. 2018;37(4):238.

for elective endotracheal intubation found that **only the combination of fentanyl and midazolam significantly decreased pain scores and the stress response of an increase in blood glucose.**[72] Even though this study found that the most immature preterms responded similarly to infants of older gestational ages, **the most immature infants were less likely to receive premedication.**[72]

INTUBATION PROCEDURE

ETT placement must be immediately verified by auscultation and confirmed by a chest x-ray examination; ultrasound imaging may also be used for secondary confirmation. Findings on auscultation and what they suggest are listed in Table 23.6. **End-tidal carbon dioxide ($ETCO_2$)**

TABLE 23.6 CHEST AUSCULTATION ABNORMALITIES AND UNDERLYING CAUSES

FINDING	POSSIBLE CAUSE
No air entry bilaterally	Air leak Plugged endotracheal tube
Diminished air entry	Air leak Endotracheal tube too high
Air entry over stomach	Unplanned extubation
Air entry unequal	Air leak Endotracheal tube too low
Cardiac point of maximum intensity shifted	Air leak with tension

detectors are available to immediately verify tube placement and have been tested in the delivery room and NICU.[27] In the presence of exhaled CO_2 (after six breaths), the $ETCO_2$ detector changes color from purple to yellow. The time necessary to detect proper ETT placement with these detectors is 4 to 12 seconds versus 0 to 90 seconds by clinical evaluation. This significantly faster time enables quicker extubation and reintubation if the ETT is in the esophagus.[27] **Use of $ETCO_2$ detection devices to confirm proper ETT placement is recommended by the AAP in the Neonatal Resuscitation Program (NRP) Guidelines.**[561] This device also is useful for ongoing assessment of ETT placement.[129] Other available devices are capnometry, with a numeric display, and capnography, with both a numeric and waveform display (see Chapter 7).[129]

For long-term stability, commercially available ETT anchors prevent accidental extubation. Some nurseries still prefer fixing tubes with tape or sutures.

EXTUBATION PROCEDURE

Assess the infant's condition by observing the heart rate, color, and respiratory rate and effort, and by auscultating the chest. If the infant's condition is stable, proceed with extubation. **Before extubating, do not feed the infant or empty stomach contents to prevent vomiting. Neonates are obligatory nasal breathers; the nasopharynx also must be suctioned and patent for extubation.**

Hyperinflate with deep breaths with the infant's head in the midline and remove the tube (1) on inflation (to provide adequate lung expansion and prevent atelectasis), (2) on expiration[194] (so that secretions that have accumulated around the tracheal tube are "blown away" on exhalation and tube removal), or (3) while suctioning (to remove secretions that have accumulated around the tube). Place the neonate in a warm, humidified oxygen hood at FiO_2 to keep pulse oximeter at 92% to 94%.

Reassess the infant's condition, especially for signs of increased work of breathing and distress. Document the tube removal and infant's tolerance to extubation. Check arterial blood gases 15 to 20 minutes after extubation to assess oxygenation and ventilation status. Perform a chest x-ray examination to document atelectasis or fully expanded lungs. Observe for complications of intubation (Table 23.10).

BOX 23.8 CRITICAL FINDING

CRITERIA THAT QUALIFY NEWBORNS FOR ASSISTED VENTILATION

Blood Gases

- Severe hypoxemia (PaO_2 <50 to 60 mm Hg with FiO_2 ≥0.60 or PaO_2 <60 mm Hg with FiO_2 >0.40 in infant weighing <1250 g)
- Severe hypercapnia ($PaCO_2$ >55 to 65 mm Hg with pH <7.20 to 7.25)

Clinical

- Apnea and bradycardia requiring resuscitation in infants with lung disease or unresponsive to CPAP or requiring theophylline therapy in preterm infants with normal lungs
- Inefficient respiratory effort, such as gasping respirations from asphyxia, narcosis, or primary cardiopulmonary disease
- Shock and asphyxia with hypoperfusion and hypotension
- RDS in infants weighing <1000 g, frequently making them incapable of maintaining ventilation

CPAP, Continuous positive airway pressure; *RDS*, respiratory distress syndrome.

MECHANICAL VENTILATION

Mechanical ventilation is used in neonates to correct abnormalities in oxygenation (decreased PaO_2), alveolar ventilation (increased $PaCO_2$), or respiratory effort (apnea, ineffectual respirations, or increased work of breathing) (Box 23.8). It may not be used to treat the primary disease but is frequently used to support the infant until the disease is treated or resolved.

Ventilator Settings. To individualize assisted ventilation, knowledge of the ventilator capabilities is essential.

Intermittent Mandatory Ventilation. Most mechanical ventilators in common use today allow for intermittent mandatory ventilation (IMV). **IMV provides a continuous flow of gas that is available to the infant during spontaneous respirations. Periodic occlusion of the system diverts gas under pressure to the infant.** Because IMV provides for spontaneous and mechanical ventilation, only the amount of ventilatory assistance that is needed by the individual infant is provided.

Using the noninvasive, nasal route to provide intermittent mandatory ventilation (NIPPV) as a primary ventilation strategy (rather than just for postextubation care) is common. An RCT of

40 infants with transient tachypnea of the newborn (TTN) found that nasal intermittent mandatory ventilation was well tolerated and as effective (i.e., similar duration of support, oxygen therapy, duration of TTN, and length of stay) as NCPAP.[132] A *Cochrane* review of 10 RCTs found that early NIPPV is superior to NCPAP alone for decreasing respiratory failure, the need for intubation, and invasive mechanical ventilation in 1061 preterm infants with RDS.[314]

Continuous Distending Pressure. **CDP is expressed in centimeters of water. CDP may be given without IMV (CPAP) or with it (PEEP).** The effects of CDP include increased alveolar stability, increased functional residual capacity, decreased risk for atelectasis, increased intrathoracic pressure, and impeded passage of fluid from lung capillaries to alveolar spaces, aiding in the prevention or treatment of pulmonary edema. Effects of changes in PEEP depend on severity of lung disease and degree of lung inflation. **High PEEP in the presence of relatively compliant lungs will cause overdistention, worsen PaO_2, and increase pulmonary vascular resistance (PVR). In addition, overdistention may increase the risk for barotrauma. However, the use of levels of PEEP that are too low contributes to hypoxia and pulmonary hypertension because of low lung volumes. Acute lung injury is actually worsened by the failure to recruit adequate lung volume by using insufficient PEEP.**

Peak Inspiratory Pressure. **Peak inspiratory pressure (PIP) is the maximum pressure measured during the delivery of gas (inspiration) during conventional mechanical ventilation. PIP reflects the effects of the amount of gas delivered to the lungs in a given breath (tidal volume: 4 to 6 mL/kg in preterms; 8 to 10 mL/kg in term infants) and the underlying mechanical properties of the lungs.** For example, if the same PIP is used in neonates with severe RDS (with stiff, noncompliant lungs) as in neonates ventilated for apnea with minimal lung disease, the tidal volume will be much greater in the latter group. Recent **studies suggest that overdistention of the lungs caused by excessive tidal volumes, and not pressure itself, worsens acute lung injury (so-called *volutrauma*).** Thus adverse effects of high PIP depend on the degree of lung disease.

When questioning whether **PIP or PEEP is more likely to cause air leaks, the answer is PIP. Both PIP and PEEP cause air leaks if they are excessive and are influenced by the lung compliance of the infant.** Evidence strongly suggests that lung injury results from excessive tidal volume (excessive PIP).[266] It would be difficult to overexpand the lungs with PEEP to the point of air leak. Too little PEEP is far more often the cause of air leaks.[266]

Rate. **The rate reflects how often a volume of gas in the system is delivered to the infant. It is expressed as breaths per minute.** Too rapid a rate, especially with a poorly inflated lung, can cause lung injury caused by gas trapping ("inadvertent PEEP").

Inspiratory-Expiratory Ratio. **The inspiration-expiration ratio (I/E ratio) reflects the relationship between time spent in inspiration and time spent in expiration.** When the rate is 60 breaths/min and the total respiratory cycle is 1 second, an I/E ratio of 1:1 means 0.5 second is inspiration and 0.5 second is expiration. If the I/E ratio is 1:2 with a rate of 60 and the total respiratory cycle is 1 second, inspiration is 0.33 second and expiration is 0.66 second.

Prolonged inspiration may be associated with more efficient ventilation, optimal arterial oxygenation, a higher risk for air leak, and impeding venous return. Prolonged expiration also improves oxygenation, especially in air-trapping conditions (e.g., rapid-rate ventilation or airway disease).[62]

Mean Airway Pressure. **Mean airway pressure (MAP) is the amount of pressure transmitted to the airway throughout an entire respiratory cycle.[62] *Any* change in ventilator settings affects the MAP.** MAP is most affected by changes in PEEP, inspiratory time, or I/E ratio.[62] **MAP is associated with optimal oxygenation (increased PaO_2) and ventilation (decreased $PaCO_2$) when pressures range between 6 and 14 cm H_2O.[62] When MAP exceeds 14 cm H_2O, there is a progressive deterioration of the blood gases (decreased PaO_2, increased $PaCO_2$).[62]** The effects of any given level of MAP depend on the changes in mechanical properties of the lung caused by the primary disease. For example, high MAP may be needed to improve oxygenation in severe RDS or meconium aspiration syndrome, especially in term neonates. Low MAP in this setting causes sustained hypoxemia and atelectasis. In contrast, use of high MAP in neonates in the presence of minimal lung disease causes overdistention and deterioration of arterial blood gas tensions. In general, the goal of increasing MAP is to improve PaO_2 and usually is achieved by small increases in

PEEP or prolongation of inspiratory time. Repeat chest x-ray examination and continuous monitoring of blood pressure and oxygenation (by pulse oximeter) help determine the optimal level of MAP.

Usual starting pressures for beginning ventilatory support are listed in Table 23.7. The inspired oxygen tension is adjusted to provide an adequate arterial oxygen tension. If the infant still has difficulty maintaining an adequate carbon dioxide tension, a faster rate or greater inspiratory pressure would be indicated. Table 23.8 **lists the usual effects to be expected from changing specific ventilator settings.**

TABLE 23.7 STARTING PRESSURES FOR BEGINNING VENTILATORY SUPPORT

PARAMETER	RANGE
FiO_2	At previous level or 10% higher than previously required concentration
PEEP	4–6 cm H_2O
PIP	16–20 cm H_2O
Rate	40–60
I/E ratio	1:1–1:2

I/E, Inspiration to expiration; *PEEP,* positive end-expiratory pressure; *PIP,* peak inspiratory pressure.

To evaluate the efficacy of mechanical ventilation and any adjustments made with the system, continuous monitoring with pulse oximeters (see Chapters 7 and 8**) must be maintained and/or blood gases obtained.** During the acute phase of illness, blood gases should be obtained 15 to 30 min after beginning ventilatory support or after any change in settings, every 4 to 6 hours if no change is made in ventilator settings, and as needed based on the clinical condition of the infant.

Arterial blood gases should be maintained in the following range (see Chapter 8**):**

- **PaO_2: 60 to 80 mm Hg**
- **$PaCO_2$: 35 to 45 mm Hg**
- **pH: 7.35 to 7.45**

Optimal arterial blood gas tensions are somewhat controversial. **To decrease the risk for acute lung injury by minimizing lung overdistention and barotrauma, some investigators advocate strategies that target lower PaO_2 and higher $PaCO_2$ ("permissive hypercapnia").**[75,442] The risks and benefits of such strategies depend on the specific clinical setting. If excessive ventilator settings are necessary to lower $PaCO_2$, allowing $PaCO_2$ to rise (to 50 to 60 mm Hg) (as long as the pH is greater than 7.25) is often accepted in an attempt to avoid lung injury. In addition, because the goal of respiratory care is to optimize

TABLE 23.8 USUAL EFFECTS OF CHANGING CONVENTIONAL MECHANICAL VENTILATOR SETTINGS

	CAUSES			
INCREASING	PAO_2	$PACO_2$	PH	COMPLICATIONS
FiO_2	↑	0	0	Oxygen toxicity (CLD/BPD, ROP); absorption atelectasis; FiO_2 may have no effect on oxygenation in the presence of severe R→L (right to left) shunt (PPHN), congenital heart disease, or marked intrapulmonary shunting as a result of severe parenchymal lung disease
CPAP/PEEP	↑	0/↑	0/↓	Hypoventilation with respiratory acidosis; decreased cardiac output with metabolic acidosis; air leaks
PIP	↑	↓	↑	Barotrauma with air leaks and CLD/BPD; respiratory alkalosis
Rate	↓	↓	↑	Respiratory alkalosis
I/E ratio (1:1–1:2)	↑	0	0	Increased intrapleural pressure; decreased venous return

CLD/BPD, Chronic lung disease/bronchopulmonary dysplasia; *CPAP,* continuous positive airway pressure; *I/E ratio,* inspiration to expiration ratio; *PEEP,* positive end-expiratory pressure; *PIP,* peak inspiratory pressure; *PPHN,* persistent pulmonary hypertension of the newborn; *ROP,* retinopathy of prematurity.

oxygen delivery to tissues, the effect of a given PaO_2 depends partly on cardiac function (see Chapter 24) and hemoglobin level (see Chapter 20). Accepting lower PaO_2 and O_2 saturation may lead to worse outcomes in the setting of systemic hypotension and poor cardiac function (e.g., sepsis). However, a recent follow-up study of the outcomes of ELBW preterm infants (24⅞ to 27⅞ weeks' gestation) from the SUPPORT trial found an association between higher $PaCO_2$ levels in the first 2 postnatal weeks and severe intraventricular hemorrhage and death, BPD and death, and neurodevelopmental impairment and death.[13]

Recognizing that aggressive ventilator management (e.g., intubation, high PIP, high MAP) is associated with increased lung injury and CLD/BPD, gentler ventilator techniques and management have been developed and are being used. Many gentler strategies incorporate relinquishment of traditional ventilator controls (from the health care provider) to patient control of ventilator parameters. Facilitated by computer-assisted technology, newer types of ventilators are being used. Volume-targeted versus pressure-limited ventilation results in significant reductions in death or BPD/CLD, duration of ventilation, pneumothorax, hypocarbia, and severe cranial ultrasound pathologies.[275]

Patient-Triggered Ventilation. Asynchrony between the infant's respiratory efforts and the ventilator is uncomfortable for the neonate and causes increased barotrauma, which contributes to lung injury (e.g., CLD/BPD). Altered cerebral blood flow may contribute to IVH. **Patient-ventilator synchrony occurs when patient-triggered ventilation (PTV) responds to the neonate's signal representing spontaneous respiratory effort and delivers a mechanical breath timed to the onset of inspiration.** PTV has been demonstrated to do the following[139,404]:

- Decrease asynchrony
- Improve gaseous exchange (e.g., oxygenation and carbon dioxide elimination)
- Create respiratory support that is more synergistic with the neonate's respiratory efforts
- Increase comfort for the infant, thus reducing the need for use of sedatives, narcotics, and paralyzing medications
- Decrease the need for ventilatory support

A recent systematic review of 22 studies comparing PTV with conventional mechanical ventilation (CMV) found fewer air leaks and a shorter duration of mechanical ventilation.[191]

Modes of PTV include the following:

- Synchronized intermittent mandatory ventilation (SIMV)
- Assist-control ventilation (ACV)—oxygenation, volume-guarantee ventilation (VGV), neurally adjusted ventilator assist (NAVA), and minute ventilation (V_{min})
- Pressure-support ventilation (PSV)
- Pressure-regulated volume control (PRVC)
- Proportional assist ventilation (PAV)

Synchronized Intermittent Mandatory Ventilation. **SIMV, a commonly used form of PTV, delivers mechanical breaths at a fixed rate. SIMV enables synchronization of ventilation breaths by sensing (through an airway or diaphragmatic sensor) the neonate's initiation of respiration and then triggering a mechanical breath.** Synchronized ventilation prevents the generation of excessive pressure within the respiratory tract when infant exhalation coincides with mechanical ventilation. Use of SIMV is associated with a decrease in (1) oxygen need, (2) duration of ventilator therapy, (3) incidence of BPD, and (4) severity of IVH and is more comfortable for the infant.[404] Use of SIMV is also associated with fewer episodes of hypoxia and better oxygenation as a result of improved ventilation-perfusion and increased resting lung volume (FRC) compared with IMV of VLBW infants.[168] Noninvasive ventilation strategies using synchronized nasal intermittent positive-pressure ventilation (SNIPPV) as a primary mode of support for preterm infants with RDS shows similar results compared with bilevel NCPAP.[446]

Assist-Control Ventilation. Newer neonatal ventilators are equipped with computer technology with rapid digital feedback circuits. **Computer-assisted control enables adjustments of FiO_2, PIP to control tidal volume, and ventilatory rate to control minute ventilation.** ACV is used in preterms with RDS, infants with a strong respiratory drive, and infants who are not heavily sedated. ACV is also more comfortable for the infant but may result in difficulty weaning from the ventilator because of diaphragmatic muscle atrophy.[404] Small studies have reported that

computer-assisted maintenance of target oxygen saturation is as effective as manual FiO_2 adjustments. Larger RCTs on safety and efficacy are warranted.

In volume-guarantee ventilation, a preset target tidal volume is maintained by the ventilator because the pressure limit varies inversely with lung compliance and the neonate's respiratory effort. Volume-targeted ventilation holds a significant advantage over pressure-targeted ventilation by delivering a physiologic tidal volume (about 4 to 5 mL/kg), potentially limiting excessive pressure and potential barotrauma. Historically, measuring physiologic tidal volume in the smallest infants, the location of flow sensor, and compensating for ET air leak had limited the utility of volume-targeted ventilation in the premature population.

Combining volume-guarantee with assist-control ventilation in the acute phase of RDS and SIMV in the weaning process results in less variable tidal volumes, shorter duration of ventilation, and a significant improvement in the combined outcomes of mortality and BPD/CLD rates in VLBW infants.[145] Another RCT of volume-guarantee SIMV ventilation and surfactant therapy found a shorter duration of ventilation and significantly fewer morbidities (i.e., ROP, BPD/CLD and IVH) in preterms with RDS.[204] Use of lower backup ventilation rates (i.e., 30 breaths/min rather than 50 breaths/min) enables greater triggering of ventilator inflations.[567] Certainly larger RCTs are necessary.

Neurally adjusted ventilator assist (NAVA) is a mode of ventilation that uses electromyographic (EMG) signaling from the diaphragm to match ventilator support to the infant's respiratory drive. EMG signaling from the diaphragm is acquired by electrodes embedded in a nasogastric tube and incorporated into a mechanical ventilator that converts the EMG signaling into a proportional assisted breath that is synchronized to infant-initiated breath. Diaphragm EMG activity is measured in magnitude (Edi signal). Ventilator support is adjusted by monitor Edi signal to optimize respiratory support. Early studies in neonates suggest improved patient ventilator interaction and synchrony with lower peak pressures.[48,67] Three studies compared NAVA to pressure-control ventilation[441,491] and to SIMV[308,441] in preterm infants and found that a lower PIP was required for adequate ventilation. Compared with pressure-control ventilation, NAVA also required the use of lower FiO_2, lower respiratory rate to achieve a lower pCO_2, and better compliance in five ventilated preterms less than 1500 g.[491] In the most recent study, 24 neonates receiving NAVA had higher respiratory rates, although their estimated work of breathing was improved.[441] Use of NAVA did not increase respiratory severity scores or resting energy expenditure.[441]

NAVA is available noninvasively by using nasal prongs, mask, or nasopharyngeal tube. An RCT of 15 premature infants under 32 weeks' gestation receiving noninvasive NAVA ventilation found improved patient-ventilator synchrony, even in the presence of large air leaks.[307] Premature infants may require a higher NAVA level[328] when transitioning from intubated to noninvasive NAVA. A *Cochrane* review of NAVA found no difference in rates of BPD/CLD, pneumothoraces, or IVH, and the duration of ventilation in one RCT. Well-designed trials to evaluate NAVA, a new type of triggered device, are needed.[440]

Minute ventilation (i.e., the volume of gas moving in and out of the lungs over time, expressed in mL per kg per minute) is a successful predictor of readiness to wean, extubate, and establish optimal pulmonary mechanics.[180] Mandatory minute ventilation (MMV), a new ventilator mode in the NICU, provides mechanically generated breaths only if the neonate's spontaneous breathing does not meet a minimum level of minute ventilation (chosen by the health care provider). If the infant's spontaneous pressure-supported breaths exceed the minimum minute ventilation, no additional breaths are delivered by the ventilator. If the infant fails to meet the specified minute ventilation, intermittent mandatory breaths are delivered at the preset tidal volume. **MMV enables the infant to control the rate, flow, and inspiratory time of the ventilator, which enhances synchrony and ensures a "backup" system to assume the work of breathing if the infant cannot maintain adequate minute ventilation.**[203]

Pressure-Support Ventilation. PSV complements the infant's respiratory effort by triggering a mechanical breath preset to a specific pressure. PSV decreases the work of breathing created by airway resistance (e.g., narrowed diameter of neonatal ETT) and ventilator circuit resistance.

PSV also decreases the work of breathing by assisting the activity of the infant's respiratory muscles. PSV is used alone (if the infant has effective respiratory drive) or in conjunction with SIMV. A recent systematic review found that SIMV + PS resulted in a longer duration of MV and more BPD/CLD when compared to high frequency oscillation.[191] PSV is useful in chronic and acute situations and in weaning chronically ventilator-dependent infants. When PSV was compared with SIMV, preterms exhibited better respiratory function (e.g., lower respiratory rates and less work of breathing), so PSV is effective for fatigued or weaning infants.[394] Another study comparing two levels of PSV with SIMV found that PSV increased total minute ventilation, stabilized breathing for preterms less than 32 weeks' gestation, and may be a useful strategy to wean preterms from mechanical ventilation.[202]

Pressure-Regulated Volume Control. PRVC delivers four breaths and modifies the ventilator's pressure to attain the prescribed tidal volume; breaths are both volume and pressure regulated. Studies show conflicting results: (1) safe and a lower incidence of air leaks and IVH[407] and (2) no benefit compared with SIMV in the treatment of RDS in preterm infants.[115]

Proportional-Assist Ventilation. In PAV, ventilator pressure increases in proportion to inspiratory volume (e.g., inspiratory flow varies to match the neonate's respiratory effort). Both volume and flow proportional assist relieve the neonate of both elastic (e.g., respiratory muscles) and resistive work of breathing. During PAV, the infant's breathing completely controls all variables of the ventilator breathing pattern through exceptionally fast computer-controlled feedback circuitry. In the initial trial using PAV in infants, lower MAP and transpulmonary pressure were used to effectively oxygenate and ventilate infants with mild to moderate respiratory insufficiency.[460] Respiratory rates were 50 to 80/min with a fast and shallow pattern and tidal volumes less than 5 mL/kg. A more recent RCT comparing PAV and PTV in ELBW preterms found that PAV safely maintained gaseous exchange at lower MAP compared with PTV. Although there were no adverse effects, the researchers concluded that backup conventional ventilation breaths must be provided during PAV to prevent apnea-related oxygen desaturations.[461] Two studies of PAV and SIMV for ventilation of neonates with RDS and MAS found that both were equally as effective with the infants on PAV having a shallower, more rapid breathing pattern with similar tidal volume and lower PIP and MAP.[579,580]

High-Frequency Ventilation. Barotrauma/volutrauma is a major contributing factor to the development of chronic lung disease or death from progressive lung injury in newborns treated with conventional mechanical ventilation. **The goal of HFV is to reduce barotrauma by the application of HFV early in the course of RDS or to reduce the progression of injury in infants who already have pulmonary interstitial emphysema, recurrent pneumothorax, or bronchopleural fistula. In addition to minimizing lung injury, the goal of HFV is to effectively enhance oxygenation over conventional ventilation.**

HFV differs from conventional modes of ventilator support, using smaller tidal volumes (less than anatomic dead space) at supraphysiologic frequencies and allowing for generation of lower intrathoracic pressure. At high frequencies, the calculated tidal volume is less than dead space. Thus the physics of gas flow and exchange are different from the traditional teaching of lung mechanics and are related to augmented diffusion. Reduction in barotrauma occurs by allowing for ventilation with very small pressure amplitude around the mean airway pressure in the distal airway. Therefore at high frequencies (commonly 10 to 15 Hz), the peak inspiratory and expiratory pressures approach MAP (i.e., lower downstream pressures). Because of this effect, higher MAP can be used to improve oxygenation without worsening lung injury.

HFV can be achieved by jet ventilators, oscillators, or high-frequency flow interrupters. Jet ventilators and HFV deliver short bursts of high-flow gases directly into the proximal airway via a small cannula and have a passive exhalation cycle. This ventilatory mode is usually augmented with a backup rate by a conventional ventilator that gives sigh breaths. The frequency range of high-frequency jet ventilation (HFJV) is 240 to 660 breaths/min (4 to 11 Hz).[139]

Oscillators vibrate columns of air and have active exhalation cycles. The usual frequency is 600 to 900 breaths/min (10 to 15 Hz). Oscillators (high-frequency oscillatory ventilation [HFOV]) are used both as a rescue therapy when

CMV is unsuccessful and electively as a primary mode of ventilation. The HFOV ventilator most commonly used is the SensorMedics 3100A, which uses a piston with a diaphragm to actively move gas into and out of the lung. Systematic reviews of early elective use of HFOV, compared with CMV, in preterm, late-preterm, and term infants found the following[104]:

- No effect on mortality rate at 28 to 30 days of life or at term equivalent age
- Significant reduction in risk of BPD/CLD at term equivalent age but effect was inconsistent across studies
- More air leaks and pulmonary interstitial emphysema
- Short-term neurologic morbidity (found in some studies; not statistically significant)
- No significant difference in rates of severe IVH (grades 3 or 4) and PVL
- Overall reduction of ROP
- No significant difference in long-term neurodevelopmental outcomes; one recent trial found significant reduction in the risk of cerebral palsy (CP) and poor mental development

Reviewers concluded that there was a small reduction in the incidence of CLD with the use of elective HFOV, but this result is weakened by its inconsistency across trials and is offset by an increased incidence of air leaks.[104]

An RCT comparing HFOV and SIMV in preterms with RDS found better early oxygenation, reduction in oxygenation index, and shorter length of stay in the HFOV-treated group; survival and complication rates were similar.[478] One small (n = 19 preterms 30 weeks' gestation or less) retrospective cohort study of HFOV with low oscillatory frequency found benefits (i.e., improved oxygenation, reduced MAP, survival) in preterms with PIE.[489]

When HFOV was compared with PSV plus volume guarantee (VG), early use of HFOV treatment was associated with a reduction in lung inflammation in preterms less than 30 weeks' gestation[117]; another study found VG to result in lower inflammation markers than HFOV.[320] A more recent RCT of HFOV versus SIMV-PSV in 366 preterm infants with severe RDS found (1) significantly higher mortality and BPD/CLD rates in the SIMV-PSV group; (2) fewer days of mechanical ventilation and hospitalization, as well as less ROP and need for surfactant with HFOV; and (3) less moderate to severe neurologic disability at 18 months in the HFOV group.[502] Discordance in study findings may be attributed to (1) maturity/immaturity of preterm infants, (2) time to initiation of HFOV, (3) use of antenatal steroids, (4) use of surfactant replacement, (5) differences in techniques used (e.g., presence or absence of lung volume recruitment strategy), (6) level of MAP, (7) duration of use, and (8) variations in cerebral blood flow (CBF) secondary to changes in pCO_2.[352] **Some researchers recommend that CMV be the first choice in treatment of preterm infants with RDS and HFOV be reserved for rescue therapy** if CMV is unsuccessful.[352] Further research is needed to clarify which ventilator should be used initially.

BOX 23.9 MINUTE VENTILATION (V_{min})

$$CV{:}V_{min} = TV \times RR$$

$$HFOV^{*}{:}V_{min} = fx\left(\text{Amplitude}, \text{Hz}^{-1}\right)$$

*There is a paradoxic effect with HFOV in which an increase in the frequency (Hz) actually decreases ventilation and therefore increases pCO_2. Conversely, decreasing Hz increases ventilation and decreases pCO_2.

CV, Conventional ventilation; *HFOV,* high-frequency oscillating ventilation; *Hz,* hertz; *RR,* respiratory rate; *TV,* tidal volume (PIP-PEEP).

Data from Donn SM, Sinha S. Invasive and noninvasive neonatal mechanical ventilation. *Respir Care.* 2003;48(4):426.

Remember that the rate of carbon dioxide removal is determined by minute ventilation. **Minute ventilation is the product of tidal volume and respiratory rate (TV × RR).** In CMV, the tidal volume and rate can both be adjusted by increasing or decreasing the breaths per minute (rate) and by increasing or decreasing the PIP or PEEP for tidal volume (TV = PIP − PEEP). In HFV, the same minute ventilation equation holds true, but the rate is set by breaths/min (hertz) and the tidal volume is determined by the amplitude (Box 23.9).

In HFOV, tidal volume is adjusted primarily by changing the amplitude setting. Amplitude is the amount of pressure oscillation that occurs around the MAP. **Increasing the amplitude will increase the tidal volume and therefore decrease pCO_2.** Conversely, decreasing the amplitude will

TABLE 23.9 CRITICAL FINDINGS
Comparison of Ventilator Options.

	LOW O_2	HIGH O_2	LOW CO_2	HIGH CO_2
CMV/SIMV	Increase PEEP Increase PIP Increase FiO_2	Wean PIP Wean PEEP Wean FiO_2	Decrease rate Decrease TV	Increase rate Increase TV
HFOV	Increase MAP Increase FiO_2	Decrease MAP Decrease FiO_2	Decrease Amp Increase Hz	Increase Amp Decrease Hz
HFJV	Increase MAP Increase FiO_2	Decrease MAP Decrease FiO_2	Decrease Amp Increase Hz	Increase Amp Decrease Hz

Amp, Amplitude; *CMV,* conventional mechanical ventilation; *Hz,* hertz; *HFJV,* high-frequency jet ventilation; *HFOV,* high-frequency oscillatory ventilation; *IMV,* intermittent mandatory ventilation; *MAP,* mean airway pressure; *PEEP,* positive end-expiratory pressure; *PIP,* peak inspiratory pressure; *SIMV,* synchronized intermittent mandatory ventilation; *TV,* tidal volume.
Data from Donn SM, Sinha S. Invasive and noninvasive neonatal mechanical ventilation. *Respir Care.* 2003;48(4):426.

decrease the tidal volume and therefore increase the pCO_2. Amplitude is initially set when chest rise is adequate and then slowly adjusted up or down in increments of one or two.

The respiratory rate in HFV is determined by the hertz setting. One hertz equals 60 breaths per minute. Therefore 10 hertz equals 600 breaths/min. The rate is initially set between 10 and 15 Hz. **There is a paradoxic effect of high-frequency breaths in the bronchi of the lungs so that when the hertz setting is increased, the pCO_2 increases. The opposite is also true.** Whereas HFOV has an active expiration phase, HFJV has a passive expiration phase and therefore uses a low CMV backup rate to deliver intermittent sigh breaths to prevent air trapping and augment pCO_2 removal.

Oxygenation in CMV and HFV is determined by the FiO_2 and the MAP. With use of HFOV in the rescue mode, the MAP is initially set 1 to 2 cm H_2O above the previous CMV setting. Adjustments for oxygenation (MAP, FiO_2) and ventilation (amplitude, Hz) can be made independently and can therefore be done simultaneously (Table 23.9). Chest x-ray studies are helpful in determining optimal lung volume. **As lung compliance improves—and it can improve quite rapidly after surfactant administration—there is a risk for overinflating the lungs with too much MAP.**[546] This increase in MAP leads to an increase in intrathoracic pressure that may result in air leaks or IVH or may impede venous return, which can in turn lead to hypotension. MAP is generally slowly increased or decreased in increments of 1 or 2. Chest x-ray studies, blood gases, and blood pressure should be monitored closely during HFV.

Synchronized mechanical ventilation, delivered as high-frequency positive-pressure ventilation (HFPPV), is another mode of oxygenation and ventilation in which positive airway pressure and spontaneous inspiration occur simultaneously. Adequate gas exchange should be achievable at lower peak airway pressures. HFPPV results in a reduction of air leaks and ventilator duration.

Nasal high-frequency oscillator ventilation (NHFOV) is a relatively new method of combining the benefits of high-frequency and noninvasive technologies.[359] A survey of European NICUs found that NHFOV, with binasal prongs, is used for preterm infants under 1500 g who fail NCPAP or NIPPV.[170] The most common adverse effects of NHFOV were abdominal distension, highly viscous secretions, and upper airway obstruction due to the secretions. A retrospective case series of 79 cases of NHFOV found: (1) 73% used as a rescue after failing another noninvasive therapy and for postextubation prophylaxis, (2) 58% transitioned to another noninvasive mode without needing intubation, and (3) there was a significant reduction in apnea, bradycardia and desaturations without any complications.[360] In a pilot study, NHFOV was compared to biphasic NCPAP in preterm infants

under 1250 g who failed CPAP and was found not to be superior to the biphasic NCPAP.[361] Large, multicenter trials of NHFOV are needed.

Inhaled Nitric Oxide. Vascular endothelial cells endogenously produce a potent vasodilator substance ("endothelium-derived relaxing factor"), later identified as nitric oxide. **Nitric oxide (NO), delivered as a gas, causes potent, selective, and sustained pulmonary vasodilation in the perinatal pulmonary circulation.**[271] The vasodilator response occurs as a result of inhaled nitric oxide (iNO) stimulation of soluble guanylate cyclase activity, increasing cyclic guanosine monophosphate (cGMP) in vascular smooth muscle and causing vasorelaxation. Selectivity of iNO for the pulmonary circulation is based on direct delivery of NO into the lung; because NO is avidly bound by hemoglobin in red blood cells and inactivated after metabolism to nitrite and nitrate, there are no direct effects on systemic arterial pressure.[271] In laboratory studies, iNO also reduces oxidative stress and pulmonary inflammation and enhances pulmonary alveolization and growth.[273] Potential toxicities include decreased platelet aggregation, hemorrhage, and methemoglobinemia.

Inhaled NO has been approved by the U.S. Food and Drug Administration (FDA) for treatment of late-preterm (>34 weeks' GA) and term neonates with persistent pulmonary hypertension of the newborn (PPHN)[271] **(see Persistent Pulmonary Hypertension of the Newborn later in this chapter). Use of iNO in term and late-preterm neonates with PPHN and respiratory failure decreases the need for extracorporeal membrane oxygenation.**[292] **Use of iNO in preterm infants (<34 weeks' GA) remains controversial with a National Institutes of Health (NIH) consensus statement recommending against the routine use of iNO in preterms (<34 weeks' GA).**[99]

Extracorporeal Membrane Oxygenation/Extracorporeal Life Support. Extracorporeal membrane oxygenation/extracorporeal life support (ECMO/ECLS) is a modification of cardiopulmonary bypass that allows more prolonged therapy than is traditionally performed in the operating room for cardiac surgery.[164] **ECMO/ECLS establishes a pulmonary bypass circuit, allowing gas exchange to occur outside the lung by perfusion of blood through a membrane oxygenator.** Blood is drawn from a catheter in the right internal jugular vein or right atrium, oxygenated as it crosses the membrane, and then returned to the patient via the right common carotid artery (venoarterial ECMO/ECLS) or the femoral vein (venovenous ECMO/ECLS). The pump produces a continuous, nonpulsatile flow through the membrane oxygenator as the patient is kept heparinized and continues to be ventilated at low pressures, rates, and oxygen tensions. **The goal of this therapy is to "buy time" for the severely injured lung to heal while attenuating ongoing lung injury by decreasing exposure to hyperoxia and barotrauma.** Therapy can be continued for several days until lung recovery appears sufficient to maintain adequate gas tension without ECMO/ECLS.

ECMO/ECLS therapy improves survival in term neonates with severe hypoxemic respiratory failure and PPHN. **ECMO/ECLS is used as a treatment of last option when neonates are unresponsive to maximum conventional support.** ECMO/ECLS criteria include the following[164]:

- GA 34 weeks or older, weight 2000 g or more
- Mechanical ventilation less than 10 to 12 days
- No significant coagulopathy or uncontrollable bleeding
- No major intracranial hemorrhage
- Reversible lung disease
- No lethal malformations
- No major uncorrectable cardiac lesions
- No severe asphyxia
- Failure of optimal medical management
- PaO_2 less than 50 mm Hg for 4 hours; Oxygenation Index (MAP × FiO_2 × 100/ PaO_2) of 25 to 40

Conditions treated with ECMO/ECLS include meconium aspiration syndrome, congenital diaphragmatic hernia, sepsis, pneumonia, PPHN, and air leak syndromes.

In the past two decade, the number of neonates being treated with ECMO/ECLS has declined by 40% to 50%.[492] Because ECMO/ECLS is invasive, labor intensive, costly, and involves risks associated with systemic anticoagulation (e.g., intracranial hemorrhage), alternative therapies (e.g., surfactant replacement, iNO, HFV, and pharmacotherapies) are used initially and have reduced the need for ECMO.[374] These therapies have changed the population being treated with ECMO/ECLS, shortened

length of stay, reduced costs, and raised concerns in delay of use of ECMO/ECLS.

Complications of ECMO/ECLS depend on initial disease process, pre-ECMO/ECLS factors (e.g., asphyxia, coagulopathy, hypoventilation, hyperventilation), and type of ECMO/ECLS used (e.g., venoarterial vs. venovenous). **The most common complications are hemorrhagic and nonhemorrhagic CNS insults.** A retrospective cohort study of data reported to the ECLS Organization from 7190 neonates receiving ECMO found 20% with neurologic complications and increased mortality.[413] Neonates who develop intracranial hemorrhage are at highest risk for mortality and poor neurodevelopmental outcomes. There is a high (74%) survival rate with ECMO/ECLS in neonates with PPHN; survival for congenital diaphragmatic hernia is 50%.[36] A recent cohort study of 130 neonates and children with pulmonary artery hypertension found that only 1.4% were treated with ECMO. Of those treated with ECMO, there was a higher risk of acute kidney injury, neurologic complications, sepsis, thrombotic conditions, and higher mortality rate.[370]

Partial Liquid Ventilation. Although prenatal administration of steroidal agents, use of surfactant, and HFOV therapies have improved the clinical course of sick preterm newborns with respiratory failure, the morbidity of severe RDS persists. Based on 40 years of experimental (animal) studies, perfluorocarbon (PFC) liquids have been found to improve gaseous exchange, lung mechanics, and cardiopulmonary stability in various respiratory diseases.[110,192] PFC liquids are suitable for liquid ventilation because of their high solubility of respiratory gases, easy elimination by evaporation from the lungs, and lack of metabolism by the body.[192] Instillation of an FRC of PFC liquid into the lungs during gaseous ventilation constitutes partial liquid ventilation (PLV). The best ventilator management during PLV has not been determined and may differ with underlying lung pathology.[192]

PLV is applicable to the surfactant and structurally deficient preterm lung because it reduces or eliminates surface tension forces, optimizes lung recruitment, and reexpands atelectatic lung. In a term infant, PLV is applicable to structural lung disease (e.g., diaphragmatic hernia) or lung disease associated with airway debris (e.g., aspiration syndromes or pneumonia). A nonrandomized, nonblinded clinical study of 13 preterm infants with severe RDS who failed to improve with CMV showed improved oxygenation within 1 hour of initiation of PLV.[306] A case report of partial liquid ventilation accompanying HFV showed improved gas exchange with a decrease in oxygenation index.[345] In infants with respiratory failure, a combination of PLV, iNO, and surfactant may produce optimal response. The safety and efficacy of PLV are undergoing phase III trials in adults in the United States; trials are contemplated in infants and children in Europe.

WEANING FROM THE VENTILATOR

When the infant's condition improves, ventilatory support is slowly removed. **Evidence of improvement includes biochemical and clinical parameters as follows:**

- Arterial blood gases are stable and physiologic.
- Spontaneous respiratory efforts occur in addition to ventilator-generated respirations and if the infant is disconnected from the ventilator for suctioning.
- There is increased activity and muscle tone and progressively decreasing FiO_2 requirement.
- For extremely preterm infants[84,333]:
  - Higher gestational age
  - Not SGA
  - Higher 5-minute Apgar scores
  - Arterial blood gases: pH and lower pCO_2 prior to extubation
  - Lower peak FiO_2 within the first 24 hours of life

Weaning an infant as soon as possible from intubation and the ventilator is associated with a decrease in the complications of intubation (see Table 23.10) and the incidence of CLD/BPD resulting from barotrauma, volutrauma, and oxygen toxicity. With IMV, there is a gradual decrease in mechanical ventilation with a corresponding increase in spontaneous respiration. **One ventilator setting at a time is changed, and arterial blood gases and pulse oximetry values are evaluated to determine the infant's response before another adjustment is made.** Because each ventilator parameter has risks and benefits, each parameter must be evaluated before the decision is made as to which one will be lowered. **Because high concentrations of oxygen are toxic to lungs and hyperoxia damages eyes, oxygen is usually lowered first in 5% to 10% increments to a**

TABLE 23.10 COMPLICATIONS OF ENDOTRACHEAL INTUBATION

COMPLICATIONS	COMMENTS
Immediate	
Malposition	
Too low	Usually in right mainstem bronchus; no or diminished breath sounds in left chest or upper right lobe; asymmetric chest movement; atelectasis (withdraw tube until breath sounds are heard bilaterally and equally)
Too high	Inadequate ventilation bilaterally; especially at lung bases
Esophageal	Air movement auscultated in stomach with no or inadequate breath sounds
Obstruction	
Plug	Partial—no change or diminished breath sounds audible Complete—distant or no breath sounds audible
Kinking of the Tube	
Head position	Flexion or extension of the head results in diminished or blocked airflow
Perforation	
Vocal cords Trachea Pharynx Esophagus/gastric	
Pulmonary Hemorrhage	Rescue surfactant for respiratory failure accompanying pulmonary hemorrhage may be considered (see Box 23.15)
Infection	Colonization in the neonatal airway increases with the duration of intubation; presence of ETT longer than 72 hours is associated with colonization; this biofilm may contribute to the chondritis that precedes subglottic stenosis; MRSA tracheal infection causes subglottic stenosis. Late-onset sepsis is more common in VLBW infants with prolonged ventilation; mechanical ventilation is a risk factor for nosocomial infection.[310,336]
Air leak	ETT displacement (e.g., into the right mainstem bronchus or to the level of the carina) is a major factor in the development of air leaks.[378]
Increased intracranial pressure	Suctioning increases mean BP, which increases cerebral blood flow velocity and intracranial pressure, which increases the risk for IVH/PVL (see Box 23.7).
Postextubation	
Migratory lobar collapse	Prevent and treat with pulmonary hygiene.
Diffuse microatelectasis	In VLBW infants may be associated with apnea; treatable by pulmonary hygiene or nasal CPAP or both
Long-Term	
General	Vocal cord inflammation, stenosis, and eventual dysfunction; tracheobronchial fistula; subglottic stenosis; tracheal inflammation and stenosis; necrotizing tracheobronchitis; contributes to CLD/BPD
Specific to the Type of Tube	
Orotracheal	Abnormal dentition; gingival and palatal erosion; palatal grooves
Nasotracheal	Otitis media; erosion of alae nasi and nasal septum; nasal stenosis

BP, Blood pressure; *CLD/BPD,* chronic lung disease/bronchopulmonary dysplasia; *CPAP,* continuous positive airway pressure; *ETT,* endotracheal tube; *IVH,* intraventricular hemorrhage; *MRSA,* methicillin-resistant *Staphylococcus aureus; PVL,* periventricular leukomalacia; *VLBW,* very-low-birth-weight.

level below 80%. PIP is lowered in 1 to 2 cm increments to a level of 16 to 18 cm H_2O, and respiratory rate is lowered in increments of 1 to 5 breaths/min until the infant has a rate of 15 to 20 breaths/min.

Failure of extubation results in a reintubation rate of 25% to 50% in ELBW/VLBW infants.[146,355,503] An automated analysis of respiratory behavior during a short period of ETT CPAP is being studied as a tool to predict extubation readiness.[433,466] **Nasal CPAP is effective in preventing extubation failure and decreasing CLD/BPD by preventing atelectasis, improving oxygenation, decreasing apnea/bradycardia, and improving thoracoabdominal motion synchrony, which indicates improved breathing strategy.**[267] Using NCPAP pressures in the range of 7 to 9 cm H_2O, instead of 4 to 6 cm, has been shown to reduce extubation failure in an RCT of preterms with a birth weight of 500 to 1000 g and GA of 23 to 30 weeks.[71] **Weaning an intubated neonate to ventilator CPAP increases the work of breathing associated with ETT resistance and dead space (e.g., breathing through a straw).** A meta-analysis of three RCTs comparing use of ventilator CPAP with extubation to nasal CPAP showed a significant advantage (e.g., decreased the risk for reintubation and ventilation) for extubation to nasal CPAP, especially using nasal prongs.[127] **When weaning from invasive to noninvasive respiratory support, use of prone positioning of preterm infants has also been shown to increase end-expiratory lung volume and tidal volume.**[539]

Despite the large body of evidence supporting NCPAP in prevention of extubation failure,[128] there is increasing use of HHHFNC instead of NCPAP after extubation. The largest multicenter trial compared the reintubation rates of 303 preterms (<32 weeks' gestation) randomized to HHHFNC or NCPAP after extubation.[334] **Significantly less nasal trauma was noted, as well as a failure rate of 34.2% in the HHHFNC group and 25.8% in the NCPAP group and successful treatment of the HHHFNC failures with NCPAP.** The researchers concluded that the efficacy of HHHFNC was similar and noninferior to NCPAP in very preterm infants after extubation.[334] The most recent studies (by the same group) compared the time to wean from HHHFNC versus NCPAP and the use of HHHFNC and NCPAP after extubation of preterm infants under 32 weeks' gestation.[484,485] There was no difference in time to successfully wean from HHHFNC and NCPAP and no difference in morbidities or complications between the groups; there was significantly less nasal trauma in the HHHFNC group.[485] The second study of 49 preterm infants (<32 weeks' gestation) randomized to HHHFNC or NCPAP after extubation found no difference in reintubation rates (8.3% HHHFNC vs. 8% NCPAP) within 72 hours of extubation and no difference in morbidities and complications except for significantly less nasal trauma with HHHFNC.[484] **A *Cochrane* review states that HHHFNC is equally efficacious in preventing treatment failure, death, and BPD/CLD, as most of the evidence reviewed was use of HHHFNC after extubation.**[570] Although HHHFNC use is associated with fewer pneumothoraces and less nasal trauma than NCPAP, further adequately powered RCTs are needed.[570]

Extubation directly to nasal CPAP has also been shown to be more effective than extubation directly to supplemental oxygen in a hood. A meta-analysis of six RCTs comparing nasal CPAP (by any method) with use of an oxygen hood after extubation found that nasal CPAP (1) decreases adverse clinical events (e.g., apnea, bradycardia, respiratory acidosis, hypoxia), (2) decreases the incidence of CLD/BPD, and (3) decreases the incidence of reintubation.[128] These positive effects increase when nasal prong CPAP is used compared with nasopharyngeal CPAP, and the benefits are consistent across ranges of weight and GA.[128]

For weaning preterm infants from mechanical ventilation, prophylactic use of nasal CPAP (with nasal prongs) has been defined as the standard of care. However, variations in therapeutic methods and devices are associated with variations in outcomes. Although RCTs demonstrate a clear advantage of nasal prongs over nasopharyngeal administration, differences in design of nasal prongs may alter effectiveness. **Use of binasal prongs is more effective than a single nasal prong in weaning ELBW infants from the ventilator.**[134] Use of nasal biphasic positive airway pressure (NBiPAP) is no more effective than use of NCPAP in preventing extubation failures in preterms (<30 weeks' gestation and <2 weeks of age).[549]

Various clinical strategies for initiation, management, and weaning of NCPAP are used. Use of NCPAP with the Aladdin/Infant Flow System (i.e., residual gas pressure is provided by the constant flow

of gas) decreases the work of breathing by a more stable volume recruitment in the lungs and has been shown to facilitate extubation in VLBW infants compared with nasal pharyngeal CPAP.[109] Other studies show equal efficacy (e.g., no differences in apnea, bradycardia, or desaturation) when nasal prong CPAP is compared with nasal synchronized IMV.[134] An RCT comparison of bubble CPAP versus Infant Flow Driver CPAP for postextubation support found that use of bubble CPAP reduced the mean duration of CPAP use by 50%, and there was a higher rate of successful extubation in preterms ventilated for 14 days or less.[202]

If NCPAP fails, the nasal route may also be used to administer mechanical ventilation, which augments the effectiveness of NCPAP, reduces respiratory rate and the inspiratory work of breathing, improves rates of successful extubation, stimulates respiratory drive, increases ventilation, decreases $PaCO_2$, and is even being used as the initial method of respiratory support.[388] After extubation of preterm infants, use of NIPPV decreases the incidence of extubation failure (from 48 hours through the first week) more effectively than NCPAP.[312] However NIPPV has no effect on the incidence of BPD or mortality. NIPPV that is synchronized and the type of device used may also affect the effectiveness of NIPPV.[349] SNIPPV after extubation in VLBW infants improves gaseous exchange and decreases respiratory effort.[232] Use of nonsynchronized nasal intermittent positive-pressure ventilation (nsNIPPV) compared to NCPAP after extubation results in a significant reduction in the duration of noninvasive ventilation and oxygen supplementation and decreased rates of BPD/CLD.[244]

Once adequate oxygenation and ventilation on CPAP alone have been maintained, the infant may be placed in an oxygen hood or on an NC. **Oxygen should be adjusted by using targeted saturation ranges with pulse oximetry.**

During the recovery phase of RDS (approximately 72 hours), changes in lung compliance occur rapidly. Hyperoxia, air leaks, increased intracranial pressure, and decreased cardiac output easily occur if high pressures and high oxygen concentrations are not decreased as rapidly as the lung is recovering.

Infants who are difficult or impossible to wean from the ventilator may have CLD/BPD, PDA, or CNS damage that affects the respiratory control center.

BOX 23.10 COMPLICATIONS OF RESPIRATORY DISEASE

1. Acute
   a. Sudden deterioration of condition
   b. Air leaks
   c. Central nervous system
      Hypoxic-ischemic injury
      Increased intracranial pressure
      Hemorrhage
   d. Cardiac
      Patent ductus arteriosus
      Decreased cardiac output
   e. Infection
   f. Bleeding diathesis
   g. Tube
   h. Pulmonary hemorrhage
2. Chronic
   a. Oxygen toxicity and barotraumas (CLD/BPD)
   b. Hyperoxia (retinopathy of prematurity)
   c. Hypoxia
   d. Tube

CLD/BPD, Chronic lung disease/bronchopulmonary dysplasia.

GENERAL COMPLICATIONS

Acute Complications

Acute and chronic complications are the result of the disease process, treatment, or both. Beginning with the least invasive therapy and progressing to more complicated ones, only as needed, accomplishes two goals: It individualizes therapy and minimizes the risk for complications. Continuous monitoring of the individual infant's progress is vital to decrease complications from the disease and from the interventions used to support the infant or treat the primary condition. **Complications of respiratory diseases are listed in** Box 23.10.

Sudden deterioration of the infant's condition is an emergency, and the cause must be found and corrected as soon as possible to minimize further damage. Causes of sudden deterioration are listed in Box 23.11.

RESPIRATORY

Management of an infant who has suddenly deteriorated begins with a visual inspection. The

BOX 23.11 CAUSES OF SUDDEN DETERIORATION

1. Tube
   a. Accidental extubation
   b. Accidental disconnection
   c. Plug
2. Machine malfunction
   a. Ventilator or continuous positive airway pressure device
   b. Oxygen blender
   c. Tubing and connections
3. Alarm system "off"
4. Severe hypoxia
5. Metabolic factors
6. Air leak
7. Intraventricular hemorrhage

oxygen hood, CPAP, or ventilator must be properly connected and free of water. If all connections are intact, the infant must be disconnected from assisted ventilation and connected to a resuscitation bag (which is connected to an oxygen source and kept at the bedside). Manual ventilation matching pressure, rates, and FiO_2 to ventilator settings must be maintained. **If the infant improves with these interventions, mechanical failure of the ventilator should be suspected.** Assistance should be summoned to find the mechanical problem or replace the system. The infant's respiratory effort must be manually assisted until the problem is solved.

If the infant does not improve with manual ventilation, there is probably a problem with the tube. The infant's condition can be assessed by auscultating the chest for quality of breath sounds. Findings and what they suggest are listed in Table 23.11.

The ETT should be suctioned quickly. If there is no improvement in clinical condition or air entry, the tube should be replaced while the infant is supported with bag-and-mask ventilation. **If the tube is too low, it can be repositioned by pulling it back 0.5 to 1 cm. If air entry and clinical condition improve with auscultation, the tube must be secured in the new position and a chest x-ray examination done to confirm tube placement. If assessment of the chest leads to suspicion of accidental extubation, the tube must be removed, ventilation with bag and mask administered, and reintubation performed.**

TABLE 23.11 CRITICAL FINDINGS CHEST AUSCULTATION FOR ENDOTRACHEAL TUBE PLACEMENT

FINDING	CAUSE
No air entry bilaterally	Esophagus intubated; air leak; plugged endotracheal tube (ETT)
Air entry over left upper abdominal quadrant	Esophagus intubated; air entry heard over stomach
Diminished air entry	ETT too high; air leak
Air entry unequal; right chest better aerated than left chest	ETT too low; down right mainstem bronchus

If the infant does not improve with manual ventilation and the tube is in place, an air leak or IVH could be the cause.

Monitors and ventilators are equipped with alarm systems to warn care providers of sudden changes in the infant's condition or support systems. **It is imperative that all alarm systems be maintained in the "on" position. Turning the alarms "off" during care for such procedures as suctioning and weighing creates the risk for forgetting to turn them on again.** In a busy NICU or in a single-room NICU design, the compromised infant may not be visually noticed until the hypoxia is so severe that resuscitation is more difficult or impossible. Monitor parameters (both high and low alarm settings) must be individualized for each infant and recorded (see Chapter 7).

A sick neonate may experience a severe hypoxic insult when oxygen is too rapidly altered during caregiving procedures. **Feeding, weighing, or turning without an alternative oxygen source may cause a sudden decrease in PaO_2, pulmonary vasoconstriction, hypoperfusion, and an iatrogenic worsening of the condition.** Prolonged ETT suctioning (15 to 20 seconds) causes hypoxia and atelectasis. Care must be organized to conserve energy, minimize hypoxic insults, and maintain the infant in physiologic homeostasis. **Alternative oxygen sources must be provided when the usual method of oxygen delivery is disrupted for giving care.** Small alterations in FiO_2 prevent rapid increases or decreases in oxygen tension.

METABOLIC FACTORS

Hypoglycemia must never be overlooked as the cause of sudden collapse. Undetected infiltration

or disconnection of intravenous fluids may cause a precipitous drop in blood glucose, with respiratory irregularity, apnea, or seizures. Quickly checking the blood glucose with a glucometer is always warranted. If low blood glucose is not the cause of the sudden deterioration, it may be a complication of the asphyxial episode. After the infant is stabilized, screening for hypoglycemia and providing adequate fluids and glucose are appropriate (see Chapter 15).

Hypothermia and overwhelming sepsis with their associated metabolic derangements may be the cause of sudden deterioration. Muted response to cold stress is a consequence of asphyxial insult, and cold stress must be avoided after the acute episode. A high level of suspicion for infection should accompany sudden deterioration (see Chapters 6 and 22).

AIR LEAKS

Physiology. When air dissects from an alveolus, it follows the tracheobronchial tree and may accumulate in the mediastinum (pneumomediastinum), in the pleural space (pneumothorax), in the space surrounding the heart (pneumopericardium), in the peritoneal cavity (pneumoperitoneum), or subcutaneously (subcutaneous emphysema). **Air leaks are complications of respiratory diseases and treatment strategies.** When air continues to accumulate, pressure builds in the pleural space, compresses the lung, and pushes the mediastinum toward the unaffected side and a tension pneumothorax results.

The free air released from ruptured alveoli may lead to *pulmonary interstitial emphysema* (PIE) (Fig. 23.1). **PIE is associated with preterm infants who were resuscitated with high concentrations of oxygen and had higher PEEPs and higher need for surfactant.**[381] The free air of PIE intravasates into interstitial tissue and can compromise pulmonary vascular circulation and ventilation. Localized pulmonary interstitial emphysema sometimes resolves spontaneously. Frequently, it can continue for weeks or even months. Use of HFV has improved the outcome of these infants.

Etiology. Infants at increased risk for the development of air leaks fall into three specific categories: healthy term neonates, neonates with pulmonary diseases, and neonates receiving positive-pressure support (CPAP and IMV).

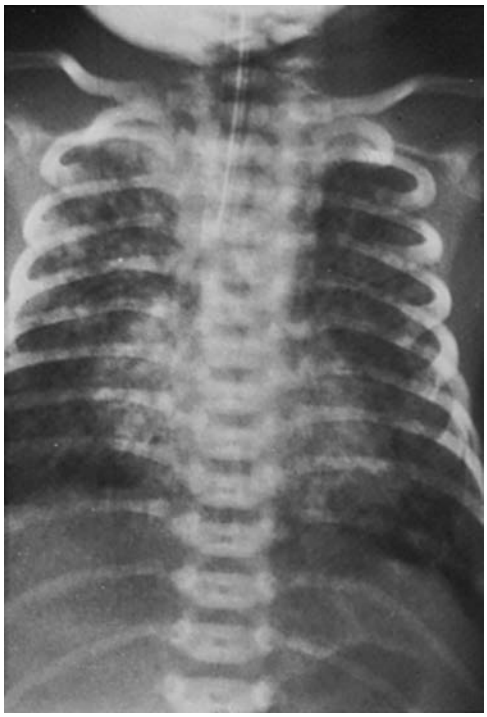

FIGURE 23.1 Pulmonary interstitial emphysema.

Healthy term neonates generate pressures of 40 to 80 cm H_2O for their first breath of life. Therefore a spontaneous air leak is more common in the neonatal period (2% to 10%) than at any other time of life.

Pulmonary diseases such as RDS result in stiff, noncompliant lungs requiring higher pressures for alveolar ventilation. Aspiration syndromes cause a ball-valve obstruction of debris with distal air trapping (meconium, milk, amniotic fluid, blood, and mucus). Hypoplastic lungs create a risk for air leaks because lung growth and development are abnormal and the lungs are stiff and noncompliant (diaphragmatic hernia and oligohydramnios syndrome). In either congenital lobar emphysema or PIE, alveolar rupture is associated with positive-pressure ventilation.

Positive-pressure ventilation, especially with excessive pressure, results in overdistention with alveolar rupture and air dissection. Air leaks occur in 16% to 36% of infants who are ventilated by CPAP or IMV or are resuscitated with a bag and mask or with an ETT and bag. **ETT displacement is a major factor in the development of air leaks** (see Table 23.10). Administration of surfactant

lowers the levels of ventilatory support necessary to ventilate the preterm infant's lungs adequately and results in a reduced incidence of pneumothorax.

Prevention. Using the least amount of positive pressure to obtain physiologic results decreases the chances of air leaks. The incidence of pneumothorax is reduced in surfactant-treated prematures and with the use of HFV. Scrupulously clearing the airway before resuscitation and using pressure gauges on resuscitation equipment may prevent aspiration and the possibility of inadvertently using pressure that is too high. Vigilance in positioning, securing, and maintaining ETT position may significantly reduce the incidence of air leaks.[378] Air leaks alter systemic hemodynamics and are associated with the development of IVH (see Chapter 26). Rapid recognition of at-risk infants, recognition of clinical manifestations and diagnosis, and rapid emergency treatment improve survival and decrease the long-term sequelae of hypoxia and ischemia.

Data Collection

History. Pneumothorax or other air leaks should be suspected when any one of the following infants takes a sudden turn for the worse:

- A preterm infant with RDS either with or without positive-pressure support
- A term or postterm infant with meconium-stained amniotic fluid
- An infant with a chest radiograph showing interstitial or lobar emphysema
- An infant requiring resuscitation at birth
- An infant receiving CPAP or positive-pressure ventilation

Signs and Symptoms. Asymptomatic air leaks occur in term neonates; these frequently require no treatment and resolve spontaneously in 24 to 48 hours. Gradual onset of symptoms is characterized by increasing difficulty in ventilation, oxygenation, and perfusion. Early clinical manifestations may include restlessness and irritability, lethargy, tachypnea, and use of accessory muscles including grunting, flaring, and retractions. These subtle clinical changes may be unnoticed until the infant progresses to a sudden, profound collapse.

Sudden and severe deterioration in clinical course is characterized by the following:

- **Profound generalized cyanosis**
- **Bradycardia**
- **Decrease in the height of the QRS complex on the monitor**
- **Air hunger, including gasping and anxious facies**
- **Diminished or shifted breath sounds**
- **Chest asymmetry**
- **Diminished, shifted, or muffled cardiac sounds and point of maximal intensity (PMI)**
- **Severe hypotension and poor peripheral perfusion**
- **Easily palpable liver and spleen**
- **Subcutaneous emphysema**
- **Cardiorespiratory arrest**

Laboratory Data. Arterial blood gas determinations reveal increasing hypoxemia (decreased PaO_2), increasing hypercapnia (increased $PaCO_2$), and a persistent metabolic acidosis with gradual onset of symptoms. Transillumination of the chest with a fiber-optic probe may reveal hyperlucency of the affected side compared with the other side. **A chest x-ray examination is the definitive diagnostic technique in air leaks. Ultrasound of the lung is highly accurate in diagnosing pneumothorax** and in one study was performed in 5.3 minutes (±5.6 minutes) versus 19 minutes (±11.7 minutes) for chest x-ray.[418] Because clinical manifestations of many other diseases may be similar to air leaks, the only way to be sure of the diagnosis is to perform a chest x-ray examination or chest ultrasound. **Anteroposterior and lateral films must be obtained, and a decubitus lateral x-ray film may be of value.** X-ray findings in pneumothorax, the most common air leak, include:

- Increased lucency, overall increase in size, and flattened diaphragm on the affected side
- Widened intercostal spaces
- Decreased or absent pulmonary vascular markings
- Sharp contrast of the cardiac border and diaphragm (sharp edge sign)

Tension pneumothorax results in mediastinal shifts with decreased volume, increased opacity of opposite lung, and deviation of heart and trachea to the other side.

Treatment. An air leak is a surgical emergency of the chest. Tension within the chest cavity compromises lung excursion and cardiac output; without prompt treatment, the infant will not survive. **Trained care providers must be available immediately to provide emergency management in any institution that provides positive-pressure ventilatory support.**

Evacuation of trapped air to decrease tension and allow proper organ function is the goal of treatment. Pneumomediastinum rarely needs to be treated, but pneumopericardium often results in cardiac tamponade and requires needle aspiration or tube drainage. Pneumoperitoneum must be differentiated from a perforated viscus.

A suggested conservative treatment is endotracheal intubation of the unaffected lung. The tube is advanced 1 to 2 cm beyond the carina to occlude the involved lung. This procedure is difficult to perform if the left lung is involved. If the pulmonary interstitial emphysema is localized to one lung or lobe of the lung, differential ventilation or surgical removal of the lobe may be curative. **Pneumothorax may be treated with needle aspiration of air. Tube thoracotomy with suction drainage is frequently necessary.**

Use of fibrin glue to treat persistent pneumothorax has been reported, with resolution within 24 hours of treatment.[450] Complications included (1) bradycardia requiring manual ventilation, (2) significant hypercalcemia, (3) diaphragmatic paralysis, (4) contralateral pneumothorax, and (5) localized tissue necrosis.

Immediate Supportive Care. **The head of the bed is elevated 30 to 40 degrees.** This decreases the work of breathing by using gravity to localize the air in the upper chest and to push the abdominal organs downward away from the diaphragm.

Oxygen at 100% concentration is administered. The two goals for using 100% oxygen for immediate care are to improve oxygenation in a severely compromised infant and to increase by as much as sixfold the rate of absorption of the trapped air by means of a nitrogen washout technique.

CAUTION: Prolonged administration of 100% oxygen to treat an air leak in term infants has been used. **Because of new understanding about the effects of oxidative stress from use of 100% oxygen, prolonged use for "nitrogen washout" should be used with caution** (see Supplemental Oxygen earlier in this chapter). Exclusive use of 100% oxygen to treat trapped air is contraindicated in preterm infants because of the risk for developing retinopathy of prematurity and the length of time necessary to obtain complete resolution.

A severely compromised infant requires immediate emergency procedures. A diagnostic and therapeutic thoracentesis may be necessary in life-threatening situations in which there is no time to wait for x-ray examination.

Needle Aspiration. **A scalp vein needle (23 to 25 gauge) or an Angiocath (24 gauge), a three-way stopcock, and a 10 to 20 mL syringe may be used for needle aspiration.** The equipment is connected (syringe-stopcock-needle/Angiocath), the chest is aseptically prepared, and the needle is inserted into the third intercostal space in the anterior axillary line. A slight pop may be felt when the pleura is entered. Air is withdrawn into the syringe and evacuated into the room by turning the stopcock. This procedure is repeated until no more air can be aspirated or a chest tube can be placed.

Chest Tube. **Chest tube thoracotomy is the definitive treatment for pneumothorax.** The insertion of a chest tube is an invasive procedure that requires strict surgical technique, with each operator wearing a gown, gloves, mask, and cap. The infant should be appropriately positioned, restrained, provided with a sucrose pacifier, and monitored before the chest is prepared for asepsis. Ideally, the anterior chest wall should be prepared with a scrub solution for a minimum of 3 minutes. If a special tray is not available, a minor suture tray will usually contain the necessary instruments.

Necessary equipment is as follows:

- Chest tube (8 to 12 Fr Argyle)
- Iodine or povidone-iodine (Betadine) scrub solution
- Gloves, gown, mask, hat
- Sterile drapes
- Syringes
- Sterile sponges (gauze)
- Medicine cups
- Lidocaine 1% without epinephrine
- Scalpel blades (no. 11 or 15)
- Hemostat (mosquito and Kelly clamps)
- Scissors
- Needle holder
- Sterile suture
- Sterile connectors (straight)
- Tubing
- Infant disposable underwater seal drainage system (two- or three-bottle or Pleur-evac system)
- Wall suction
- Sterile saline solution
- Tape, transparent dressing
- Chest tube clamp for emergency disconnection

The insertion site depends on the clinician's preference. In the lateral approach, the site is the fourth

to sixth intercostal space on or lateral to the anterior axillary line. In the superior approach, the site is the second or third intercostal space on or just lateral to the midclavicular line (Fig. 23.2). A case report of breast deformity, psychologic distress, and need for corrective surgery (in adolescent preterm girls) as a result of chest tube insertion for multiple pneumothoraces recommends a preventive strategy of using the anterior axillary line, maintaining a distance of 4 to 5 cm inferior to the nipple, and inserting the tube through the fifth or sixth intercostal space.[419]

After infiltration of the area with 1% lidocaine for pain control, a small incision is made. A purse-string suture should be placed around the incision with ends left loose. A curved hemostat is inserted into the incision and opened. The catheter is advanced through the interspace and into the pleural space. The most frequent error by an inexperienced operator is applying too little force to enter the pleural cavity. The purse-string suture is tightened and tied and then tied to the chest tube. The tube is connected to the underwater drainage system, which may then be connected to a continuous suction device (10 to 20 cm H_2O is most commonly recommended). The tube should be secured with tape. An x-ray examination is used to confirm placement of the tube and evaluate the effectiveness of the therapy. **Attention to pain control with opioids and/or nonnarcotic analgesics is also necessary after the procedure** (see Chapter 12).

Complications. In some instances, complications have arisen from the placement of chest tubes in neonates. These include hemorrhage, lung perforation, infarction, and phrenic nerve injury with eventration of the diaphragm. Clinical signs of eventration (elevation of the diaphragm into the thoracic cavity) include a shift of the umbilicus upward and toward the affected side.[338]

Care of Chest Tube and Drainage System. The chest tube drainage system removes air and fluid material from the pleural space to restore negative pressure and expand the lung. **Care providers must be familiar with the operation of the drainage system used in the nursery.** The single-bottle water seal system drains air and fluid by gravity and blocks atmospheric air from being drawn into the pleural space. In addition to the water seal, the multiple-bottle systems allow suction to be applied to facilitate drainage and expansion. The Pleur-evac system is a single plastic unit divided into three chambers: the collection, water seal, and suction chambers.

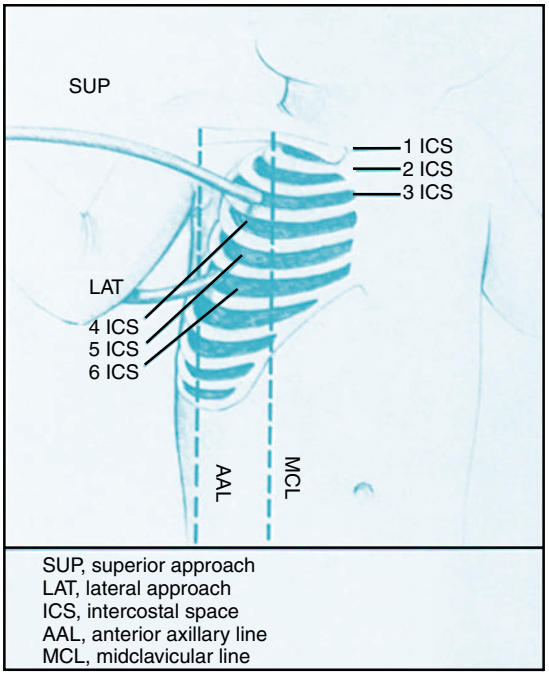

FIGURE 23.2 Chest tube insertion site. (From Oellrich RG. Pneumothorax: chest tubes and the neonate. *MCN Am J Matern Child Nurs.* 1985;10(1):31.)

Oscillation of fluid in the tube demonstrates effective communication between the pleural space and drainage bottle. In the small, sick infant, intrapleural pressure may cause only fluctuation in the tube at the chest wall. Fluctuation in either the tube or bottle should be observed. Fluctuation may cease as a result of fibrin or blood clots obstructing the tube, kinked or compressed tubing, or the suction apparatus not working properly. **Milking and stripping the chest tube generally are unnecessary if only air is being removed.** Presence of clots or debris may require gentle kneading of the tube. **Milking and stripping generate tremendously high pressures that may entrap and damage the lung in the chest tube eyelets.**

Bubbling in the drainage bottle indicates that air is being removed from the pleural space. Continuous bubbling may indicate an air leak in the system. To locate the source of the leak, the tube is momentarily clamped (beginning close to the chest and working toward the bottle) with a rubber-tipped hemostat. When the clamp is placed between the air leak and the water seal, the bubbling will stop. Patency of the tube, fluctuation, and bubbling should be observed and charted hourly.

Excessive or insufficient fluid in the drainage bottles may interfere with proper function of the drainage system. The bottle may have to be changed, or sterile saline may have to be added.

Frequent turning is important for maximum drainage and lung expansion. Proper stabilizing and positioning of the chest tube is necessary for function, comfort, and prevention of accidental removal. The tubing may be secured by encircling it with an adhesive tab, placing a safety pin through the tape (not the tube), and securing it to the bed. **If the tube becomes dislodged, the opening should be covered with sterile gauze and pressure applied until the tube can be replaced.**

When the infant is moved for such procedures as x-ray examination and weighing, the tube must be stabilized by holding it close to the chest. **If the closed system is disturbed (e.g., because of a broken bottle), the tube should be clamped with a rubber-tipped hemostat that always should be kept at the bedside.** The chest tube should be clamped for as short a time as possible. **After necessary clamping, vital signs and clinical conditions should be closely monitored.**

Bottles should be stabilized by being taped to an incubator or warmer so that they are not accidentally broken or picked up. **The bottles must always be below the level of the infant's chest to prevent water from being pulled into the pleural space.**

Removal of Chest Tubes. **The chest tube may be removed when bubbling has ceased for at least 24 hours and the chest x-ray films show no free air for 12 to 24 hours. Attention to pain relief during the removal process includes a sucrose pacifier and pharmacologic pain relief** (see Chapter 12). Rapid, sterile removal of the tube is followed by application of a petrolatum gauze pressure dressing.

CENTRAL NERVOUS SYSTEM INSULT

Acute insult to the CNS may result in increased intracranial pressure, hemorrhage, or hypoxic-ischemic brain injury (see Chapter 26).

CARDIAC COMPLICATIONS

CDP or IMV may exert sufficient pressure on the pulmonary capillary bed to raise pulmonary artery pressure and interfere with cardiac output. The effect of CDP or IMV on the pulmonary vascular bed and cardiac output may be alleviated by lowering the PIP or PEEP or both. At times, a fluid infusion to increase the intravascular volume may overcome the resistance to the pulmonary blood flow. The effect of MAP on cardiac output is difficult to monitor in most NICUs, because pulmonary artery or pulmonary wedge pressures are not routinely obtained. Until these measurements are routinely obtained, the best CPAP is determined only on clinical grounds.

PDA is the most common cardiac complication in neonates with respiratory disease. Most often it is manifested by an increasing oxygen requirement or increased dependency on ventilatory support (see Chapter 24).

INFECTION AND BLEEDING

Procedures such as intubation expose the neonate to the risk for acquired (nosocomial) infection. Scrupulous attention must be given to technique when caring for respiratory equipment, and performing procedures such as sterile suctioning of the ETT minimizes the risks for infection. **Handwashing before and after every contact with the neonate is the best method of preventing hospital-acquired infection in an already compromised, sick neonate.** Neonates who are severely ill with respiratory disease may exhibit bleeding diathesis at birth or during the acute phase of their disease. Early recognition and treatment is important (see Chapter 20).

Chronic Complications

CHRONIC LUNG DISEASE/ BRONCHOPULMONARY DYSPLASIA

Despite improvements in neonatal respiratory care, the incidence of BPD/CLD continues to be high and is the direct result of the survival of extremely premature infants (under 28 weeks' gestation).[125,303] **The incidence of CLD/BPD in mechanically ventilated preterm infants is inversely related to birth weight and GA. Need for mechanical ventilation at 7 days of life is associated with an increased risk for BPD.[303] The primary pathology of BPD/CLD is related to lung injury from positive-pressure ventilation and is a multisystem disease, and most of the treatment is supportive.**

BPD was first described by Northway and Rosan[380] as serial roentgenographic changes occurring in the lungs of premature infants who survived

hyaline membrane disease (HMD). **The clinical course of BPD is one of increasing respiratory distress and often is described as the chronic phase of RDS.** Although CLD is a more inclusive term, CLD occurs in a variety of conditions, including esophageal atresia, aspiration pneumonia, congenital heart disease, PDA, and meconium aspiration syndrome (MAS).

Recent changes in neonatal care have modified the classic stages of BPD as first described by Northway and Rosan.[380] In comparison with the infants in earlier studies, today's neonates with BPD are far more premature, have lower birth weights, and generally lack many of the radiographic changes of cystic lung disease. **The "new BPD" is characterized by arrested lung development resulting from interference with alveolarization, vascularization, and the development of excess tone and airway reactivity, primarily in preterm infants with birth weights under 1250 g.**[249]

The expanded definition and criteria for the diagnosis of BPD/CLD are listed in Table 23.12. A recent research study of infant (median age 52 weeks' PMA) pulmonary function testing in preterm infants (median GA at birth 25 weeks and median birth weight of 707 g) found that **severe BPD could be classified into obstructive (51%), restrictive (9%), and mixed (40%) types.**[470] Despite changes in care practices, the incidence of chronic lung disease in infants after NICU care remains a significant clinical problem, with an **incidence of 40% in extremely preterm infants (≤28 weeks' GA).**[125] Between 2009 and 2012, in ELBW (26 to 27 weeks' GA) born at US academic centers, the rate of BPD increased from 50% to 55%.[500] **The relative incidence of BPD/CLD is inversely related to GA:** (1) relative incidence of mild disease is 30.3%, (2) relative incidence of moderate disease is 30.2%, (3) relative incidence of severe disease of 16.4%.[2,149]

The incidence of BPD/CLD varies among NICUs[299] because of variations in respiratory management associated with oxygen toxicity and barotrauma and volutrauma. Although use of nasal CPAP is associated with lower BPD/CLD rates, increased use of intubation, mechanical ventilation, and high pressures (PIP and MAP) is associated with increased BPD/CLD rates. When mechanical ventilation is used, the shorter the duration, the less often BPD/CLD occurs.[76]

Pathophysiology. BPD/CLD is a disorder of primarily premature infants that is characterized by respiratory distress and impaired gas exchange. **The pathogenesis of BPD/CLD is one of chronic, constant and recurring lung injury with ongoing repair and healing of the injury.** Chronic injury and repair may itself prolong the need for the very factors that contribute to the development of BPD/CLD: oxygen therapy and

TABLE 23.12 DEFINITION AND CLINICAL CRITERIA OF BRONCHOPULMONARY DYSPLASIA (BPD)

GESTATIONAL AGE	<32 WEEKS	≥32 WEEKS
Time point of assessment	36 days PMA or discharge to home, whichever comes first	>28 days but <56 days postnatal age or discharge to home, whichever comes first
	TREATMENT WITH OXYGEN >21% FOR AT LEAST 28 DAYS PLUS	
Mild BPD	Breathing RA at 36 weeks' PMA or discharge, whichever comes first	Breathing RA by 56 days PMA or discharge, whichever comes first
Moderate BPD	Need* <30% oxygen at 36 weeks' PMA or at discharge, whichever comes first	Need* >30% oxygen at 56 days' postnatal age or at discharge, whichever comes first
Severe BPD	Need* ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 36 weeks' PMA or at discharge, whichever comes first	Need* ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 56 postnatal days or at discharge, whichever comes first

*A physiologic test confirming that the oxygen requirement at the assessment time point remains to be defined. This assessment may include a PO saturation range.
NCPAP, Nasal continuous positive airway pressure; *PMA*, postmenstrual age; *PPV*, positive-pressure ventilation; *RA*, room air (21%).
From Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Resp Critical Care Med.* 2001;163(7):1723. Reprinted with permission of the American Thoracic Society.

mechanical ventilation. In RDS, there is injury to the alveolar mucosa, airway mucosa, serum exudation membranes, and fibrin coagulation-forming hyaline membranes. If sufficient hypoxia occurs with resultant damage, the alveolar and airway epithelium and its basement membrane will hemorrhage and round cell infiltration will begin. Cellular and noncellular debris fill the alveoli and small airways. The obstruction causes microatelectasis, and unobstructed airways become hyperexpanded and emphysematous.

In the healing and repair process, type II alveolar cells or their precursors multiply and differentiate into type I pneumocytes, which provide alveolar epithelium. Cells of the basal layer of the pseudostratified, ciliated, columnar epithelium lining the airways multiply and migrate to cover the injured airway and rejuvenate the epithelium. During this healing phase, the rapidly multiplying and differentiating transitional cells are squamous or cuboidal and therefore appear "metaplastic." Epithelial metaplasia is one of the characteristics of BPD.

As healing occurs, increased inspired oxygen tensions, barotrauma, and infection continue to injure the cells that are taking part in the healing process.

Etiology. BPD/CLD is an iatrogenic disease caused by oxygen toxicity and barotrauma resulting from pressure ventilation. Even preterm infants with mild respiratory distress in the first week of life may develop **BPD/CLD. BPD/CLD is multifactorial, and prenatal predictors include prematurity (e.g., early GA and low birth weight), male gender, and maternal smoking and hypertension.**[356] A biomarker predictive of BPD/CLD has recently been identified by the presence or absence of microRNAs (miRNAs) in tracheal aspirates of preterm infants with severe BPD/CLD.[295] Reduction of miR-876-3p is associated with more severe BPD, whereas elevation of the same biomarker is protective. Combining a reduction in mi-876-3p with alteration in the neonatal airway (presence of Proteobacteria) strongly predicts premature infants who will develop BPD/CLD.[295]

Oxygen Toxicity. BPD/CLD has been documented in both long-term and short-term exposure to oxygen at both low and high levels (greater than 60% to 80%), as well as in infants treated with mechanical ventilation without supplemental oxygen. As a result of these findings, many units have instituted guidelines for oxygen use and monitoring of levels with pulse oximetry. **Avoidance of excessive oxygen exposure and careful attention to oxygen saturations and arterial PaO_2 may help reduce lung injury resulting from oxygen exposure.**[125] In high-risk, extremely low GA newborns, cumulative supplemental oxygen exposure is independently associated with BPD/CLD or death.[554]

Barotrauma/Volutrauma. Development of BPD/CLD is a result of barotrauma and volutrauma, almost exclusively in neonates receiving positive-pressure ventilation.[125] BPD/CLD has been described in infants who have received high PIPs and high PEEP[193] and neonates with pneumothorax and PIE.[125] The incidence of BPD/CLD is decreased when lower PIPs are used.[193] Although PIPs should be limited whenever possible, some infants with very noncompliant lungs require the use of high pressure for survival. Volutrauma (e.g., increased lung volume [stretch]) results in regional overdistention of lung units or airways, which may promote lung injury more than pressure itself.[125] **Using the smallest possible tidal volumes to inflate the lung avoids the overdistention and volutrauma that causes BPD/CLD.**[193,250]

Use of surfactant therapy and newer ventilatory techniques[75] has decreased the pressures necessary to adequately oxygenate and ventilate the neonate's lungs, as well as resultant air leaks. **A gentler ventilator strategy, "permissive hypercapnia" (e.g., accepting a $PaCO_2$ of 45 to 58 mm Hg) benefits the preterm by (1) use of lower PIP, MAP, rate, and tidal volume; (2) improving ventilation-perfusion matching; (3) decreasing days on ventilation, use of supplemental oxygen, and reintubation rates; (4) increasing oxygen availability at the tissue level; (5) increasing respiratory drive and decreasing apnea; (6) increasing cardiac output; and (7) decreasing BPD/CLD.**[75,442] An RCT in 16 tertiary centers in Germany studied the outcomes of ELBW infants with slight hypercapnia (pCO_2 values from 40–60 mm Hg) versus those with higher pCO_2 values (55–75 mm Hg).[521] The rates of BPD/CLD, death, IVH, ROP and neurodevelopmental outcomes did not differ between groups.[521,522] **Even though mild permissive hypercapnia is safe and has modest benefit, the optimal $PaCO_2$ level has not been determined.**

Use of HFV, HFV with surfactant replacement, and HFV with "high volume" technique are all associated with a decreased incidence of BPD/

CLD (see High-Frequency Ventilation earlier in this chapter).

Patent Ductus Arteriosus. **There is a high incidence of BPD among infants with PDA and congestive heart failure.** The amount of oxygen and peak inspiratory pressure necessary to support a neonate through the pulmonary complications of PDA may result in damage from oxygen toxicity and barotrauma. The increased pulmonary blood flow that occurs may also contribute to pulmonary damage. A persistent, hemodynamically significant PDA is an added risk for the development of BPD, whereas the duration of a smaller, nonsignificant PDA is not a risk factor for BPD/CLD.[455]

Because of these findings, medical closure of the ductus with indomethacin, ibuprofen, or surgical ligation is advocated (see Chapter 24) but has not affected the incidence of BPD. However, surgical ligation decreases mortality in extremely preterm infants.[562] Later PDA ligation and prolonged PDA is associated with BPD/CLD and death.[455]

Nutrition. **Preterm infants who are SGA or intrauterine growth restricted (IUGR) are undernourished in utero and at twice the risk for the development of BPD/CLD and neonatal mortality.**[160,383,411] Because growth restriction compromises lung development and function, preterm infants who are SGA/IUGR also are at increased risk for developing pulmonary hypertension with their BPD.[125,411] **Provision of adequate nutrition in the first week of life—especially enteral nutrition—is critical in decreasing the risk of BPD/CLD.**[125,411] Postnatally, inadequate **nutrition caused by poor intake or increased nutritional requirements resulting in catabolism potentiates the effects of oxygen and barotrauma on the neonatal lung. In VLBW preterm infants, exclusive breastmilk intake resulted in slower weight gain but a reduced risk of BPD/CLD.**[463,487] Enteral supplementation of docosahexaenoic acid (DHA) does not decrease the risk of BPD.[100] Optimizing nutritional support of infants at risk of BPD/CLD is an area of active research (see Chapter 17).

Fluids. **BPD/CLD is common in preterms who have developed symptoms of fluid overload within the first few days of life.** Fluid balance in a VLBW infant is complicated by huge insensible water loss and often intolerance for enteral feedings. **Intake, output, and changes in weight must be closely monitored to calculate the fluid needs.** A retrospective chart review of preterm infants (<32 weeks' GA and <1500 g birth weight) found that those infants with a **higher fluid intake in the first 2 to 4 days of life were at an increased risk for the development of severe BPD/CLD.**[199]

Family History of Asthma. **Maternal asthma is associated with an increased risk of BPD/CLD in their preterm infants,** particularly if the mothers did not receive antenatal steroids.[175] The lungs of these infants may be less tolerant of the insults of pulmonary disease, oxygen, pressure, and fluids.

Prematurity. **Developmental immaturity is of principal importance in the etiologic picture of BPD/CLD.** Premature births alone may have a significant effect on pulmonary development, because **prematurity results in differences in the development of small airways.** As a result, premature infants are more susceptible to additional damage to the small airways from oxygen, ventilator pressure, fluids, and circulatory overload.

Oxygen and Antioxidants. Oxygen accepts free electrons generated by oxidative metabolism within the cell and produces free radicals, molecules that are toxic to living cells or tissues. Normally, antioxidants protect cells against free radicals, but this balance may be upset by increased free radical production or decreased antioxidant defense. **A preterm neonate is deficient in antioxidants and thus more susceptible to lung damage from free radicals and oxidative stress when subjected to hyperoxemia for even brief periods of time.**[125,546]

Inflammation/Infection. **Oxygen radicals, barotrauma, infection, and other factors initiate the inflammatory process,** resulting in the infiltration of leukocytes, with release of other inflammatory mediators, resulting in pulmonary damage (e.g., decrease in capillary endothelial integrity, albumin leakage in the alveoli resulting in pulmonary edema). **Neonates whose lungs are mechanically ventilated have increased pulmonary cytokine and phagocyte levels within 1 to 3 hours after the onset of mechanical ventilation.**[530] Blood cytokine levels differ among preterm infants with classic versus atypical BPD and those without lung disease.[114] Activated neutrophils release enzymes that directly destroy the elastin and collagen of the lung. **Lung inflammation and injury predispose the lung to increased susceptibility to volutrauma and oxidant-induced lung injury.**[125] This inflammatory cycle produces significant pulmonary injury during a critical period of rapid lung growth and development (24–40 weeks) (see Table 23.1). Two systematic reviews show that chorioamnionitis is not a risk factor for the development of BPD/

CLD, but postnatal infection, including nosocomial infection, is a risk factor for the development of BPD/CLD.[33,213,299,336] Variation in nosocomial infection rates may be a factor in the variation in inter-NICU BPD/CLD rates.

Prevention. Potentially better practices to reduce the BPD/CLD in VLBW infants are listed in Box 23.12. Widespread use of antenatal steroids and surfactant administration has not reduced the rate of BPD/CLD or the NICU disparities in BPD/CLD rates in extremely preterm infants.[500] **A single course of antenatal steroid therapy decreases the incidence and severity of BPD/CLD.**[372] Premature and full-term infants (with pneumonia or MAS) treated with surfactant replacement have a lower incidence of BPD/CLD because of (1) better ventilation and pressure distribution in the alveoli, (2) stabilization of the alveoli, (3) prevention of overdistention, and (4) decreased cytokines and inflammatory response.

Noninvasive respiratory support using NCPAP or mechanical ventilation using the nasal route reduces or eliminates the need for intubation and mechanical ventilation.[127,312,314,501] However, despite the increased use of noninvasive ventilation strategies, one prospective, longitudinal follow-up study of extremely preterm infants found an increase in oxygen dependence at 36 weeks and worse lung function at 8 years of age.[143] In an attempt to prevent reinjury and allow healing, **inspired oxygen tensions should be kept as low as is reasonable to provide adequate arterial oxygen tension. Pressures on the ventilator should be reduced when possible to prevent barotrauma.**

Use of iNO in care of preterms with RDS remains controversial. A systematic review of 17 RCTs of inhaled nitric oxide therapy in preterm infants found that iNO does not improve survival without BPD/CLD.[41] Although iNO reduces inflammatory markers in tracheal aspirate of preterm infants, there was no effect on survival without

BOX 23.12 POTENTIALLY BETTER PRACTICES TO REDUCE THE INCIDENCE OF CLD/BPD IN THE VERY-LOW-BIRTH-WEIGHT PRETERM INFANT

- Use NCPAP in delivery room and as initial respiratory support as an alternative to routine intubation and early/prophylactic use of surfactant*
- Early NCPAP as the initial respiratory support decreases the need for surfactant*
- Combine early NCPAP with selective noninvasive surfactant therapy in extremely preterm infants[14,412,513,590] (see Table 23.15)
- Avoid endotracheal intubation for surfactant administration[417;457,513] (see Table 23.15) and mechanical ventilation[171]
- Use noninvasive mechanical ventilation strategies such as NCPAP, NSIPPV, BiPAP: compared with mechanical ventilation, prophylactic noninvasive ventilation reduces the need for invasive (endotracheal intubation) mechanical ventilation and surfactant, the incidence of BPD/CLD and death or BPD/CLD in very preterm infants†
- Use of the antioxidant *vitamin A*[124,462,533]
- Optimal nutritional management (exclusively with human milk)[463,487] to promote adequate growth and pulmonary healing[125,411] and prevent postnatal growth restriction[160,383] (see Chapters 17 and 18)
- Use of permissive hypercapnia[75,442]
- Decrease the incidence of sentinel events such as air leaks and unplanned extubations
- Minimize exposure in the delivery room to supplemental oxygen by titrating FiO_2 and monitoring oxygen saturations with PO to maintain normoxia[452]
- Early closure of PDA, either medically or surgically
- Monitor and minimize tidal volumes on mechanically ventilated preterms
- Extubate from assisted ventilation as soon as possible[174,245,432]
- Use nasal bubble CPAP[174,258,339,363,444]
- Improve teamwork in the delivery room[452]
- Use Neopuff instead of hand ventilation to minimize overinflation of the preterm lung
- Provide consistent respiratory management and consistent ventilator weaning
- Provide blended FiO_2 in the delivery room and during transport to the NICU to minimize exposure to unnecessary levels of supplemental oxygen[452]
- Early use of steroids: low-dose hydrocortisone therapy,[46,47] inhaled budesonide,[44] or budesonide/surfactant intratracheal instillation[58,584,585]
- Early use of caffeine therapy‡
- Prevent and treat infections[160,300,595]

* References 14, 150, 359, 417, 441, 453, 457, 502, 506, 508, 518, 595.
† References 242, 316, 317, 392, 452, 506.
‡ References 11, 147, 288, 331, 353, 597.

BiPAP, Biphasic positive airway pressure; *BPD,* bronchopulmonary dysplasia; *CLD,* chronic lung disease; *CPAP,* continuous positive airway pressure; FiO_2, fraction of inspired oxygen; *NCPAP,* nasal continuous positive airway pressure; *NICU,* neonatal intensive care unit; *NSIPPV,* nasal synchronized intermittent positive-pressure ventilation; *PDA,* patent ductus arteriosus; *PO,* pulse oximeter. Adapted from Geary C, Caskey M, Fonseca R, et al. Decreased incidence of bronchopulmonary dysplasia after early management changes, including surfactant and nasal continuous positive airway pressure treatment at delivery, lowered oxygen saturation goals, and early amino acid administration: a historical cohort study. *Pediatrics.* 2008;121(1):89; Payne NR, LaCorte M, Sun S, et al, and the Breathsavers Group. Evaluation and development of potentially better practices to reduce bronchopulmonary dysplasia in very low birth weight infants. *Pediatrics.* 2006;118(suppl 2):S65.

BPD/CLD.[302] Other studies show that early low-dose therapy with iNO did not decrease the overall risk of chronic lung disease and mortality or survival without neurodevelopmental impairment.[214,247] Long-term pulmonary outcomes of preterm infants treated with iNO remain inconclusive and study results inconsistent.[492]

In a multicenter trial, administration of vitamin A (e.g., 5000 international units IM three times a week for 4 weeks) to VLBW infants slightly reduced the risk for BPD/CLD.[533] Monitoring of serum levels (the desired range of plasma vitamin A concentrations is 30–60 mcg/dL; the desired plasma retinol-binding protein [RBP] concentration is >25 mg/dL)[462] and assessment for manifestations of toxicity (e.g., lesions on skin/mucous membranes, bone and joint abnormalities, jaundice, hepatomegaly, and increased intracranial pressure) should accompany vitamin A administration.[469] However, in another study, oral supplementation of vitamin A (e.g., 5000 international units/day for 28 days) in ELBW infants did not significantly alter the incidence of BPD/CLD.[557] A *Cochrane* review of 11 RCTs found that supplementing VLBW infants (<1000 g) with vitamin A is associated with a small benefit in the reduction in death, oxygen requirement at 1 month of age, and chronic lung disease (oxygen requirement at 36 weeks' PMA).[124] The *Cochrane* review concludes that use of repeated IM doses of vitamin A may be based on: (1) the local incidence of BPD/CLD, (2) the value of a "modest" reduction of BPD/CLD, (3) acceptability, and (4) the lack of evidence of either benefit or harm (neurodevelopmentally) from use of vitamin A.[124] Another systematic review of four studies concluded that vitamin A injections have benefit with minimal risk and supplementation is warranted.[462] The multicenter NeoVitaA Trial evaluating the efficacy of high-dose oral vitamin A supplementation for 28 days on the incidence of BPD or death in ELBW preterm infants is now in progress.[344]

Prevention of oxygen free radical injury to the pulmonary tree and CNS (e.g., CLD/BPD and IVH/PVL)[294] occurs with intratracheal injection of recombinant human CuZn superoxide dismutase (rhSOD). A significant decrease in markers of pulmonary inflammation occurred in rhSOD-treated preterm infants without short- or long-term abnormalities.[126]

Data Collection

History. A history of prematurity, moderate to severe RDS, intubation with oxygen and positive-pressure ventilation in the first week of life, inability to be weaned from the ventilator, and increasing oxygen requirement at the end of the first week of life are associated with BPD/CLD. Long-term features include tachypnea, rales, retractions, abnormal chest x-ray examination results, and the need for supplemental oxygen for more than 28 to 30 days of life or at 36 weeks' postmenstrual age.

Signs and Symptoms. Tachypnea, exercise intolerance (feeding and handling), oxygen dependence, and respiratory distress (retractions, nasal flaring, fine rales at the bases or throughout the lung fields) are associated with BPD/CLD.

Laboratory Data. X-ray findings (Fig. 23.3) correlate with the stage of disease, but the pathologic changes are often more severe than the chest x-ray findings indicate[380]:

- Stage I: Reticulogranular pattern and air bronchogram or RDS (first 3 days of life)
- Stage II: Coarse granular infiltrates that are dense enough to obscure the cardiac markings (first 3 to 10 days of life)
- Stage III: Multiple small cyst formation within the opaque lungs and visible cardiac borders (first 10 to 20 days of life)
- Stage IV: Irregular larger cyst formation that alternates with areas of increased density (after 28 days of life)

Mild hyperinflation as demonstrated on a chest x-ray film is a common finding in VLBW infants with BPD/CLD.

Cardiovascular changes include (1) right ventricular hypertrophy on ECG, (2) elevated right ventricular systolic time intervals or left ventricular and septal wall thickening on echocardiogram, or (3) elevated pulmonary vascular pressures and resistance at cardiac catheterization.

Treatment. The therapeutic goal is to reduce those factors that produce reinjury and to allow the lung to heal so that normal function can resume. This process may take weeks, months, or even years in severe lung injuries or in small infants under 1000 g.

Concurrent supportive therapies include (1) maintenance of adequate oxygenation and ventilation, (2) adequate nutrition and fluid restriction, (3) early PDA closure, and (4)

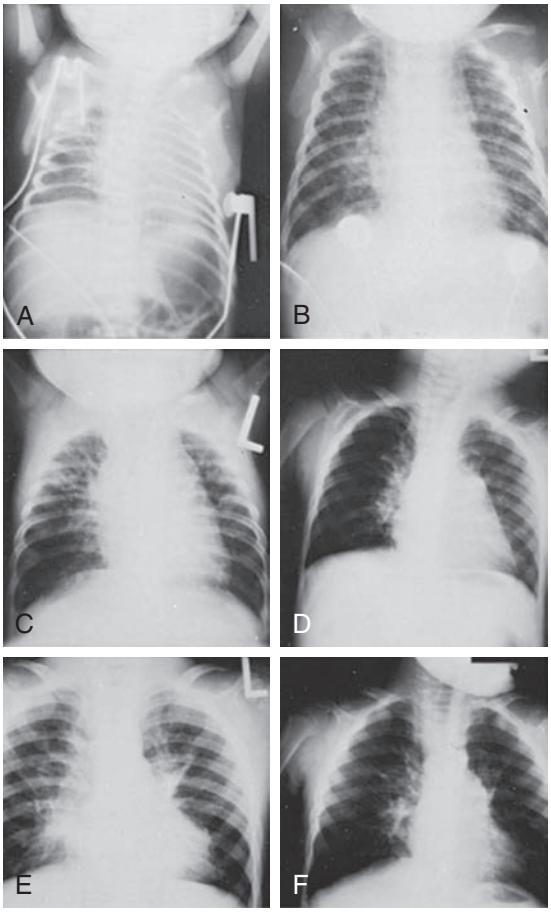

FIGURE 23.3 Serial chest x-ray films of premature infant with bronchopulmonary dysplasia over 2-year period. **A,** Newborn. **B,** Two months. **C,** Three months. **D,** One year. **E,** Two years. Infant's disease process was characterized by multiple hospitalizations for reactive airway disease and pulmonary hypertension. Note progressive lung disease characterized by hyperinflation and eventual clearing of infiltrate by 2 years of age **(F)**.

pharmacologic management. Sufficient PIP should be used to prevent atelectasis while maintaining the lowest FiO_2 (if possible, 0.5 or lower) to maintain adequate oxygenation (i.e., PaO_2 60–80 mm Hg; O_2 saturation 90%–95%). Weaning from mechanical ventilation is done slowly and may be facilitated by (1) use of SIMV that reduces the work of breathing, (2) use of methylxanthines before extubation, and (3) use of nasal CPAP after extubation.[127,128] **Usually in BPD/CLD, the infant's ability to maintain ventilation develops before the ability to maintain adequate oxygenation.** Often infants are discharged from the NICU on home oxygen therapy. **Infants with BPD/CLD who require oxygen at a rate of 20 mL/kg/min or less and those who can maintain oxygen saturations of 92% or above after 40 minutes of breathing room air are ready to begin successful weaning from supplemental oxygen.**[476]

Neonates with BPD/CLD have an increased resting metabolic expenditure as the major reason for growth failure, especially in the smallest, sickest infants.[290] **These infants may require 150 to 200 kcal/kg/day to support adequate growth** (i.e., 10–30 g/day weight gain). Without adequate protein or caloric intake, damaged pulmonary tissue cannot heal, and provision of appropriate nutrition to the neonate with BPD is essential (see Chapters 14 through 18).

Pharmacologic management of BPD/CLD includes the use of bronchodilators, steroids, and diuretics (see Table 23.12). Inhaled and systemic bronchodilators improve lung mechanics and gaseous exchange by relaxation of bronchial smooth muscle.[125] However, bronchodilators may fail to relieve airway obstruction because of relatively poor development of bronchial smooth muscle in preterm infants.

Methylxanthine therapy promotes weaning of infants with RDS from low rates of ventilatory support.[218] A meta-analysis of seven trials evaluating the prophylactic use of methylxanthine treatment for successful extubation observed a significant reduction in the incidence of failed extubation within the first week of life.[218]

Diuretics alone and diuretics combined with methylxanthines improve lung mechanics, clinical respiratory status, and ability to wean from mechanical ventilation (Table 23.13). Aerosolized diuretics (e.g., a single dose of furosemide at 1 mg/kg) transiently improve lung mechanics in preterms older than 3 weeks with BPD/CLD. RCTs are needed to evaluate the effects of aerosolized diuretics on oxygen dependence, mortality rates, duration of ventilator use, length of stay, and long-term outcomes.[66]

Steroids reduce lung inflammation and improve pulmonary function in severe RDS. Use of a single course of antenatal steroid (ANS) therapy is associated with (1) improved survival, (2) more rapid ventilator weaning and less need for mechanical ventilation because of decreased severity of RDS, (3) decreased need for supplemental oxygen (e.g., BPD/CLD), (4) lowered incidence of IVH, PDA, NEC, and (5) less systemic infection in the first 48 hours of life.[372,431] **ANS is most effective when**

TABLE 23.13 PHARMACOLOGIC AGENTS USED IN TREATMENT OF CHRONIC LUNG DISEASE/BRONCHOPULMONARY DYSPLASIA

DRUG	DOSAGE	COMMENTS
I. Bronchodilators A. Inhaled 1. Beta$_2$-agonists		During first month of life, longer duration of MV is associated with bronchodilator use. Among US CHs, use ranges from 0%–81%.[481] Response to bronchodilator therapy depends on the type of severe BPD with the best response, 74% in obstructive BPD, 63% in mixed types, and 25% in restrictive types.[470] Further clinical trials are needed to assess the role of bronchodilators in the treatment and prevention of CLD/BPD.[376]
a. Albuterol (Proventil; Ventolin)	0.1 mg/kg up to 5 mg in 2 mL of NS solution q 4–6 hr Max dose: 0.5 mL or 2.5 mg/ treatment; up to six treatments/24 hr Onset: 5–15 min Peak action: 30 min to 2 hr Duration: 3–4 hr	Drug of choice for bronchospasm—improves pulmonary resistance and lung compliance by bronchial smooth muscle relaxation; tachycardia, tremors, nausea and vomiting; can cause paradoxic bronchoconstriction, irritability. MDI dosage improves lung function and nebulization and is faster and more cost effective.
b. Terbutaline (Brethine)	0.03–0.3 mg/kg/day Onset: 5–30 min Duration: 3–4 hr	Same as for albuterol.
2. Histamine inhibitor (Cromolyn: 20 mg/2 mL solution for nebulizer)	10–20 mg TID	Prevents release of inflammatory mediators and reduces airway hypersensitivity; urticaria, rash, and throat irritation; dosage may need adjusting in patients with hepatic or renal dysfunction. A systematic review showed no significant evidence that cromolyn has a role in the treatment or prevention of CLD/BPD.[377]
B. Systemic 1. Methylxanthines		
a. Caffeine citrate	Loading: 20 mg/kg Maintenance: 5 mg/kg/day IV or PO Half-life: as long as 100 hr	Promotes weaning from low rates of ventilatory support by reduction of pulmonary resistance, improved lung compliance, and improved skeletal muscle and diaphragmatic contractility; has diuretic effect; excreted unchanged in urine; safer drug with fewer side effects than theophylline. Side effects are rare but include tachycardia, diuresis, dysrhythmias, glucosuria, seizures, ketonuria, vomiting, hyperglycemia, jitteriness, hemorrhagic gastritis.
b. Theophylline	PO: 4–6 mg of active theophylline, which should produce a serum level of 10–20 mcg/mL Maintenance: calculated by rate of plasma clearance, usually 3–7 mg/kg/day q 12 hr Half-life: 30–40 hr IV: Loading: 4.6 mg/kg over 30 min. Maintenance: From 0 to 24 days of age: 1 mg/kg IV q 12 hr > 24 days of age: 1.5mg/kg IV q 12 hr	Metabolized to caffeine in the liver and excreted in urine; multisystem effect; CNS stimulant; increases respiratory rate, inspiratory drive, and surfactant production; increases GFR; increases heart rate, contractility, and output; decreases GI motility and increases GI secretions; increases glucose levels, ketonuria, and glycosuria; increases muscle contractility; increases catecholamine and insulin levels. Side effects: same as for caffeine citrate.
2. Beta$_2$-agonists		
a. Terbutaline	5 mcg/kg subcutaneously q 4–6 hr	Improves pulmonary mechanics; side effects same as for albuterol; adjunct to methylxanthines.
b. Albuterol	0.15 mg/kg/dose PO q 8 hr	Reduces pulmonary resistance; adjunct to methylxanthines; side effects same as albuterol.

Continued

TABLE 23.13 PHARMACOLOGIC AGENTS USED IN TREATMENT OF CHRONIC LUNG DISEASE/BRONCHOPULMONARY DYSPLASIA—CONT'D

DRUG	DOSAGE	COMMENTS
III. Steroids		
A. Inhaled		
1. Corticosteroids (dexamethasone [Decadron])	100 mcg/inhalation from MDI	30%–60% systemic bioavailability versus 53%–78% from oral intake; majority removed from lung within 20 min after administration; anatomic, physiologic, and pathophysiologic variations in the neonate, coupled with the aerosol delivery system and its use, influence the amount of drug actually administered and the aerosol's efficacy. Side effects: oral candidiasis, bronchospasm, and pituitary-adrenal suppression, tongue hypertrophy. Increasing evidence that early administration of inhaled corticosteroids to VLBW neonates is effective in decreasing the incidence of death and chronic lung disease.[43–45]
2. Glucocorticoids		
a. Flunisolide (Aerobid)	250 mcg/inhalation	Unknown stability—do not mix with other drugs; bronchospasm may result from buffers and/or preservatives.
b. Beclomethasone (Beconase; Vancenase)	42 mcg/inhalation	Side effects: same as for dexamethasone.
c. Budesonide (Symbicort; Pulmicort)	1 neb every 12–24 hr 2 puffs/MDI (200 mcg/puff) q 12 hr for first 2 weeks of life; 1 puff q 12 hr from day 15 of life till 32 weeks' PMA or no longer needs supplemental oxygen or positive-pressure support[43,44] 2 puffs every 12 hours	Side effects: same as for dexamethasone.
B. Systemic (corticosteroids—dexamethasone [Decadron])	0.5 mg/kg/day IV or PO q 12 hr for 3 days; decrease to 0.3 mg/kg/day for 3 days Taper 10%–20% q 3 days	Hyperglycemia; hypothalamic-pituitary-adrenal axis suppression; renal calcification; protein depletion and/or tissue catabolism (increase BUN; failure to gain weight); gastric irritation, perforation, bleeding; restlessness and/or irritability; myocardial hypertrophy; hypertension; increased risk for infection (see Box 23.13).
	Initial dose: 0.1–0.2 mg/kg/day for 3 days[246]	Use for ventilator-dependent infant at 14–28 days of age who is developing CLD/BPD to accomplish extubation.
	If extubated, taper dose over 3–6 days (total treatment 6–9 days) If unable to extubate after initial 3 days of therapy, discontinue therapy[248]	Lower dose for shorter treatment period. Avoids hyperglycemia and hypertension seen in the higher doses of longer duration.[248]
III. Diuretics		The frequency, type, and therapeutic regimen of diuretics use at CHs in the US varies markedly. Safety and efficacy of long-term diuretic use needs to be researched to inform development of evidence-based recommendations.[480]

TABLE 23.13 PHARMACOLOGIC AGENTS USED IN TREATMENT OF CHRONIC LUNG DISEASE/BRONCHOPULMONARY DYSPLASIA—CONT'D

DRUG	DOSAGE	COMMENTS
a. Furosemide (Lasix)	Initial dose: 1 mg/kg IV, IM, PO May increase by 1 mg/kg no sooner than 2 hours after previous dose Maximum dose: Preterm: 1 mg/kg/day Full term: 6 mg/kg/dose Onset: 5 min IV; 1 hr PO Duration: 2–4 hr	Acute and chronic administration of furosemide in preterm infants >3 weeks of age with CLD/BPD improves lung compliance. Chronic administration of IV or PO furosemide also improves oxygenation. Routine or sustained use of systemic loop diuretics in infants with or developing CLD/BPD cannot be recommended based on current evidence.[498,499] Treatment of choice for fluid overload in CLD/BPD—decrease interstitial edema and PVR; daily or alternate-day administration improves pulmonary mechanics and facilitates weaning from ventilator. Side effects: metabolic acidosis, hypokalemia, hypocalcemia, hypochloremia, hyponatremia, renal calcifications, gallstones, ototoxicity, requires KCl supplementation. For preterms >3 weeks of age with CLD/BPD, administration of distal diuretics improves pulmonary compliance; chronic use improves oxygenation and lung compliance.[499] Acute and chronic administration of thiazides to preterms >3 weeks of age with BPD/CLD improves pulmonary mechanics and reduces the need for furosemide.[498]
B. Thiazide		
1. Chlorothiazide (Diuril)	5–20 mg/kg/dose IV or PO BID	Less potent than furosemide; promotes potassium and bicarbonate excretion with sodium and chloride; spares calcium given with spironolactone. Combination of thiazide and spironolactone results in improved lung mechanics and increased urine output. Side effects: electrolyte imbalance, hypercalcemia, hyperglycemia, decreased magnesium level, hypersensitivity, GI upset, glycosuria.
2. Hydrochlorothiazide (HydroDIURIL)	1–2 mg/kg/dose PO BID Onset: 1–2 hr Duration: 6–12 hr	Side effects: electrolyte imbalance, hypercalcemia, hyperglycemia, metabolic alkalosis, increased urinary losses of sodium, potassium, magnesium, chloride, phosphorus, and bicarbonate; spares calcium.
3. Spironolactone (Aldactone)	1.5 mg/kg/dose PO BID Onset: 2–3 days	Weak diuretic; causes increased sodium chloride and water loss; spares potassium. Side effects: irritability, lethargy, vomiting, diarrhea, rash.
4. Bumetanide (Bumex)	0.015 mg/kg/day up to 0.1 mg/kg/day PO	40 times the potency of furosemide; used in neonates and infants with CLD/BPD refractory to furosemide therapy. Side effects: same as for furosemide plus hypophosphatemia.

BID, Two times/day; *BUN,* blood urea nitrogen; *CH,* children's hospitals; *CLD/BPD,* chronic lung disease/bronchopulmonary dysplasia; *CNS,* central nervous system; *GFR,* glomerular filtration rate; *GI,* gastrointestinal; *IV,* intravenously; *KCl,* potassium chloride; *LOS,* length of stay; *MDI,* metered-dose inhaler; *MV,* mechanical ventilation; *NS,* normal saline; *PO,* per os, orally; *PVR,* pulmonary vascular resistance; *TID,* three times/day; *US,* United States

birth occurs within 7 days after a completed dose in preterms less than 33 weeks' gestation (especially in preterms of 24–29 weeks' gestation).[18] Use of antenatal steroids in 34 weeks' or later gestation reduces the risk of respiratory morbidities (i.e., RDS, TTN, mechanical ventilation and duration and amount of supplemental oxygen).[205,443] **Use of antenatal steroids should be considered for women between 34 and 36 weeks' gestation who are at risk of premature delivery within the next 7 days and who have not yet received antenatal steroids.**[18] However, caution in use of antenatal steroids in late-preterm pregnancies has been raised because of unanswered questions about the safety and efficacy in this population.[254]

Extremely preterm infants (22–27 weeks' gestation age) exposed to a complete course of ANS have lower mortality and better neurodevelopmental outcomes at 18 to 22 months compared with preterms exposed to an incomplete course or no ANS.[83] Use of antenatal steroids in extremely preterm multiple gestations is associated with lower mortality with no significant differences in the composite of neurodevelopmental impairment or death.[59] Although benefits of antenatal steroids occur in a dose-dependent manner, an incomplete course of antenatal steroids is beneficial (i.e., significant reduction in need for vasopressors and less mortality) when compared to no antenatal steroids.[379]

The NIH consensus statement[372] **discourages multiple courses of ANS** because of (1) impaired head/fetal growth, in a dose-dependent manner; (2) impaired brain development and behavior and psychomotor development; (3) increased incidence of IVH; (4) increased sepsis, mortality, and lung disease; (5) associated gastroesophageal reflux[90]; and (6) increased severity of ROP. **The American College of Obstetricians and Gynecologists (ACOG) recommends a repeat course of ANS if the fetus is less than 34 weeks' gestation and the previous ANS course was more than 14 days age.**[18] Long-term effects of multiple ANS therapy are associated with increased cortisol activity in response to stress,[5] a non-statistically significant difference in the incidence of CP (e.g., 2.9% in the repeated-doses group vs. 0.5% in the placebo group),[556] and a reduced risk of neurodevelopmental delay at 2 years of age due to a reduction in inflammation.[94] **An evaluation of the risk-benefit ratio of multiple courses of ANS found that administration at under 29 weeks' gestation has more benefits, but administration of multiple courses after 29 weeks has more risks than benefits.**[591]

Postnatal steroid use became widespread in the 1990s without properly conducted RCTs for safety and efficacy,[166] despite warnings from researchers in the 1970s about serious potential dangers. Steroid use has been enthusiastically accepted because of the dramatic short-term improvements in respiratory status (e.g., facilitates extubation, more rapid ventilator weaning, reduced risk for BPD/CLD and PDA).[140,145;170] Large RCTs of postnatal steroid use were halted because of serious short-term complications—intestinal perforation, growth restriction, PVL, hyperglycemia, hypertension, and infection.[490] **Adverse long-term outcomes are listed in** Box 23.13. **Adverse developmental outcomes are the result of the effects of steroids on the developing nervous system.** The most recent *Cochrane*

BOX 23.13 LONG-TERM ADVERSE EFFECTS OF STEROID USE

Slower Growth[490]

- Somatic and head/brain growth[393] (even into adolescence)[89]
- Arrested lung development caused by interference in pulmonary alveolarization and vascularization

"Neurotoxic" Substances[6,39]

- Further reduces size of cerebral and cerebellar[509] tissue/gray matter volume of premature brain[389] (effects lasting into adolescence)[89]
- Increased rate of cerebral palsy (CP)[142,575]
- Increased risk for CP significantly related to the total cumulative doses of dexamethasone[414]
- Reprogramming of the hypothalamus-pituitary-adrenal axis that alters the ability to adjust to the environment resulting in more social problems and anxious, depressed behaviors in adolescent girls between 14–17 years of age[515]
- Increased cognitive deficits at school age, children had lower scores on verbal or written language skills, math, perceptual organization, freedom from distractibility, and processing speed[575]
- Increased special education, poorer performance on neuropsychological tasks (i.e., alertness, visuomotor coordination, emotion recognition), poorer gross motor skills at 14 to 17 years of age[514]
- Increased severity of retinopathy of prematurity

Contributes to Long-Term

- Cardiovascular disease
- Immune system disorders/autoimmune diseases
- Renal calcifications
- Neurologic and behavioral deficits

review on the use of systemic postnatal steroids to prevent BPD cautions that recommendations about the optimal type of steroid, dosage, or timing of initiation to prevent BPD/CLD in preterm infants cannot be made based on the current level of evidence. Large, well-designed RCTs are needed.[389] Additionally, two *Cochrane* reviews caution that the short-term benefits of early (<7 days) and late (>7 days) **postnatal steroids may not outweigh the actual or potential adverse effects.**[140,141]

The administration of inhaled corticosteroids to prevent or treat BPD/CLD in ventilated VLBW infants without exposing them to systemic steroids is an attractive alternative. **Increasingly, there is evidence that early administration of inhaled steroids to VLBW neonates is effective in significantly decreasing the incidence of CLD at 36 weeks' PMA.**[465,473] An RCT of early inhaled budesonide in 23 to 27 weeks' GA preterm infants found a lower incidence of BPD/CLD, surgical closure of PDA, and need for reintubation.[44] The group who received the inhaled budesonide had a mortality rate of 16.9% compared to the placebo group with a mortality rate of 13.6%.[43] The rate of neurodevelopmental disability in this cohort of preterm infants does not differ from the group receiving placebo, but the mortality rate was higher in the early inhaled budesonide group.[45] One systematic review found less mortality,[465] whereas another found no impact on mortality, adverse events, or other morbidities.[473] However, the clinical relevance of these studies remains to be elucidated by studies of variations in delivery methods and dosing regimens, short- and long-term benefits, and adverse effects, especially growth, respiratory, and neurodevelopmental outcomes of VLBW preterms exposed to inhaled corticosteroids.[465,473] Late (≥7 days) administration of inhaled corticosteroids did not reduce the outcomes of death or death and BPD, did not decrease mechanical ventilation or oxygen supplementation, and is not currently recommended to reduce BPD.[389]

A pilot study and a larger RCT of intratracheal instillation of budesonide (using surfactant as a vehicle) in VLBW infants with severe RDS significantly decreased the incidence of BPD/CLD or death when compared to the group who received only surfactant.[58,584,585] No short-term adverse effects were noted, and follow-up at 2 years showed comparable neurodevelopmental outcomes.[288,585] However, appropriately powered studies to determine long-term neurodevelopmental outcomes and the safety of this regimen need to be conducted before this strategy is used in clinical practice.[58]

Historically, steroids have been used "routinely," with widely varying practices about type of medication (e.g., natural hormone [hydrocortisone] or synthetic hormones [dexamethasone, betamethasone]), dosage (e.g., standard or low dose), timing (e.g., early or late), and duration (e.g., weaning after 7 to 10 days or 42-day treatment).[166,248] Because it was considered routine practice, parents were rarely asked to give informed consent. **Parents (in addition to health care providers)**[38,490] **must be informed honestly about the experimental nature of steroid use and its short-term and long-term complications,** so that they are able to participate in giving or withholding their fully informed consent.[38,211] The DART Study of low-dose steroid use was halted because infants could not be recruited; fully informed parents concerned about risks to their infant refused permission to be part of the study.[142]

Based on the premise that very preterm infants have early adrenal insufficiency, early use of hydrocortisone therapy to decrease BPD/CLD has been studied in four RCTs.[60,397,558,559] **In all four studies the hydrocortisone-treated preterms were favored with a significant increase in survival without BPD/CLD.** The largest multicenter randomized trial to test early low-dose hydrocortisone therapy was halted because of an increase in spontaneous GI perforations in the treated preterms, especially those also receiving indomethacin.[558] Prophylaxis of early adrenal insufficiency decreased mortality rate and improved survival rate without BPD/CLD only in the chorioamnionitis-exposed preterms.[558] Another RCT of early administration (within the first 36 hours of life) of hydrocortisone to prevent BPD/CLD was terminated early because of the increased incidence of GI perforations and found lower rates of BPD/CLD.[397,398] The 18- to 22-month follow-up of the infants in both of these RCTs showed no difference in growth, no increase in CP, and indicators of improved neurodevelopmental outcome in those treated with early, low-dose hydrocortisone.[398,559] However, the follow-up at 5 to 7 years of age in one of the cohorts who received hydrocortisone found minor to severe neurologic dysfunction in 61% of the treated group compared to only 39% of the placebo group. More

of the treated children had lower IQs, and 22% required physical therapy compared to none of the placebo group.[399] **Comparison of preterm infants born at less than 27 weeks' GA in two centers found BPD/CLD rates significantly lower in the center using hydrocortisone after 14 days of ventilation without apparent effects on neurodevelopment at 2 years' corrected age.**[424]

The PREMILOC trial evaluated preterm infants (24–27⁄7 weeks' GA) receiving early low-dose hydrocortisone at 22 months corrected age and found no neurodevelopmental impairment and survival free of BPD/CLD in the treated group.[46,47] Early low-dose hydrocortisone benefits extremely preterm infants and especially those born after placental vascular disease.[223]

After reviewing the short-term and long-term effects of systemic and inhaled corticosteroid use for the prevention and treatment of CLD/BPD in the VLBW infant, both the AAP and the Canadian Paediatric Society have issued and reaffirmed position statements about use of postnatal steroids.[16,246] These policy statements on use of postnatal corticosteroids to prevent or treat BPD recommend the following[16,246]:

- High-dose dexamethasone (0.5 mg/kg/day) cannot be recommended until RCTs show improved short- and long-term outcomes.
- Low-dose dexamethasone (less than 0.2 mg/kg/day) cannot be recommended because of insufficient evidence.
- Early hydrocortisone therapy (low dose: 1 mg/kg/day in the first 2 weeks of life) may be beneficial in a specific population of preterms (i.e., prenatal inflammation). However, hydrocortisone therapy cannot be recommended for all infants at risk for BPD because of insufficient evidence.
- High-dose hydrocortisone (3 to 6 mg/kg/day; started after the first week of postnatal age) cannot be recommended because of insufficient data.

The dose and duration of use of late postnatal corticosteroids should be minimized and reserved for preterms who cannot wean from the ventilator and are still being mechanically ventilated at 7 to 14 days of life.[141,209,248] Table 23.13 gives a proposed (expert opinion rather than evidence-based) dosing regimen for low-dose, short-duration treatment with dexamethasone.[248]

Complications. ***Pulmonary hypertension*** **complicates approximately 25% of BPD/CLD cases and results in a 14% to 38% mortality rate.**[125] Early pulmonary vascular disease, as evidenced on echocardiogram at 7 days of age, is associated with development of BPD/CLD and late pulmonary hypertension.[358] Use of phosphodiesterase inhibitors, such as sildenafil, to treat the pulmonary hypertension and pulmonary artery pressure of BPD/CLD is being studied.[224] A retrospective review of 21 infants with BPD-associated pulmonary hypertension were treated with oral sildenafil to determine the effects of sildenafil on gas exchange.[382] Although sildenafil decreased pulmonary artery pressure, there was no corresponding improvement in gas exchange in the 48 hours after treatment. Chronic sildenafil therapy for BPD-associated pulmonary hypertension should be done cautiously, awaiting clinical studies and adequate evidence.[382] The most recent *Cochrane* review of sildenafil use to treat pulmonary hypertension found that it improved oxygenation and has the potential to decrease mortality, especially in resource-limited settings when iNO is not available but cautions that large RCTs are needed.[263]

Complications of CLD/BPD are most common in the smallest, sickest infants (Box 23.14). Surviving preterm infants with BPD/CLD have persistent pulmonary dysfunction and exercise intolerance and more frequently develop asthma and early onset emphysema.[101,125] Survival (75%–80%) of infants with severe BPD/CLD is improved with an interdisciplinary approach to care.[2,180]

Acute Respiratory Diseases

RESPIRATORY DISTRESS SYNDROME

Pathophysiology. RDS is a disease of immature lung anatomy and physiology. Anatomically, the preterm lung cannot support oxygenation and ventilation, because alveolar saccules are insufficiently developed, causing a deficient surface area for gas exchange. Also, the pulmonary capillary bed is deficient and the interstitial mesenchyme is present to a greater extent, increasing the distance between the alveolar and endothelial cell membranes.

Physiologically, the volume of surfactant is insufficient to prevent collapse of unstable alveoli. Because the alveoli collapse with each breath, normal FRC is not established. **Because of alveolar collapse, oxygenation and ventilation are**

BOX 23.14 COMPLICATIONS OF CHRONIC LUNG DISEASE/BRONCHOPULMONARY DYSPLASIA

Increased Mortality

Increased Morbidity

Pulmonary.

- *Acute:* pulmonary interstitial emphysema, air leaks, pulmonary hypertension, cyst formation
- *Chronic:* altered pulmonary function, pulmonary hypertension, respiratory infections, rehospitalizations, home oxygen/ventilator[2]

Cardiac.

- Cor pulmonale and right-sided heart failure
- Systemic hypertension[2]
- Feeding difficulties[2]
  - GERD

Growth Restriction.

- Somatic growth (weight)
- Head growth
- Orthopedic
  - Fractures, rickets

Neurodevelopmental Delay.

- Cognitive impairment/impaired intelligence/increased need for special education services
- Cerebral palsy/delays in gross motor skills
- Behavior/attention/school problems
- Cerebral ventriculomegaly

Sensory Deficits.

- Sensorineural hearing loss
- Increased severity (stage 3) retinopathy of prematurity

Gene Expression[406].

- Alteration of gene expression—nearly 10%

Long-Term Effects of Steroid Use

- See Box 23.13

insufficient and each breath requires increased energy output.

Compliance is related to the volume achieved during a given application of pressure. **Compliance of the lung is equal to the ratio of the change in volume to the change in pressure. The lung in RDS has low compliance (i.e., little change in volume is achieved with a relatively great application of pressure), thereby contributing to increased work of breathing.** However, the chest wall of the neonate unfortunately is very compliant; a slight application of pressure results in a large change in volume. The infant may not be able to create enough inspiratory pressure to open the alveoli as the chest wall retracts and collapses about the relatively stiff lung. Thus in RDS, the diaphragm contracts, creating an inspiratory pressure that moves less volume into the lung than expected and simultaneously causes large sternal and intercostal retractions of the chest wall.

The increased effort of these opposing forces usually results in hypoxemia and acidemia, which cause constriction of the pulmonary vascular (arterial) musculature, severely limiting pulmonary capillary blood flow. The integrity of pulmonary capillary blood flow is critical for the integrity of the alveolar epithelial membrane and the production of surfactant. Without adequate pulmonary capillary blood flow, the type II pneumocytes become deficient in the precursor material necessary for production of surfactant. Lack of surfactant production compounds the deficiency and leads to low compliance. **These physiologic factors (surfactant deficiency and decreased lung compliance) promote increased work of breathing, fatigue, atelectasis, reduced FRC, and ventilation-perfusion (V/Q) mismatch.**

In the fetus, PVR is high, and pulmonary artery blood pressure is greater than systemic blood pressure, causing blood flow from the main pulmonary artery to travel through the open ductus arteriosus to the descending aorta. A second right-to-left shunt occurs across the foramen ovale in the fetus. The high PVR is "reactive" to the normal fetal "hypoxemia" because the PVR and the pulmonary artery blood pressure decrease as the PaO_2 of the neonate increases. At birth, the ductus arteriosus actively constricts in response to the increase in PaO_2 (PaO_2 >50 mm Hg), eliminating blood flow across the ductus and completing the transition to neonatal circulation.

The fetal circulatory pattern may persist from birth or be initiated by a transient hypoxemic episode. **In the instance of neonatal hypoxemia, the pulmonary vasculature "reacts" by vasoconstriction, raising PVR, and the ductus arteriosus "reacts" by relaxing, once again allowing blood flow from the pulmonary artery to the descending aorta, as normally occurs in the fetus.** PVR is increased with shunting through the ductus arteriosus. Fetal circulatory patterns are perpetuated by hypoxemia and acidemia and produce systemic hypoxemia that aggravates and perpetuates the condition.

Endothelial damage and alveolar necrosis aggravate the already existing surfactant deficiency. A cyclic deterioration is established, and hypoxia and acidosis persist unless treatment is initiated.

Microscopically, the events that occur in the lung include injury to and death of the alveolar epithelial cells and airway epithelial cells. This injury and death are followed by sloughing of the cells from the respiratory basement membrane—leaving the basement membrane denuded—followed by exudation of serum. Fibrin in the serum clots and hyaline membranes are formed, covering the denuded basement membranes in the airways and alveolar spaces. If there is sufficient hypoxic damage to the cells and basement membranes, frank hemorrhage may fill the alveolar spaces. These factors decrease the total surface area of the gas exchange membrane. The result is hypoxemia, acidemia, and increasing respiratory distress.

The entire sequence of events in RDS is related to the inability to maintain lung expansion and alveolar stability as a result of surfactant deficiency. **RDS evolves from two interrelated problems: atelectasis and persistence of pulmonary hypertension** (Figs. 23.4 and 23.5).

Etiology. RDS occurs in infants born prematurely (including the late-preterm infant of 34⁶⁄₇–36⁶⁄₇ weeks' gestation) and is a consequence of immature lung anatomy and physiology. In premature or stressed infants, atelectasis from the collapse of the terminal alveoli resulting from lack of surfactant appears after the first few hours of life. **In a premature infant, surfactant production is limited and stores are quickly depleted.** Surfactant production may be further diminished by other unfavorable conditions, such as high oxygen concentration, poor pulmonary drainage, excessive pulmonary hygiene, or effects of respirator management.

Data Collection

History. A history of prematurity, cesarean section, birth order (second-born twin),[65] or asphyxial episodes may be seen in infants with RDS. In one study, elective cesarean section at "term" (i.e., ≥34 weeks' gestation) resulted in infants of 37 to 38 weeks' gestation being 120 times more likely to have surfactant deficiency requiring ventilatory support than those born at 39 to 41 weeks. Recommendations include only using delivery by elective induction or elective cesarean section at

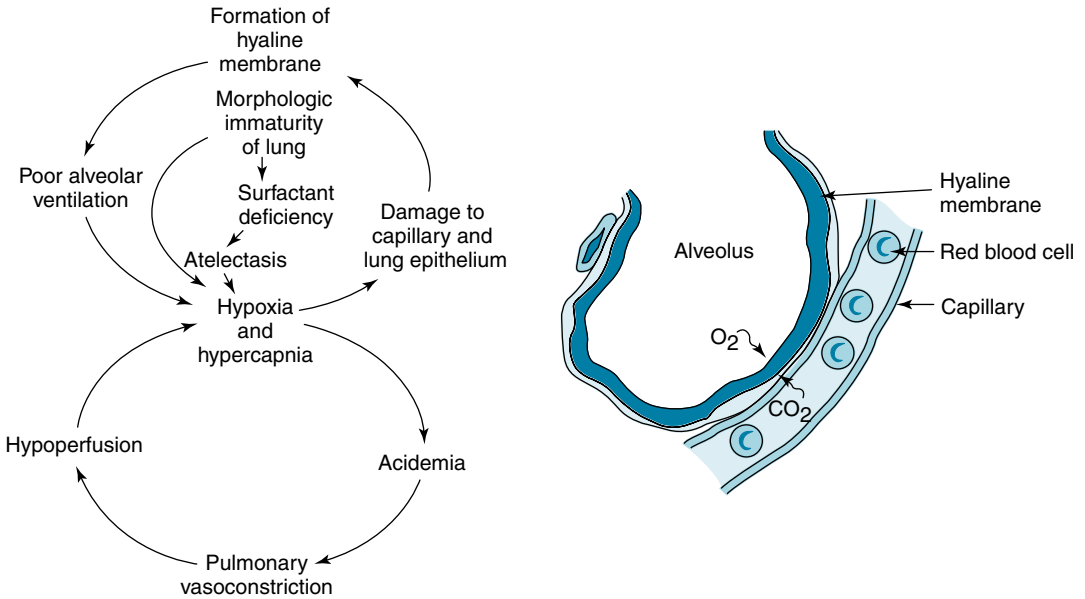

FIGURE 23.4 Interdependent relationship of factors involved in pathology of respiratory distress syndrome. (From Pierog SH, Ferrara A. *Medical Care of the Sick Newborn.* 2nd ed. St Louis, MO: Mosby; 1976.)

39 weeks' gestation (see Chapter 5). Moderately preterm, late-preterm, and term newborns who are monozygotic twins (especially the second-born twin), are of European descent, male sex, delivered by C-section, and with low 5-minute Apgars are at higher risk for developing RDS.[468]

Physical Examination. **Infants with RDS are often tachypneic and demonstrate grunting, nasal flaring, and chest retractions within the first few minutes to hours of life. Pallor or cyanosis also may be present.** The trachea is midline, and the apical pulse is normal. **Auscultation of the chest reveals decreased breath sounds and often rales. Many of these infants may be hypotensive with prolonged capillary refill.**

Laboratory Data. **Chest x-ray findings in RDS include (1) reduced lung volume, (2) air bronchograms, (3) reticulogranularity, and (4) lung opacification.** Surfactant deficiency results in diffuse atelectasis, a reduction in lung volume, and decreased lung expansion as demonstrated on x-ray examination. **Atelectasis increases lung density and results in visible outlines of air-filled bronchi (e.g., air bronchograms) against opaque lung tissue.** Chest x-ray examination also reveals a ground-glass appearance that represents areas of atelectatic respiratory alveoli adjacent to expanded or even hyperexpanded respiratory units. **This bilateral reticulogranular pattern is uniformly distributed throughout the lung fields and may also contain air bronchograms (Fig. 23.6).** Diffuse opacification caused by (1) nonexpanded alveoli with little or no terminal airway aeration, (2) pulmonary edema, or (3) pulmonary hemorrhage results in loss of visible heart borders, with a **"whiteout" appearance on chest x-ray films** (Fig. 23.7). Early radiologic evidence of severe RDS is predictive of nasal CPAP failure, especially ELBW premature infants (<26 weeks' gestation).[500] Lung ultrasound has been shown to have sensitivity (95.6%) and specificity (94.4%) in diagnosing both RDS and TTN.[548]

Arterial blood gases reveal hypoxemia and often acidemia that may be metabolic, respiratory, or a combination of both (see Chapter 8).

A noninvasive surfactant adsorption test (SAT) reliably identifies preterm infants who will fail

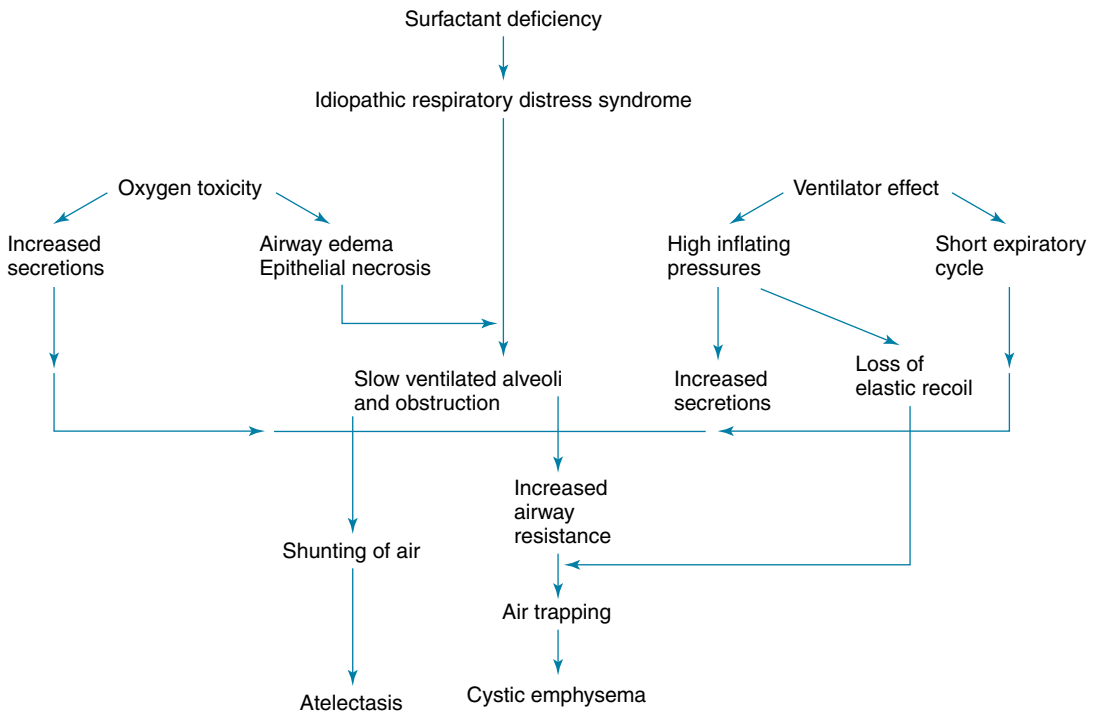

FIGURE 23.5 Schematic representation of pathogenesis of respiratory distress syndrome.

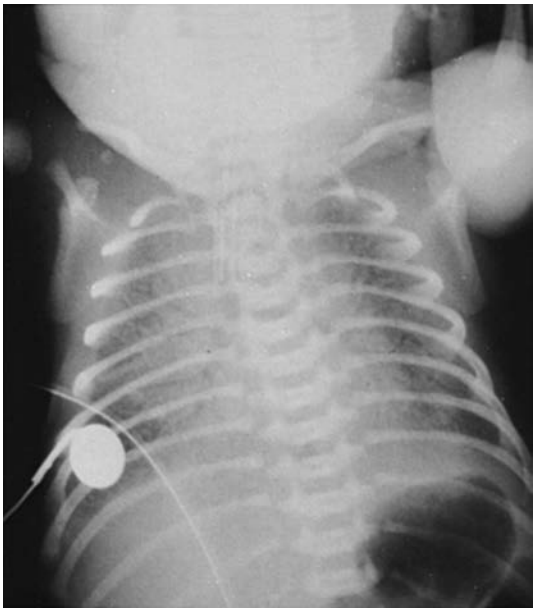

FIGURE 23.6 Chest x-ray film of a preterm infant (27 weeks' gestation) with respiratory distress syndrome. Note characteristic infiltrate pattern with air bronchograms.

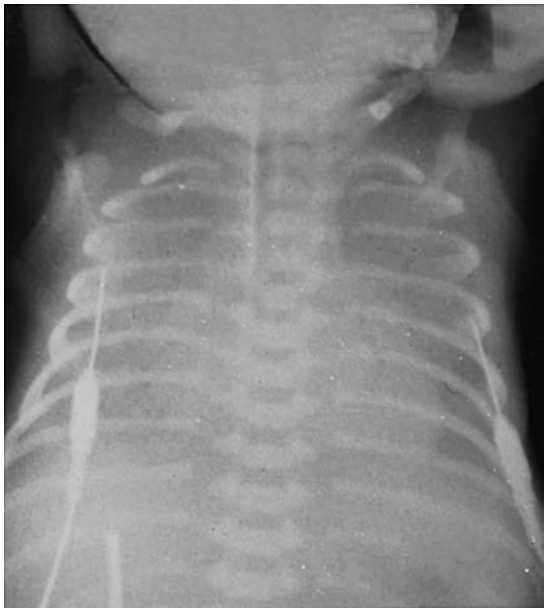

FIGURE 23.7 Chest x-ray film of a preterm infant (28 weeks' gestation) with severe respiratory distress syndrome. Note "whiteout" appearance.

CPAP and may be developed into a screening test for surfactant replacement in preterm infants.[25]

Prevention. **A single course of antenatal steroids decreases the incidence and severity of RDS,** comorbid conditions (e.g., NEC, intracranial hemorrhage, CLD), and mortality in infants of less than 32 weeks' gestation. **Very premature infants, as young as 23 weeks' GA, benefit from antenatal steroids.**[529] Even a partial course appears to be beneficial.[372] **For women at risk for late-preterm delivery, antenatal steroids also reduce the risk of RDS.**[205] Between 1993 and 2012, the use of antenatal steroids for women at risk for delivering an extremely preterm infant increased from 24% to 87% in 26 academic centers in the United States.[500]

Before the routine use of NCPAP initially after birth, prophylactic use of surfactant was associated with lower mortality rate, less air leak, and less BPD/CLD than rescue use of surfactant. After routine use of NCPAP, the benefits of prophylactic surfactant were no longer demonstrated.[503]

Treatment

Surfactant Replacement Therapy. Because **surfactant deficiency is the primary abnormality of RDS,** the development of an effective clinical strategy for administering exogenous surface-active material to premature infants was the focus of research efforts for many years. **Administration of surfactant leads to**[118,546]**:**

- **Reduction in surface tension**
- **Dramatic and rapid improvement in gas exchange**
- **Decreased need for high levels of supplemental oxygen and ventilatory support**
- **Less barotrauma**
- **Reduction in air leaks**
- **Improved chest x-ray findings** because of improved lung compliance and lung volume
- **Improvement in perfusion index** after a short decline in first minute (that occurs earlier with beractant compared to poractant); transcutaneous carbon monoxide levels decrease and normalized earlier in poractant[516]
- **Improved survival**

The use of lower levels of ventilatory support decreases the mortality rate and the incidence of pneumothorax. However, surfactant administration does not fully correct lung abnormalities of

the VLBW infant with RDS,[257] nor does surfactant improve short-term outcomes in late-preterm infants with RDS.[118]

Optimal clinical strategies—the type of surfactant to use, the timing and method of administration, the number of doses, and the GA of the neonates—affect surfactant safety, efficacy, and outcomes.

Types of Surfactant. **Both animal-derived and synthetic surfactant are effective in preventing and treating RDS.**[22] A meta-analysis of 16 RCTs comparing animal-derived surfactants found that infants treated with bovine versus porcine surfactant extract had a higher risk of death prior to discharge, death or oxygen requirement at 36 weeks' PMA, PDA requiring treatment, and receiving more than one dose of surfactant.[477] Because these studies used a higher dose of porcine surfactant, it is not clear whether the difference in outcomes are due to the higher dose or the origin of the surfactant. There were no differences in clinical outcomes between the use of bovine lavage or bovine minced surfactant.[477]

Use of animal-derived surfactants entail the risks of infection, immunogenicity, proinflammatory mediators, and variability of concentration of active ingredients in different aliquots. Lucinactant, a synthetic surfactant, is as safe and effective as the natural surfactants without these potential risks (Table 23.14). This synthetic surfactant contains sinapultide, a peptide that mimics surfactant protein B (SP-B) and its effects on lung tissue.[520] Another synthetic surfactant (CHF5633) has been tested in vitro and in vivo and found to be as effective as poractant alfa.[427] The first human study of CHF5633 in 20 preterm infants with RDS receiving 100 mg/kg and 20 infants receiving 200 mg/kg showed tolerance and clinical efficacy; more ongoing RCTs are planned.[507]

Methods of Surfactant Administration. **Numerous methods and outcomes of surfactant administration are compared in** Table 23.15. Even though noninvasive surfactant administration does not use an ETT, the preterm infant must be laryngoscoped for instillation. **A recent study of the use of premedication (i.e., atropine and ketamine) for less-invasive surfactant administration found low pain scores,** stable hemodynamic parameters (i.e., transient increase in heart rate and blood pressure), and more frequent and prolonged oxygen desaturations or apnea requiring intubation.[63]

Even in low- and middle-income countries, surfactant replacement therapy has the potential to reduce air leaks and neonatal mortality in low-resource settings, although the cost effectiveness and incidence of BPD/CLD have not been well studied.[449] **When compared to early NCPAP and selective surfactant use, prophylactic surfactant and rapid extubation to NCPAP are associated with a higher risk of mortality, less BPD/CLD, and higher rates of intubation, surfactant use, and the need for multiple doses of surfactant.**[92,146,436] **When early NCPAP is used**[146,569] **as recommended in the AAP respiratory support and surfactant therapy guidelines,**[14,412] **there is no benefit of the INSURE method of surfactant administration.**

Bolus injection improves the homogenous distribution of surfactant in lungs when compared with slow injection or ultrasonic nebulization.

Aerosolized surfactant therapy may prevent the need for intubation. Pilot studies showing clinical efficacy despite low total administered dose, enhanced pulmonary distribution, and cost effectiveness need to be confirmed in RCTs.[1] In animal studies, intratracheal aerosolized surfactant is as safe as bolus surfactant with the added benefit of more stable cerebral hemodynamics and oxygen metabolism during administration when compared to bolus.[425]

Timing of Administration. **Timing of surfactant may be early (usually defined to be within 30–60 minutes of birth) or late (between 7 and 14 days of life).** Early surfactant administration is associated with less time being mechanically ventilated, longer duration of CPAP, and longer length of stay but is not significantly protective against the development of BPD/CLD or death among treated preterm infants.[415] Another study of early surfactant therapy and NIPPV as the initial respiratory therapy for preterm infants found significantly fewer NIPPV failures, resulting in less use of invasive MV when early surfactant was used.[144] The *Cochrane* review of early (within the first 2 hours of life) versus late selective treatment found benefit for early therapy.[31] **However, for those preterm infants initiated on NCPAP at birth, many do not ever need to be treated with surfactant.**[14,412,569]

The multisite Trial of Late Surfactant (TOLSURF) to assess the effect of late doses of surfactant on BPD in extremely preterm infants (≤28 weeks' GA) who required invasive mechanical ventilation between 7

TABLE 23.14 COMMERCIALLY AVAILABLE SURFACTANTS FOR REPLACEMENT THERAPY

DRUG/SOURCE	INDICATIONS	ADMINISTRATION AND DOSAGE	ADVERSE EVENTS
Beractant* (Survanta) Exogenous surfactant from bovine lung extract	Prophylaxis and treatment ("rescue") of RDS in preterm infants; significantly reduces the incidence of RDS, mortality, and air leak complications[486] Prophylaxis: In preterm infants <1250 g BW or with evidence of surfactant deficiency, give as soon as possible, preferably within 15 min of birth Rescue: To treat infants with RDS confirmed by x-ray examination and requiring mechanical ventilation, given within the first 12 hours after birth[412]	Administration: For intratracheal administration only; instillation through a 5-Fr end-hole catheter inserted into the infant's ETT and/or via a thin catheter during spontaneous breathing or on NCPAP[120,121] above the infant's carina; each dose is 100 mg of phospholipids/kg BW (4 mL/kg; 100 mg/kg); four doses can be administered in the first 48 hr of life; give doses no more frequently than every 12 hr (unless surfactant is being inactivated by blood, meconium, or an infectious process[412]); repeat doses are based on the infant's BW	The most commonly reported adverse experiences are associated with the dosage procedure: transient bradycardia, oxygen desaturation, alterations in BP, drug reflux.
Poractant alpha* (Curosurf) Modified porcine-derived minced lung extract	Prophylaxis and treatment ("rescue") of RDS in preterm infants	For *intratracheal* administration, see above Dosage: *Initial dose:* 2.5 mL/kg divided into aliquots *Subsequent dose:* Up to two doses of 1.25 mL/kg/dose given 12 hr apart, if needed Systematic analysis found higher mortality risk, death or oxygen requirement at 36 weeks' PMA; PDA requiring treatment and receiving more than 1 dose when beractant compared to poractant[477]	As for beractant
Calfactant* (Infasurf) Natural surfactant extracted from calf lung lavage	Prophylaxis and treatment ("rescue") of RDS in preterm infants	Administration: For *intratracheal* administration, see above Dosage: *Initial dose:* 3 mL/kg (105 mg/kg) divided into two aliquots *Subsequent dose:* Up to three doses of 3 mL/kg/dose given 12 hr apart, if needed	As for beractant
Lucinactant (Surfaxin) Synthetic surfactant containing sinapultide, a peptide that mimics surfactant protein B (SP-B)	Prophylaxis and treatment ("rescue") of RDS in preterm infants	For *intratracheal* administration, see procedure for beractant Dosage: *Initial dose:* 5.8 mL/kg (175 mg/kg) dosing q 6 hr based on clinical response Gels when stored at 4° C; requires up to 15 min of warming at 44° C in a heating block to liquefy; rapidly cools to body temperature when removed from heating block	As for beractant

*Use of bovine and porcine products may be objectionable to persons of Jewish, Islamic, and/or Hindu beliefs; informed consent from parents is essential.
BP, Blood pressure; *BW,* birth weight; *C,* centigrade; *ETT,* endotracheal tube; *PDA,* patent ductus arteriosus; *PMA,* post menstrual age; *RDS,* respiratory distress syndrome.

TABLE 23.15 INVASIVE AND NONINVASIVE METHODS OF SURFACTANT ADMINISTRATION

METHOD	DEFINITION	RESEARCH EVIDENCE
Invasive:		
INSURE	**I**ntubation- **SUR**factant-**E**xtubation	Early INSURE and NCPAP after birth decreased the need for MV and decreased the incidence of air leak. No difference in death, BPD/CLD, or need for MV among preterm infants (27–34 weeks' GA) randomized to NCPAP or INSURE and NCPAP.[365]
IN-REC-SUR-E	**IN**tubate-**REC**ruit-**SUR**factant-**E**xtubate	Comparison of lung recruitment with HFOV prior to surfactant versus INSURE alone in spontaneously breathing preterm infants requiring NCPAP as initial respiratory support/reaching CPAP failure is being studied.[544]
Noninvasive LIST	**L**ess **I**nvasive **S**urfactant **T**herapy	

LISA	**L**ess **I**nvasive **S**urfactant **A**dministration (thin endotracheal catheter placed during spontaneous breathing and surfactant instilled.)	LISA/LIST vs INSURE:
		• Less intubation and MV[†]
		• Both increase MAP during administration. Transient change in cerebral autoregulation (oxygenation and BP) with surfactant administration[53,316]:
		  • Less than 5 minutes with LISA and 5–10 minutes with INSURE[316]
		  • Higher decrease in cerebral oxygenation with LISA accompanied by an increase in cerebral fractional oxygen extraction rate that suggests a compensatory mechanism.[53]
		• Shorter duration of MV[281,301*]
		• Shorter duration of NCPAP[281,301*]
		• Shorter duration of oxygen supplementation[301*]
		• Decreases the risk of death, of death or BPD/CLD,[‡] and of CPAP failure[429*]
		• Less incidence of pneumothorax[282]; no significant difference in incidence of pnemothorax[301*]
		• Less IVH[550] and less severe IVH[238*,282]
		• No difference in rate of MV in first 72 hours[35]
		• No difference in mean duration of oxygen requirement between groups[35]
		• No difference in death,[301*] BPD/ CLD, IVH, ROP, NEC, or duration of respiratory support[35,581*]
		• Lacks long-term follow-up[429*]
		LISA vs INTUBATION and MV[298]:
		• Significantly less MV, days with supplemental oxygen, and rates of BPD/CLD
		• Less use of analgesics and sedatives

MIST	Minimally Invasive Surfactant Therapy (orogastric tube used for tracheal catheterization to deliver surfactant)	Comparison of MIST and historical cohort of INSURE administration of surfactant: • No differences in intubation and MV, morbidity/mortality rates. Duration of MV and CPAP significantly shorter in MIST group.[524] • Rapid increase in end-expiratory volume in dependent, then independent pulmonary regions within 5 minutes and oxygenation improved within 1 hour of instillation[538] • Significant reduction in MV and pneumothoraces among moderate and late-preterm infants with RDS[385]
CALMEST	Catheter And Laryngeal Mask Endotracheal Surfactant Therapy	On mannequin and in vivo pilot trial that was quick, effective, and with less neonatal stress; alternative approach for staff with low expertise in laryngoscopy and intubation[541]

*Systematic review.

[†] References 5*, 35, 53, 190, 281, 282, 301*, 581*.

[‡] References 5*, 190, 238*, 301*, 550, 581*.

BP, Blood pressure; *BPD,* bronchopulmonary dysplasia; *CLD,* chronic lung disease; *CPAP,* continuous positive airway pressure; *GA,* gestational age; *HFOV,* high frequency oscillator ventilation; *IVH,* intraventricular hemorrhage; *MAP,* mean airway pressure; *MV,* mechanical ventilation; *NCPAP,* nasal continuous positive airway pressure; *NEC,* necrotizing enterocolitis; *ROP,* retinopathy of prematurity.

BOX 23.15 RECOMMENDATIONS FOR SURFACTANT REPLACEMENT THERAPY[412]

- Initiate NCPAP at birth as an alternative to routine intubation and early/prophylactic surfactant therapy.[14]
- Combine early NCPAP with selective surfactant therapy in extremely preterm infants.[14]
- Use less invasive surfactant administration (LISA) for preterm infants (<33 weeks' gestation) that lowers the risk of mortality, BPD, and severe intraventricular hemorrhage when compared to mechanical ventilation and a lower incidence of mortality, death, and air leaks when compared to NCPAP alone.[238]
- Preterm infants <30 weeks' gestation who require mechanical ventilation for severe RDS should be given surfactant after initial stabilization.
- Rescue surfactant may be considered when respiratory failure is due to secondary surfactant deficiency occurring with meconium aspiration syndrome, sepsis, pneumonia, or pulmonary hemorrhage.
- Nursery and transport professionals with experience in administering surfactant and managing multisystem illness should care for preterm and term neonates receiving surfactant.
- Providers inexperienced with surfactant administration and managing multisystem illness should wait for transport team to arrive.

BOX 23.16 TREATMENT FOR RESPIRATORY DISTRESS SYNDROME

1. Reducing hypoxemia (see General Treatment Strategies in this chapter and in Chapter 8)
   a. Maintain in thermoneutral environment (see Chapter 6)
   b. Maintain blood pressure and hematocrit (see Chapters 5 and 20)
   c. Decrease stimuli from the neonatal intensive care environment (see Chapter 13)
   d. Recognize and relieve pain or agitation (see Chapter 12)
2. Correcting acidemia (see Chapter 8)
3. Increasing the functional residual capacity (see General Treatment Strategies)
   a. Maintain appropriate temperature (see Chapter 6)
   b. Monitor vital signs and arterial blood gases (see Chapters 7 and 8)
   c. Provide appropriate fluid, electrolytes, glucose, and calories (see Unit Three)
   d. Observe for complications of disease and treatments (see General Complications)
4. Monitoring for complications (see Acute Complications and Chronic Complications under General Complications)
5. Caring for parents (see Chapters 29, 30, and 32)
6. Preparing for discharge and follow-up care (see Chapter 31)

and 14 days of age and were receiving iNO therapy found no difference in survival without BPD at 36 or 40 weeks' PMA when these neonates received as many as five doses of late surfactant.[34] A French study in 13 level III perinatal centers also found that late surfactant therapy did not alter the course of BPD/CLD but did result in less respiratory morbidity in the first year of life.[215] Two follow-up studies of the TOLSURF group found that rising mean airway pressure (MAP) is a marker for prolonged ventilation and need for tracheotomy and a lower incidence of the use of home respiratory equipment and better respiratory outcomes at 1 year corrected age.[262,553]

Methods of resuscitation, types of ventilators (NCPAP vs. CMV vs. HFOV), and ventilation style (e.g., **as few as six large tidal volume breaths in a surfactant-deficient lung causes lung injury)**[237] also contribute to lung injury resulting in BPD/CLD. **Use of noninvasive ventilation strategies benefits the preterm lung by optimizing pulmonary mechanics, improving gaseous exchange, and reducing metabolic demands.**[7] The first study of SNIPPV as the primary method of respiratory support for RDS compared the outcomes of 600 to 1250 g preterms who were randomized to CMV or SNIPPV after their initial dose of surfactant.[54] Only 20% of the preterms receiving SNIPPV versus 52% receiving CMV had the primary outcome of BPD/CLD/death, with no difference in the groups on mental/psychomotor indices.[54]

Recommendations for surfactant replacement therapy for RDS are outlined in Box 23.15. **Other treatment for RDS is directed toward the indications in** Box 23.16.

Inositol Therapy. Inositol, an essential nutrient, promotes maturation of several components of surfactant. A systematic review of inositol supplementation for RDS found significant reductions in (1) mortality, (2) ROP, and (3) >grade II IVH with no increase in sepsis or NEC but no significant reduction in BPD/CLD.[231] A large multicenter RCT of multiple dose myo-inositol given to preterm infants of 29 weeks' or earlier GA found that at 80 mg/kg/day

there were no adverse side effects, previously effective serum levels were obtained, and that a phase III trial is warrented.[405]

Inhaled Nitric Oxide Therapy. **Inhaled nitric oxide (iNO) therapy is not only a selective pulmonary vasodilator but also improves oxygenation by redirecting blood from poorly aerated (atelectatic) and diseased lung (with RDS) regions to better aerated distal air spaces.**[271] Early RCTs of iNO in late-preterm infants found improved oxygenation, decreased need for mechanical ventilation, improved survival without increase in IVH, and a trend toward a decrease in CLD/BPD.[373] Recent meta-analysis,[41] NIH Consensus panel,[99] and AAP clinical report[286] on use of iNO in preterm infants found no improvement in (1) survival of preterms with respiratory failure, (2) incidence of BPD/CLD, (3) severe IVH, (4) neurodevelopmental outcomes,[147] or (5) pulmonary outcomes.[286] **Therefore inhaled nitric oxide is not recommended for use in preterm infants** (see Table 23.21). However iNO continues to be used in an off-label fashion with a reported increase of 23% in 23 to 29 week preterm infants from 2009 to 2013 with an expenditure of $153 million for preterms under 34 weeks' GA in the United States.[156] This off-label use is not associated with a reduction in mortality among extremely premature neonates with RDS.[74]

PULMONARY INSUFFICIENCY OF THE NEWBORN

Pulmonary insufficiency continues to be a diagnosis used in term newborns demonstrating respiratory symptoms soon after delivery. This condition was first described as the insufficiency of gas exchange commonly caused by atelectasis of the lung, congenital abnormalities, and in infants with aspiration syndrome.[51]

Pathophysiology. This is a **condition of term infants and consists of the insufficiency of gas exchange secondary to atelectasis, congenital anomalies, or aspiration syndrome.**

Etiology. **These infants are often term or near term and born with adequate respiratory effort.** Within minutes to a few hours after delivery, they decline, requiring supplemental oxygen support.

Data Collection

History. **Late preterm or term infants who usually start with normal Apgar scores and then decline within minutes to a few hours after delivery.**

Physical Examination. Evidence for respiratory distress may be seen, including tachypnea, mild retractions, grunting, and flaring. Cyanosis in room air also may be present.

Laboratory Data. **Mild hypoxemia (requiring less than 40% oxygen) and mild acidemia are usually present.**

Treatment. In general, **support of the neonate with pulmonary insufficiency requires only the provision of sufficient supplemental oxygen to maintain an arterial oxygen tension of more than 70 to 80 mm Hg and maintenance of usual supportive neonatal care.** These infants are often discharged on low-flow oxygen until respiratory status improves.

TRANSIENT TACHYPNEA OF THE NEWBORN (RESPIRATORY DISTRESS SYNDROME TYPE 2)

Pathophysiology. **TTN is the result of delayed reabsorption of normal lung fluid, and thus an alternative name is *wet lung syndrome,* or *RDS type 2.*** Lung fluid accumulates in the peribronchiolar lymphatics and the bronchovascular spaces. **Thus TTN is an "obstructive" lung disease, whereas RDS is a "restrictive" lung disease.** Abnormalities in lung function of neonates with TTN include high total ventilation, high breathing frequency, low tidal volume, high dead space, prolonged nitrogen clearance, and low dynamic compliance. Reabsorption of lung fluid occurs by the following: (1) lung liquid production slows; (2) pulmonary epithelium changes from chloride-secreting to sodium-absorbing barrier; (3) air intake at birth shifts fluid from alveoli to interstitium and perivascular spaces; and (4) a higher protein content and osmotic pressure of blood/lymph facilitates flow of lung fluid.

Etiology. **TTN generally occurs in term or late-preterm infants with a history of cesarean section (especially elective section in the late-preterm infant**—see Chapter 5), low Apgar

scores, pulmonary artery hypertension, poor left ventricular function, lower umbilical artery pH (less than 7.25), vitamin D deficiency, higher/lower TSH levels depending on GA, and precipitous delivery.[32,135,259,387] **In these situations, there is a lack of the gradual compression of the chest that eliminates some fluid during a normal vaginal delivery.** Accumulation of interstitial fluid interferes with the forces that hold the bronchioli open, causing collapse and air trapping. In term infants with TTN, decreased surfactant function may also contribute to TTN, as well as a prolonged course.[329]

Prevention. Two recent RCTs of late-preterm and term neonates randomized to free flow oxygen or **20 minutes of facemask CPAP after C-section delivery showed a shorter duration and severity of TTN in the CPAP group.**[78,390] There also were fewer admissions to the NICU, less mechanical ventilation, and higher plasma B-type natriuretic peptide that correlated with the duration of tachypnea and the length of stay in the CPAP group.[78,390]

Data Collection

History. Term or late-preterm male infants with a history of cesarean section, precipitous delivery, prenatal exposure to methamphetamine, or other abnormalities of labor and transition are predisposed to TTN.[135] **Onset is usually 2 to 6 hours after birth. At initial presentation, TTN has a similar presentation as pneumonia.** However, the presence of perinatal infectious agents is more common in pneumonia and the course of pneumonia is for a longer period and with more support (i.e., oxygen and ventilation).[108]

Physical Examination. **Evidence for respiratory distress, including tachypnea, mild retractions, grunting, and flaring, may be seen. Cyanosis in room air also may be present.**

Laboratory Data. **Mild hypoxemia (requiring less than 40% oxygen) and mild acidemia are usually present.** A significant degree of hypoxemia or acidemia tends to constrict the pulmonary vasculature and aggravate the problem. Lower umbilical cord levels of cortisol, adrenocorticotropic hormone, and free triiodothyronine, as well as a higher epinephrine level, have been found in neonates developing TTN who were delivered by cesarean section.[24]

Chest x-ray examination reveals hyperexpansion with streaky infiltrates radiating from the hilum. These infiltrates are thought to represent interstitial fluid along the bronchovascular spaces. Air trapping causes the appearance of mild to moderate hyperaeration or inflation on the chest radiograph. Visible fluid in the pulmonary fissures and cardiomegaly also may be seen on chest radiograph.

Echocardiography may also be necessary because significantly more newborns with TTN have been found to also have structural cardiac lesions.[368]

Use of **lung ultrasonography** in infants with TTN shows pulmonary edema, alveolar-interstitial syndrome, "white lung," and the presence of comet-tail artifacts ("double lung point") in the inferior lung fields.[323] Lung ultrasound shows a high sensitivity (95.6%) and specificity (96.5%) in diagnosing TTN and RDS,[548] with no increased risk for pulmonary hemorrhage.[240] Fetal pulmonary artery Doppler acceleration to ejection time (PATET) is a noninvasive test to rule out the subsequent diagnosis of TTN.[69] A significantly lower fetal PATET ratio is indicative of TTN in the subsequently born neonate.

Treatment. In general, **support of the neonate with TTN requires only provision of sufficient supplemental oxygen to maintain an arterial oxygen tension of more than 70 to 80 mm Hg and maintenance of usual supportive neonatal care.** Usually little more than general support is necessary while the normal absorption of lung fluid through the lymphatics takes place. **As the lung fluid clears, both the x-ray abnormalities and clinical presentation resolve within 72 hours.** Use of the nasal route for CPAP or mechanical ventilation is well tolerated and effective.[132]

Although diuretic agents have been advocated, a recent *Cochrane* systematic review found no benefit and recommends against use of oral or intravenous diuretics, including furosemide for treatment of TTN.[255] Use of empiric antibiotics in infants with TTN who do not have risk factors for infection is not warranted.[130] In one study, fluid restriction for infants with TTN was safe and resulted in a shorter duration of respiratory support.[131] One small study of 40 neonates with TTN found a shorter duration of supplemental oxygen and use of empiric antibiotics with inhaled albuterol therapy, with no adverse effects.[270] Inhaled racemic

epinephrine,[354] salbutamol[353] and early inhaled corticosteroids in late-preterm and term newborns have no effect on the clinical course of TTN.[536]

Complications. TTN is independently and significantly associated with the development of childhood wheezing and asthma, especially in male infants.[188]

MECONIUM ASPIRATION SYNDROME

Pathophysiology. Before meconium aspiration can occur, meconium must find its way into the amniotic fluid. A hypoxic event before birth stimulates intestinal peristalsis and relaxation of the anal sphincter. **Colonic peristalsis ensues, resulting in the expelling of meconium into the amniotic fluid and, in severe cases, gasping in utero that leads to meconium aspiration. Respirations after birth draw meconium first into major airways and, subsequently, into the smaller airways, causing obstruction, atelectasis, air trapping, and pneumothorax. Meconium can also cause chemical pneumonitis and inactivation of surfactant,** further impairing gas exchange and potentiating barotrauma. **This condition occurs more often in term or postterm infants when a hypoxic episode is experienced in utero.**[543] These movements open the glottis so that meconium flows into the oropharynx and on into the lung. Thus the pathophysiology of lung disease in meconium aspiration syndrome (MAS) is related to the mechanisms causing fetal stress and the direct adverse effects of meconium in the lung. MAS is a common reason for lung disease in neonates.

Etiology. Meconium aspiration produces disease by several mechanisms: (1) meconium physically obstructs the glottis, trachea, or any number of smaller airways, resulting in atelectasis, air trapping, alveolar collapse, and ventilation-perfusion mismatching; (2) it promotes an inflammatory response known as *chemical pneumonitis;* (3) it contains increased levels of secreted phospholipase A_2 that promote inflammation[438]; (4) it inhibits surfactant function; and (5) it increases PVR, caused by asphyxial episodes, resulting in increased right-to-left shunting and the development of PPHN (Fig. 23.8).[177] While the incidence of being born through meconium-stained amniotic fluid varies from 7.93%[169] to 9.2%,[309] the incidence of developing MAS also varies from 0.067%[169] to 10.2 %.[309]

Prevention. Before an infant is born, meconium aspiration may be prevented by early recognition of the compromised fetus, elective induction for pregnancy at 41 weeks' gestation or later, aggressive management of abnormal fetal heart rate patterns, and fewer infants with low Apgar scores.[505] Amnioinfusion is associated with improvements in perinatal outcomes only in settings where facilities for surveillance are limited; in settings with standard perinatal surveillance, amnioinfusion is either ineffective or masked by other strategies to optimize perinatal outcomes.[228]

A large multicenter (12-hospital) RCT of intrapartum oropharyngeal or nasopharyngeal suctioning for term infants born through meconium-stained amniotic fluid showed **no significant difference in the incidence of MAS (e.g., 4% for both the suction and the no-suction group),** the need for mechanical ventilation, mortality rate, duration of oxygen use, days of ventilation, and length of stay.[535] The study's conclusion that routine suctioning does not prevent MAS (confirmed in more recent studies)[86,551,561] has resulted in revision of present recommendations for care of these infants (see Chapter 4). **Routine tracheal suction is no longer recommended for nonvigorous or depressed infants (e.g., nonvigorous infants with depressed tone and respirations and/or heart rate less than 100 beats/min).**[81,366,561] An interdisciplinary health care team for "rapid response" prepared and credentialed (e.g., NRP) for management of the neonate born through meconium-stained amniotic fluid, coupled with interdisciplinary postnatal assessment, observation, and prompt treatment, is recommended for prevention of MAS and its associated morbidity and mortality risks.

Use of orogastric suctioning and chest physiotherapy to prevent MAS is not supported by evidence from any studies.

Data Collection

History. A history of asphyxia, IUGR, postterm delivery, caesarean delivery, meconium-stained amniotic fluid, thick meconium, nonreassuring fetal heart tracing, fetal tachycardia, intrapartal maternal fever, low Apgar scores (≤3 at 1 minute;

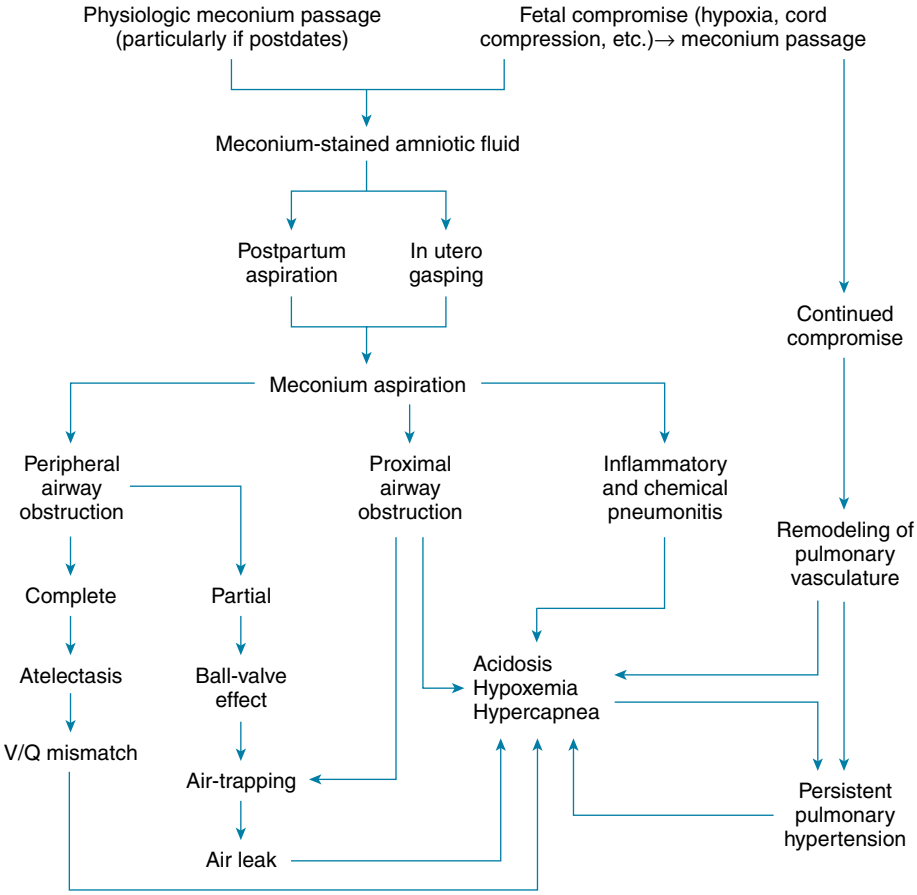

FIGURE 23.8 Pathophysiology of meconium passage and the meconium aspiration syndrome. *V/Q*, Ventilation-perfusion. (From Wiswell T, Bent R. Meconium staining and the meconium aspiration syndrome: unresolved issues. *Pediatr Clin North Am.* 1993;40[5]:957.)

<5 at 5 minutes), need for endotracheal intubation at birth, and African American race may be present.[144,169,384,479] **There is a positive association between chorioamnionitis, funisitis, or infection with the passage of meconium at term gestation and the severity of MAS.**[269,309] Maternal risk factors associated with placental insufficiency (e.g., hypertension, pregnancy-induced hypertension, chronic respiratory/cardiovascular disease, diabetes, IUGR, heavy cigarette smoking, drug use, and postterm pregnancy) may also lead to fetal asphyxia and meconium passage.[568]

Physical Examination. **Tachypnea, rales, and cyanosis are seen in mild cases.** Respiratory distress occurs in 33.4% of infants born through meconium-stained amniotic fluid, and 25.9% are MAS.[479] Respiratory distress occurs within 12 hours in 97.9% and is severe in 21.7% of cases.[479] **In moderately severe cases, grunting, retractions, and nasal flaring also may be seen. In severe cases, the infant is asphyxiated and severely depressed at birth. There is profound cyanosis and pallor, irregular gasping respirations, and an increased anteroposterior diameter of the chest (a barrel chest) as a result of gas trapping and alveolar overdistention.**

Laboratory Data. **The chest x-ray examination shows marked air trapping, hyperexpansion, and hyperinflation. There are bilateral, diffuse, coarse, patchy infiltrates** (Fig. 23.9). **Complete occlusion by debris results in atelectatic areas. Air leaks are frequently seen.** Pleural effusion may

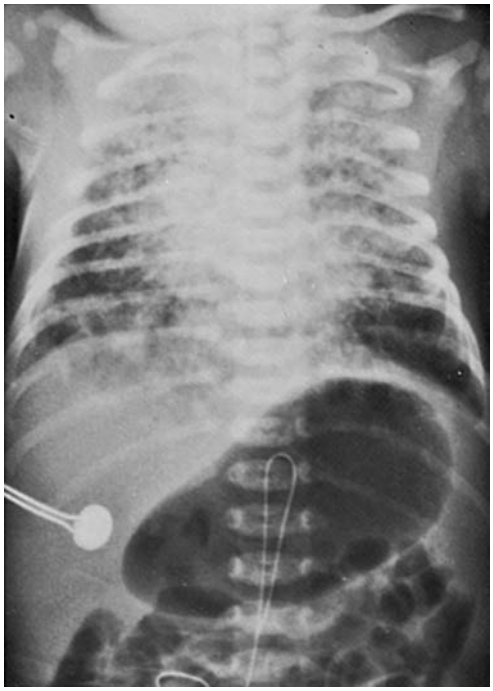

FIGURE 23.9 Chest x-ray film of infant with meconium aspiration. Note diffuse infiltrates.

occur as a result of the inflammatory process in the lung. Cardiomegaly may be present; this results from intrauterine asphyxia or cardiac hypoxia.

Severe hypoxemia and hypercapnia as a result of ventilation-perfusion mismatching and right-to-left shunting caused by pulmonary hypertension are present. Severe acidosis usually is combined respiratory and metabolic acidosis. A retrospective analysis of the inflammatory markers in 239 infants with MAS (without early onset sepsis) found a correlation between elevated C-reactive protein (CRP) levels and immature-to-total neutrophil ration (IT-ratio) with low white blood count (WBC) and absolute neutrophil count (ANC) and the severity of MAS.[226]

Lung ultrasonography findings in MAS include: (1) pulmonary consolidation with air bronchogram (100% of newborns), (2) alveolar-interstitial syndrome (100%), (3) pleural line anomalies and disappearance of A-line (100%), (4) severe massive atelectasis (16.2%), and (5) pleural effusion (13.7%).[322]

Treatment. **Hypoxemia is the major problem in meconium aspiration, and treatment should be directed at improving oxygenation.** Mildly affected infants will frequently require only warmed, humidified oxygen by hood. **Increasing severity of meconium aspiration will require increased levels of intervention. The need for surfactant therapy (see later) is a predictor of the severity of MAS.**[384] About 30% to 50% of infants with MAS require CPAP or mechanical ventilation.[120] **Some infants respond to CPAP (4 to 6 cm H_2O), but others require full ventilator support.** Use of bubble NCPAP as a primary respiratory therapy for MAS versus standard care was recently studied in an RCT of 67 neonates over 34 weeks' gestation. **Bubble NCPAP reduced the need for mechanical ventilation in the first 7 days of life in infants with MAS,** but there was no difference in the incidence of PPHN or length of stay between the two groups.[392]

Because these infants are usually term or postterm, they resist assisted ventilation and may require paralyzation (Table 23.16), sedation, and/or analgesia (see Chapter 12) to ventilate and oxygenate the lungs adequately. With paralysis, these infants may require rapid rates, high peak inspiratory pressure, and PEEP for adequate oxygenation and ventilation. Although the majority of MAS infants are able to be treated with CPAP and CMV, use of other treatment modalities (e.g., HFV, iNO, ECMO/ECLS) may become necessary with accompanying PPHN and severe respiratory failure.[120] **When using CMV to ventilate infants with MAS, a higher tidal volume (26% higher) and a higher minute ventilation (42% higher) are necessary to achieve similar alveolar ventilation.**[467] **Early use of HFOV with surfactant therapy results in significant reduction in the duration of oxygen supplementation and mechanical ventilation and reduced length of stay** when compared to CMV or HFOV alone.[88]

Meconium in the lung inhibits surfactant function in a dose-dependent manner. To decrease surfactant inactivation in MAS, the following is recommended: (1) aspirate meconium from the airway and lungs to decrease the amount that interacts with surfactant in the alveoli, (2) provide surfactant replacement at a sufficient dose to replace inactivated endogenous surfactant and repeat as necessary, and (3) combine surfactant replacement with antiinflammatory drugs to reduce meconium-induced inflammation.[350,351] Studies of

TABLE 23.16 DRUGS FOR PARALYZATION

DRUG	DOSAGE	COMMENTS
Pancuronium (Pavulon)	Give a test dose of 0.02 mg/kg IV to measure responsiveness 0.1 mg/kg IV push (0.04-0.15 mg/kg) q 1-2 hr based on duration of paralysis Onset: 1-2 min	*Indications:* paralysis for mechanical ventilation to improve oxygenation/ventilation; reduce barotrauma and alteration in cerebral blood flow Although paralyzed, neonate still feels pain—analgesia necessary for painful procedures and to accompany paralysis (see Chapter 12) *Adverse effects:* corneal drying (lubricate eyes); tachycardia; increased salivation; blood pressure changes (hypotension and hypertension) Reversed by: Neostigmine: 0.04-0.08 mg/kg IV Atropine: 0.02 mg/kg
Vecuronium	0.1 mg/kg IV push (0.03-0.15 mg/kg) q 1-2 hr based on duration of paralysis Onset: 1-2 min	*Indications:* same as above *Adverse effects:* corneal drying (lubricate eyes); decreases in heart rate and blood pressure when used with narcotics; special sensitivity in preterms (that diminishes with age); duration of effect prolonged in preterms *Reversed by:* same as above

surfactant replacement to infants with MAS suggest improvement in some neonates with severe respiratory failure and MAS. Improved oxygenation/ventilation, decreased severity of respiratory compromise, no increase in air leaks, and less use of ECMO have been observed in some studies.[158] Variable study results of surfactant use in MAS may result from timing, type, amount, and method of surfactant administration. Animal studies of surfactant replacement in MAS show that a combination of glucocorticoid and surfactant therapies improved gaseous exchange and lasted longer than surfactant alone.[346] A recent study of controlled hypothermia in 10 asphyxiated newborns with/without MAS found improved surfactant function after 48 to 72 hours of whole-body cooling that persisted for 6 hours after rewarming.[26]

Surfactant lavage has been shown to result in (1) improved oxygenation/ventilation and pulmonary function measurements (e.g., increased lung compliance and decrease in airway resistance), (2) earlier weaning from assisted ventilation, (3) need for less oxygen, (4) less mortality and use of ECMO, and (5) more rapid weaning of mean airway pressure.[122,279] Recovery of lung lavage fluid is associated with lower MAP at 24 hours and shorter duration of respiratory support and should be a priority in the lavage procedure.[123] **Complications of lung lavage include hypoxemia (transient or severe) and no alterations in heart rate and blood pressure or systemic hypotension.**[122] A systematic review of surfactant lung lavage and bolus surfactant found a shorter length of stay and duration of mechanical ventilation, and bolus surfactant reduced the need for ECMO, but there was no reduced risk of mortality.[371] **Surfactant lavage remains an experimental therapy.**

Mucosal irritation and increased mucosal secretion hamper respiratory and mucociliary clearance efforts. **Frequent pulmonary hygiene (every 2 to 3 hours)** may help alleviate this problem.

Antibiotic use in MAS shows no clinical benefits and no evidence of sepsis in neonates with MAS; the small number of studies and number of subjects necessitates more evidence about the efficacy and cost-effectiveness of antibiotics (and surfactant) to treat MAS.[371] The latest *Cochrane* review found **no difference in infection rates of infants who were born through meconium-stained amniotic fluid and those with MAS occurring in neonates with or without antibiotics.**[264]

As with any sick infant, close attention must be given to physiologic support and homeostasis. (See General Treatment Strategies earlier in this chapter; see also Chapters 6, 7, and 8 and Unit Three.)

Complications. Use of new treatments has decreased the mortality rate to less than 5%.[543] **Persistent pulmonary hypertension frequently complicates MAS, potentiates the difficulties in**

oxygenation, and contributes to a large portion of the mortality associated with MAS.[177] Air leaks are complications of both the disease (ball-valve obstruction causing air trapping) and the treatment. Infants with MAS are at increased risk for adverse neurologic outcomes (e.g., CP and global delays)[49] and long-term pulmonary problems (e.g., increased airway reactivity, abnormal pulmonary function).[589] A recent study found elevated aspartate aminotransferase levels in infants with MAS at birth who eventually have poor neurodevelopmental outcomes.[85] These researchers recommend early intervention to improve the neurodevelopmental outcomes of those MAS infants with high levels of aspartate aminotransferase at birth.[85]

NEONATAL PNEUMONIA

Neonatal pneumonia occurs perinatally or postnatally in about 1% of term neonates and 10% of preterm neonates and may be as high as 28% for ventilated ELBW infants in the NICU.[50] **Neonates requiring prolonged hospitalization in the NICU are at risk for developing pneumonia from nosocomially acquired organisms.** The organisms most often causing neonatal pneumonia are mainly group B streptococci and gram-negative organisms (e.g., *Escherichia coli, Klebsiella, Pseudomonas,* and *Serratia marcescens*) but also include *Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae,* and *Candida*. Less commonly acquired viral infections include herpes, cytomegalovirus, varicella-zoster, and syphilis. Community-acquired viral infections also occur in the NICU setting and include respiratory syncytial virus, enterovirus, adenovirus, and parainfluenza virus infections (see Table 23.16).[50]

Pathophysiology. In bacterial pneumonia, alveoli are often more edematous and inflamed than in viral infections. Protein-rich fluid may partially or completely fill the alveoli. Reduced pulmonary compliance during neonatal pneumonia is due to an increase in surfactant proteins that resolves with the resolution of the pneumonia.[116] This is often followed by an influx of polymorphonuclear leukocytes and red blood cells. Macrophages enter the alveoli and remove intraalveolar debris, restoring normal lung functioning. *S. aureus* and *Klebsiella* organisms often cause severe damage to alveoli and destroy lung tissue by causing necrosis of the septum between the alveoli. In some cases, abscesses form.

Viruses and *Mycoplasma* organisms may also be acquired transplacentally, during the delivery, or postnatally. Viral and mycoplasmal pneumonias commonly involve the bronchi and peribronchial interstitium more often than the alveoli. Viral and mycoplasmal organisms cause loss of epithelial ciliary appendages and sloughing into the airways. This results in stasis of mucus and secretions and bronchial obstruction with atelectasis. A secondary inflammatory response is characterized by mononuclear infiltration into the submucosa and perivascular areas causing narrowing of the airway lumen. Another response to this inflammatory process is smooth muscle constriction, which leads to increased airway obstruction and bronchospasm. In severe cases of viral and mycoplasmal infection, the inflammatory process involves the alveoli.

Fungal infections, the most common being *Candida* infection, may be acquired in utero, during the birth process, or in the postnatal period. Congenitally acquired pneumonia can be diffuse, resulting from the inflammatory process at birth. *Candida* often invades the pharynx and larynx and may produce a thick layer of hyphae that lines the upper and lower respiratory tract. Ulceration of the pharynx, larynx, and the lower respiratory tract can occur.

Etiology. Predisposing factors that lead to the development of neonatal infections and pneumonia include the immaturity of the immune system, colonization of the mother's genital and vaginal tracts with pathogens, amnionitis, prolonged rupture of membranes, prematurity requiring intubation and assisted ventilation, and nosocomial infections acquired in the NICU.[50] Bacterial pneumonia can be secondary to the spread of pathogens from the mother to the baby in utero.[108] Pneumonia acquired in utero often leads to stillbirth and premature delivery.

Neonates who require NICU care are at particularly high risk for colonization of their upper respiratory tract with pathogenic organisms and the passage of pathogens from caregivers or contaminated equipment.[80] *Ventilator-associated pneumonia* (VAP), a nosocomial-acquired infection in a neonate who has been ventilated for longer than 48 hours, occurs from 1.4 to 7 episodes per 1000 ventilator days in developed countries to 16

to 89 episodes per 1000 ventilator days in developing countries.[80] **Risk factors for VAP include (1) prematurity, (2) LBW/VLBW/ELBW, (3) reintubation, (4) use of sedatives, (5) use of TPN, and (5) prolonged duration of mechanical ventilation resulting in an ETT biofilm.**[50,80,310,391,518] Most causative agents of VAP are gram-negative bacteria (i.e., *E. coli, Klebsiella,* and *Pseudomonas*), followed by gram-positive organisms (i.e., *S. aureus*) and fungi (i.e., candida).[391]

Prevention. Prevention **begins with identifying mothers at risk for infection** (e.g., group B *Streptococcus* [GBS], herpes, chlamydial infection, syphilis, gonorrhea); **early management of infections with antibiotic therapy; meticulous equipment disinfection and hand hygiene practices** (handwashing/alcohol-based hand sanitizers) by health care providers in the NICU[435]; and **restricting the entry of *anyone* with respiratory infections into the NICU** (see Chapter 22).

Rapid extubation and use of noninvasive ventilator strategies prevent and reduce the incidence of VAP.[80] **Prophylactic use of probiotics prevents sepsis in the NICU**[259] **and may also prevent neonatal VAP.**[80] An RCT of 60 intubated infants (half in supine position and the other half in side-lying) investigated whether positioning would decrease VAP. Despite no significant difference in the number of positive tracheal cultures after 2 days, **after 5 days cultures were positive in 87% of the supine versus 30% of the side-lying group.**[10] In developing countries, initiation of multidimensional infection control strategies has resulted in reduction of VAP rates.[439] **Adaptation of adult practices to prevent VAP into an evidence-based neonatal VAP bundle in one tertiary center reduced the incidence of VAP** over a 4-year period, including a zero incidence over a 20-month period.[560] Elements of the evidence-based bundle included: (1) hand hygiene, (2) intubation, (3) feeding, (4) suctioning, (5) positioning, (6) oral care, and (7) respiratory care equipment.[560]

Data Collection

History. The clinical presentation of neonatal pneumonia varies depending on the infecting organism and the incidence of acquisition. **Acute respiratory distress** is frequently seen in intrauterine and intrapartally acquired secondary infections. Neonates with pneumonia often have a history of low Apgar scores, temperature instability, and poor tone and activity. **The clinical signs and symptoms of pneumonia are similar to those of respiratory distress, TTN (RDS type II)/retained lung fluid, or sepsis.** Late-acquired pneumonia may have a gradual or abrupt onset, depending on the organism. Infants with chlamydial pneumonia frequently present with a characteristic staccato cough.

Physical Examination. The infant with pneumonia often presents with respiratory distress (e.g., tachypnea, low pulse oximetry readings, respiratory deterioration, apnea, temperature instability, hypoglycemia). **The signs and symptoms of pneumonia often are nonspecific and difficult to differentiate from other neonatal respiratory problems** without the aid of chest x-ray evaluation. Combined viral (usually RSV) and bacterial pneumonia is often associated with more serious clinical findings, including recurrent wheezing.[594] **VAP results in an increase in the volume and character of secretions** (i.e., purulent mucus) suctioned from the ETT.[80] Many NICU infants with viral respiratory tract infections are asymptomatic.[50]

Laboratory Data. The appearance of pneumonia varies depending on the duration of infection, cause of the pneumonia, and presence of underlying respiratory disease (e.g., RDS, BPD). **Serial x-ray films are more valuable than one isolated x-ray examination in making the diagnosis and following the course of the disease.** Infiltration patterns on chest x-ray films include lobar consolidation; patchy alveolar infiltrates; hilar and peribronchial infiltrates; reticulogranular, nodular, or miliary infiltrates; and hazy or opaque lungs (Table 23.17). **Lung ultrasound has been shown to be a reliable diagnostic tool in neonatal pneumonia.**[324]

Endotracheal aspirate examination/culture and blood culture also are useful tools in identifying the organisms of pneumonia, including VAP.[200] A **workup for sepsis** is often part of the diagnostic evaluation for these neonates (see Chapter 22).

Treatment. **Treatment of neonatal pneumonia includes supportive care** (e.g., thermoregulation, nutrition, oxygenation, ventilation if necessary, and parenteral support). If the **causative agent is bacterial, antibiotic therapy must be instituted after a sepsis workup; if viral, an antiviral agent is considered; if fungal, an antifungal agent is used** (see Chapter 22). Neonatal pneumonia may be accompanied by surfactant

TABLE 23.17 ETIOLOGIC FACTORS AND CHEST X-RAY FINDINGS IN NEONATAL PNEUMONIA

CAUSATIVE AGENT	CHEST X-RAY FINDINGS
Bacterial	
Group B beta-hemolytic streptococci (GBS)	Diffuse reticulogranular pattern, opacity ("whiteout"), patchy infiltrates, and pleural effusion
Streptococcus pneumoniae	Patchy infiltrates (lobar), pleural effusion
Staphylococcus aureus	Diffuse infiltrates; pneumatocele
Methicillin-resistant *Staphylococcus aureus* (MRSA)	Diffuse infiltrates; abscess formation
Staphylococcus epidermidis	Hazy lung fields; infiltrates
Listeria monocytogenes	Bilateral patchy infiltrates
Escherichia coli	Lobular consolidation; pneumatocele
Klebsiella	Bilateral consolidation; lung abscess, pneumatocele
Pseudomonas and *Serratia*	Parenchymal consolidation (patchy or basilar); pneumatocele
Haemophilus influenzae	Nonspecific; x-ray findings similar to those of GBS (above) or respiratory distress syndrome
Viral	
Herpes virus	Perihilar infiltrates; streaky, lobar consolidation; pleural effusion (late onset)
Cytomegalovirus	Nonspecific, perihilar streaking; hazy lung fields; infiltrates; opacification
Rubella virus	Interstitial infiltrates; hazy lung fields
Respiratory syncytial virus	Hyperexpansion; patchy consolidation
Adenovirus, enterovirus	Hyperexpansion; patchy consolidation
Fungal	
Candida albicans	Diffuse granularity; coarse infiltrates; opacification
Mycoplasma	
Ureaplasma urealyticum	Fine reticular pattern progressing to opacification and consolidation
Mycoplasma hominis	Diffuse reticular pattern, opacity, and pleural effusion
Other	
Treponema pallidum (syphilis)	Diffuse opacification; consolidation
Chlamydia trachomatis	Hyperinflation; streaky infiltrates
Pneumocystis jiroveci (formerly *carinii*)	Diffuse haziness; granularity; opacity

Modified from Carey B, Trotter C. Neonatal pneumonia. *Neonatal Netw.* 2000;19(4):46.

inactivation; **use of rescue surfactant for respiratory failure accompanying neonatal pneumonia is effective in improving oxygenation in late-preterm and term neonates requiring mechanical ventilation**[137] (see Box 23.15). Early use of surfactant in pneumonia is associated with lower risk of mortality and use of ECMO.[278]

Nebulized ambroxol (a mucolytic and secretolytic) improved lung function index and decreased inflammatory factors and inhibition of cell apoptosis when compared to a group receiving standard supportive care.[583] **Use of nebulized budesonide to treat VAP has been shown to decrease mortality and shorten mechanical ventilation and length**

of stay while improving pulmonary diffusion function.[315]

Complications. The mortality rate for perinatally acquired pneumonia is variable but has been estimated at 20%, with a higher mortality rate (50%) for postnatally acquired pneumonia. In a review of perinatally acquired neonatal infections, the overall mortality rate for pneumonia was 10%.[80] The decline in mortality rate is the result of perinatal antibiotic use. VAP in the NICU results in longer length of stay, higher cost, and higher mortality rate.[80,517]

PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

PPHN manifests as severe pulmonary hypertension with pulmonary artery pressure elevation to levels equal to systemic pressure or higher and large right-to-left shunts through the foramen ovale and the ductus arteriosus. PPHN manifests early in life: 77% of cases are diagnosed in the first 24 hours of life, 93% in the first 48 hours, and 97% by 72 hours of age. The incidence of PPHN is 2 to 6 in 1000 live births and complicates one-third of infants with moderate to severe CLD/BPD.[289]

Pathophysiology. Once the placental blood source is severed, adequate oxygenation of the newborn depends on inflation of the lungs, closure of the fetal shunts, a decrease in PVR, and an increase in pulmonary blood flow (an eightfold to tenfold increase at the first breath). **Normally, PVR decreases with the first breath of life.** When it remains high, successful transition from fetal to neonatal circulation is impaired. **In an infant manifesting PPHN, high PVR and pulmonary hypertension impede pulmonary blood flow. Factors that increase and decrease PVR are listed in** Table 23.18.

Increased PVR leads to hypoxemia, acidemia, hypercarbia, and eventually lactic acidosis. The pulmonary arterioles respond to this process with further constriction, promoting an additional decrease in blood flow; thus a cyclic pattern is established.[289] **PVR also maintains higher right-sided pressures in the heart that equal or exceed systemic pressures, resulting in right-to-left shunting, which is characteristic of PPHN.** PPHN also produces direct and indirect effects on myocardial function. A combination of pressure alterations, hypoxia, and acidemia leads to a cyclic pattern of decreased cardiac output, decreased pulmonary blood flow, and further vasoconstriction (Fig. 23.10).

TABLE 23.18 FACTORS THAT ALTER PULMONARY VASCULAR RESISTANCE (PVR)

LOWERS PVR	INCREASES PVR
Endogenous mediators and mechanisms:	Endogenous mediators and mechanisms:
Oxygen	Hypoxia
Nitric oxide	Acidosis
PGI2, PGE2, PGD2	Endothelin-1
Adenosine, ATP, magnesium	Leukotrienes
Bradykinin	Thromboxanes
Atrial natriuretic factor	Platelet-activating factor
Alkalosis	Ca2+ channel activation
K+ channel activation	Alpha-adrenergic stimulation
Histamine	PGF2α
Acetylcholine	
Beta-adrenergic stimulation	
Mechanical factors:	Mechanical factors
Lung infection	Overinflation or underinflation
Vascular cell structural changes	Excessive muscularization, vascular remodeling
Interstitial fluid and pressure changes	Altered mechanical properties of smooth muscle
Shear stress	Pulmonary hypoplasia
	Alveolar capillary dysplasia
	Pulmonary thromboemboli
	Main pulmonary artery distention
	Ventricular dysfunction, venous hypertension

ATP, Adenosine triphosphate; *$PGF_2\alpha$*, prostaglandin $F_2\alpha$; *PGI_2*, *PGE_2*, *PGD_2*, prostaglandins I_2, E_2, and D_2; *PVR*, pulmonary vascular resistance.

From Kinsella J, Abman S. Recent developments in the pathophysiology and treatment of *PPHN*. *J Pediatr*. 1995;126(6):855.

Etiology. Pulmonary vascular resistance (PVR) remains high after birth because of underdevelopment, maldevelopment, or maladaptation of pulmonary vasculature (Table 23.19). In utero, development of increased vascular smooth muscle or perinatal factors that cause or contribute to vasospasm are thought to be prime mechanisms of PPHN. Independent predictors of pulmonary hypertension in the preterm infant

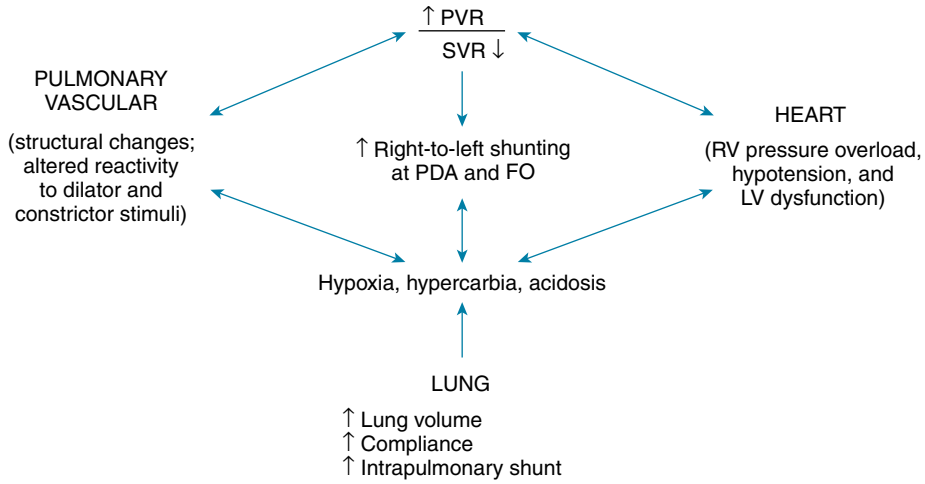

FIGURE 23.10 Cardiopulmonary interactions in persistent pulmonary hypertension of the newborn. *FO,* Foramen ovale; *LV,* left ventricle; *PDA,* patent ductus arteriosus; *PVR,* pulmonary vascular resistance; *RV,* right ventricle; *SVR,* systemic vascular resistance. (From Kinsella J, Abman S. Recent developments in the pathophysiology and treatment of PPHN. *J Pediatr.* 1995;126:855.)

include (1) low Apgar scores, (2) preterm premature rupture of membranes (PPROM), (3) oligohydramnios, (4) pulmonary hypoplasia, and (5) sepsis.[289]

Prevention. **Prevention of PPHN includes minimizing intrauterine and perinatal risk factors when possible, maintaining postnatal physiologic homeostasis, and detecting and correcting any underlying abnormality.**

Data Collection

History. In addition to the risk factors listed in Table 23.19, **maternal tobacco use, maternal obesity, premature rupture of membranes, maternal lack of private or use of public insurance, cesarean delivery, late-preterm or postterm birth, LGA infant, race (black, Asian), maternal diabetes, and maternal asthma are associated with an increased risk for PPHN.**[222]

There are two major considerations in the history of these infants: (1) the recognition of major disease processes or syndromes that are highly associated with pulmonary hypertension and (2) the timing of the onset of cyanosis and the deterioration of the infant.

Physical Examination. **The initial clinical presentation is usually a late-preterm (≥34 weeks' GA), term, or postterm infant with worsening cyanosis within the first 24 hours of life.** Tachypnea is a common finding and, when accompanied by retractions, is indicative of decreased pulmonary compliance. **Cyanosis may be either intense at birth or may progressively worsen in association with increased right-to-left shunting.**

Despite increasing FiO_2, the infant continues to have low PaO_2 (hypoxemia) as a result of right-to-left shunting. Milder cases of PPHN feature minimal tachypnea and cyanosis, frequently associated with stress from crying or feeding. **Severe cases are characterized by marked cyanosis, tachypnea, low systemic blood pressure, and decreased peripheral perfusion.**

Increased pulmonary artery pressure results in the following signs:

- Pulmonic systolic ejection clicks
- A second heart sound that is single, loud, or narrowly split with a loud pulmonary component
- A prominent right ventricular impulse that is visible or palpable at the lower left sternal border
- A soft systolic murmur in the pulmonary area

Laboratory Data. The laboratory evaluation of an infant with suspected PPHN should include a **complete blood count (CBC) with differential, platelet count, chest x-ray examination, and serum glucose, calcium, electrolytes, and arterial blood gas determinations.** The CBC is used to detect anemia, which could contribute to

TABLE 23.19 CRITICAL FINDINGS ETIOLOGIC FACTORS IN PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

DEVELOPMENTAL PROCESS	PATHOPHYSIOLOGY	ASSOCIATED CONDITIONS
Underdevelopment, a decreased number of pulmonary vessels	Interruption in lung development, resulting in shunting of blood because of fewer pulmonary vessels and less area for gaseous exchange	Pulmonary hypoplasia (e.g., diaphragmatic hernia, premature rupture of membranes, oligohydramnios, Potter syndrome)
Maldevelopment, abnormally developed pulmonary vessels	Hypertrophy of musculature and extension into nonmuscularized arteries resulting in smaller lumen size, which increases PVR	Intrauterine asphyxia/hypoxia, MAS, and maternal smoking Intrauterine fetal ductus arteriosus closure increases pulmonary blood flow Congenital heart defects that result in abnormal pulmonary vessel formation (TAPVR, pulmonary vein stenosis)
Maladaptation (from intrauterine to extrauterine life) as a result of transient or persistent vasoconstriction	Results in remodeling and abnormal muscularization of small pulmonary arteries Results in pulmonary vasospasm and vascular remodeling	Hypoxia/acidosis/asphyxia Asphyxia may result in persistent vasospasm Pulmonary parenchymal disease (RDS, MAS, pneumonia, TTN, surfactant protein B deficiency)
	Pulmonary vasospasm and decreased cardiac output resulting from release of endotoxins and reaction to systemic inflammatory response	Bacterial sepsis Prenatal pulmonary hypertension (e.g., fetal systemic hypertension or premature closure of the ductus arteriosus) associated with maternal ingestion of NSAIDs (e.g., ibuprofen, naproxen, indomethacin), salicylates, phenytoin, lithium, prostaglandin inhibitors, or SSRIs (absolute risk <1%)[52]
	Prevents normal circulatory transition at delivery	Delayed or ineffective resuscitation, narcosis, other central nervous system depression, hypothermia, hypotension, severe congenital anemias[297]
	Potentiation of vasoconstriction	Hypothermia, hypoglycemia, hypocalcemia, acidosis, hypoxia, myocardial dysfunction, and ischemia
	Functional obstruction of pulmonary vascular bed	Polycythemia, hyperviscosity

MAS, Meconium aspiration syndrome; *NSAIDs,* nonsteroidal antiinflammatory drugs; *PVR,* pulmonary vascular resistance; *RDS,* respiratory distress syndrome; *SSRI,* selective serotonin reuptake inhibitors; *TAPVR,* total anomalous pulmonary venous return; *TTN,* transient tachypnea of the newborn.

Data from VanMarter L. Persistent pulmonary hypertension of the newborn. In: Cloherty J, Stark A, eds. *Manual of Neonatal Care.* 4th ed. Philadelphia, PA: Lippincott-Raven; 1998; Weardon M, Hansen T. Persistent pulmonary hypertension of the newborn. In: Hansen T, Cooper T, Weisman L, eds. *Contemporary Diagnosis and Management of Neonatal Respiratory Diseases.* 2nd ed. Newton, PA: Handbook of Health Care; 1998; Steinhorn RH. Diagnosis and treatment of pulmonary hypertension in infancy. *Early Hum Dev.* 2013;89(5):865.

systemic hypertension; detect polycythemia, which could lead to increased PVR; and detect an infectious process, such as group B streptococcal sepsis or pneumonia.

Arterial blood gases demonstrate acidosis, hypoxia, and increased $PaCO_2$. If blood gas specimens are obtained simultaneously in the right radial artery (preductal) and the descending aorta (postductal), the right-to-left shunt can be documented (preductal PaO_2 greater than postductal). Simultaneous preductal and postductal pulse oximetry or transcutaneous oxygen measurements may also be useful in the diagnosis. Other diagnostic tests are outlined in Table 23.20.

The most common **chest x-ray findings** associated with PPHN include:

- Prominent main pulmonary artery segment
- Mild to moderate cardiomegaly
- Variable pulmonary vasculature (increased, decreased, or normal)
- Signs of left ventricular dysfunction that include pulmonary venous congestion and cardiomegaly

The ECG is usually normal but may demonstrate right ventricular hypertrophy, evidence of

TABLE 23.20 DIAGNOSTIC TESTS FOR PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN (PPHN)

TEST	USE
Hyperoxia test	If P_{O_2} does not increase in 100% oxygen, a right-to-left shunt is demonstrated (may be secondary to either PPHN or congenital heart defect)
Comparison of preductal and postductal arterial PaO_2	Demonstrates ductal shunting; if negative, it does not rule out PPHN; most infants with congenital heart disease have no ductal shunting
Contrast echocardiography "bubble echo"	Demonstrates foramen ovale shunting but should be present in most cases of PPHN
Hyperoxia-hyperventilation	Most definite test; if P_{O_2} <50 mm Hg prehyperventilation and rises above 100 mm Hg is almost always PPHN

From Duara S, Gewitz MH, Fox WW. Use of mechanical ventilation for clinical management of persistent pulmonary hypertension of the newborn. *Clin Perinatol.* 1984;11(3):641.

pulmonary hypertension, and signs of myocardial ischemia. **Echocardiography is essential** in (1) evaluating cardiac structures, (2) ruling out cyanotic cardiac lesions, (3) diagnosing the right-to-left shunting at the foramen ovale and/or ductus arteriosus, (4) estimating pulmonary artery pressure, (5) determining therapy, and (6) evaluating response to therapy.[271]

Treatment. Historically, treatment of PPHN included hyperventilation, IV infusions (e.g., systemic vasodilators, sedatives, narcotics, paralysis, alkali, and inotropes), surfactant administration, high-frequency ventilation, and ultimately ECMO/ECLS as a last resort, and in limited neonatal centers. These treatments were widely used without RCTs to test safety and efficacy, and none of these treatments improved survival in infants with PPHN.

Treatment of PPHN focuses on preventing or intervening in the development of the cyclic pattern illustrated in Fig. 23.10. Goals of current therapy include (1) **treating associated pathology** (e.g., antibiotics for sepsis/pneumonia; partial exchange transfusion for polycythemia/hyperviscosity; volume expanders), (2) **providing adequate oxygenation,** (3) **reducing PVR** by pulmonary vasodilation that improves pulmonary blood flow, (4) **increasing and maintaining systemic vascular resistance (SVR)** (e.g., systemic blood pressure), and (5) **preventing right-to-left shunting** by decreasing PVR and increasing SVR. Pulmonary blood flow should increase if PVR is decreased or if SVR is increased.[292,492,493]

Adequate Oxygenation. Maintaining adequate oxygenation is a prime goal of care of infants with PPHN. Both hypoxemia and hyperoxemia should be avoided, so that paO_2 values should be maintained in the range of 60 to 80mm Hg and PO saturations between 90% and 97% in term and late-preterm infants.[295-297,537] **To maintain adequate oxygenation, alterations in "routine" care and handling are essential. Because handling a sick newborn for *any* reason causes a fall in PaO_2, the benefits of handling for routine care such as changing linens, weighing, suctioning, and taking vital signs must be balanced against the risk for iatrogenic hypoxia. PaO_2 variations in the newborn are as follows**[113,161]**:**

- **At rest: ±15 mm Hg variation**
- **While crying: decreased PaO_2 by as much as 50 mm Hg**
- **With routine care: decreased PaO_2 by as much as 30 mm Hg**

Maintaining organized, coordinated care and minimizing disturbances are therefore very important. Keeping the infant calm is important because severe hypoxia accompanies crying. Using pacifiers and decreasing noxious stimuli (e.g., invasive procedures) keep struggling and crying to a minimum. **Continuously monitoring vital signs, blood pressure, and pulse oximetry decreases the need for physical manipulation and disturbance. These large, vigorous infants require sedation and analgesia** (see Chapter 12) or paralysis (see Table 23.16) to promote effective oxygenation and ventilation and decrease air leaks.

Ventilation Therapy. Use of CMV to produce hypocarbia (↓$PaCO_2$) and respiratory alkalosis is no longer used due to the effects resulting from (1) adverse neurologic sequelae (e.g., CP and cystic PVL); (2) exposure of the lung to barotrauma/volutrauma, CLD/BPD, and air leaks; (3) the increased risk of sensorineural hearing loss; and (4) no improvement in the clinical outcomes of PPHN.[119,505]

HFV, both oscillator and jet, is used to treat PPHN. Use of HFOV optimizes lung inflation/

recruitment[293] and oxygenation, improves ventilation, and achieves respiratory alkalosis.[272] HFOV is an effective rescue treatment for some neonates meeting ECMO/ECLS criteria who were unresponsive to CMV.[79]

A *Cochrane* review of the use of rescue HFJV compared with CMV in preterms with severe pulmonary dysfunction found no significant difference in mortality rates or adverse events.[437] However, the reviewers concluded that the existing evidence does not support the use of HFJV as recue therapy for preterm infants. A single-center retrospective review of 34 premature infants with hypercapnic respiratory failure found that infants who responded well to HFJV had lower PMA, improved capillary pCO_2, lower pH at 1 hour after therapy began, and reduced FiO_2 requirements.[566]

Inhaled Nitric Oxide (iNO). Endogenous NO production dilates the fetal pulmonary vascular bed and is essential in decreasing PVR after birth.[102] **Because endogenous production of NO in the pulmonary vasculature of neonates with PPHN is reduced, treatment with iNO is beneficial because iNO is a selective pulmonary vasodilator (e.g., decreases pulmonary hypertension and increases oxygenation without reducing systemic blood pressure).[271]** Early clinical studies of iNO demonstrated brief exposure actually improved oxygenation and lowered pulmonary artery pressure. RCTs from multicenters have confirmed that prolonged iNO treatment for PPHN (1) results in sustained improvement of oxygenation,[373] (2) decreases the need for ECMO/ECLS treatment,[373] (3) is an adjunct to CMV,[373] and (4) combined therapy (e.g., iNO, HFOV) is more effective than either therapy alone.[286] The Neonatal Inhaled Nitric Oxide Study Group (NINOSG)[374] found that iNO had no effect on mortality rate, length of stay, number of days of ventilatory support, incidence of air leak, CLD/BPD, IVH/PVL, seizures, and pulmonary and GI hemorrhages. **Use of iNO for PPHN is associated with severe coagulopathies.[510]** The effectiveness of iNO depends on (1) the initial degree of pulmonary vasoconstriction and hypoxemia, (2) the severity of parenchymal lung disease, and (3) the recruitment of adequate lung volume/inflation that decreases intrapulmonary shunting and improves iNO delivery to the pulmonary system.[271] In the ECMO/ECLS population, iNO use has increased from 0% to 24%.

Inhaled NO is an effective treatment for PPHN but "should be considered a part of the overall clinical strategy that cautiously manages parenchymal lung disease, cardiac performance, and systemic hemodynamics."[271] **Inhaled NO has been approved by the U.S. Food and Drug Administration for treatment of near-term (>34 weeks' GA) and term neonates with PPHN. Recommendations for use of iNO are listed in** Table 23.21. Use of iNO in moderate PPHN improves oxygenation,[182] decreases the amount of ventilation needed, and prevents progression to severe PPHN. A retrospective study comparing the use of HFOV and HFJV with iNO found similar short-term effects of decreasing the need for ECMO and improving oxygenation and ventilation of infants with PPHN regardless of which type of ventilator was used.[98]

Severe pulmonary hypertension in preterm infants occurs in less than 2% of all preterm births.[273] **Use of iNO to treat severe pulmonary hypertension in these infants has been reported in numerous case studies and case series.[87,91,97,464,504]** Improved survival (from 67%[91] to 90%[464]) for premature infants with severe pulmonary hypertension is due to marked improvement in oxygenation after use of iNO, similar to the responses of term and late-preterm neonates with PPHN. The Pediatric Pulmonary Hypertension Network proposed a prospective registry of premature infants with severe pulmonary hypertension who were treated with iNO, other pulmonary vasodilators or no specific pulmonary hypertension therapy.[273] A six-year cohort study of 89 preterm infants (<35 weeks' GA) treated with iNO for acute pulmonary hypertension found improved survival rate without disability, lower mortality and disability with early use of iNO especially in neonates with higher GAs, and acute hypertension associated with preterm prolonged rupture of membranes.[29] **Recommendations for the role of iNO in premature infants are listed in** Table 23.21.

Noninvasive strategies for administration of iNO have been reported. A case report of iNO administration through an NC precluded the use of MV in a spontaneously breathing term infant,[364] and noninvasive iNO administered by bubble NCPAP improved oxygenation in preterm and term infants with hypoxic respiratory failure.[445]

TABLE 23.21 RECOMMENDATIONS FOR USE OF INHALED NITRIC OXIDE (iNO)

RECOMMENDATION	RESEARCH BASIS
Gestational Age	
≥34 weeks' gestation	Clinical trials,[97,373] Canadian Pediatric Society,[396] and FDA approval support use of iNO in late-preterm/term newborns.[271]
≤34 weeks' gestation	Clinical data does not support use of iNO for early routine, early rescue, or later rescue therapy in preterm infants[41,99,286] iNO should not be used to prevent BPD/CLD[41,99,289] Beneficial for severe hypoxemia primarily due to PPHN physiology, rather than parenchymal lung disease, particularly in the presence of oligohydramnios; lung hypoplasia; prolonged rupture of membranes and sepsis Preferred pulmonary vasodilator for premature infants based on safety profile from outcomes of multicenter RCTs for BPD/CLD prevention[273]
Postnatal Age	
Within the first week of life; postnatal age alone should not define the duration of therapy when prolonged therapy could be beneficial	Clinical trials support iNO use within the first week of life; may also be used as adjunct therapy after ECMO/ECLS treatment
Severity of Illness	
Oxygenation index (OI) = (MAP × FiO_2 × 100 ÷ PaO_2) >25 with echocardiographic evidence of extrapulmonary right-to-left shunting	Mean OI in multicenter trials was 40 Earlier use of iNO at lower OI (15-25) has not resulted in reduction of mortality, ECMO/ECLS use, or outcomes[280,493] Early use of iNO (at OI ≥15 and ≤20) is associated with shorter LOS and decreased cost[278] Delayed use (OI >40) increases length of supplemental oxygen use[189]
Dose	
Initial: 20 ppm in term and near-term newborns with PPHN who do not have diaphragmatic hernia[42] Brief exposure to 40-80 ppm is safe Sustained treatment with 80 ppm increases the risk for methemoglobinemia	Increasing dose to 40–80 ppm does not improve response to 20 ppm Initial treatment with low dose (1-2 ppm) does not compromise responses to higher doses (10-20 ppm); a majority of low doses require dose increases The lowest effective starting dose has not been determined
Duration	
Typically <5 days	Longer usage may be necessary in pulmonary hypoplasia For therapy >5 days, other causes of pulmonary hypertension should be investigated
Weaning and Discontinuation	
Differing approaches toward weaning have been studied with few differences in outcomes until iNO is discontinued: After 4 hours at 20 ppm, iNO reduced to 6 ppm without change in oxygenation iNO decreased by 20% increments in stepwise fashion to dose of 1 ppm before discontinuation	Withdrawal of iNO can be associated with life-threatening elevations in PVR, profound oxygen desaturation, and systemic hypotension because of decreased cardiac output Dose-response relationship between iNO given and a drop in PaO_2 A decrease in iNO to 1 ppm before discontinuation minimizes decrease in PaO_2, and compensatory changes in FiO_2 and ventilator parameters are unnecessary

Continued

TABLE 23.21 RECOMMENDATIONS FOR USE OF INHALED NITRIC OXIDE (iNO)—CONT'D

RECOMMENDATION	RESEARCH BASIS
Ventilator Management	
High-frequency oscillatory ventilation (HFOV)	Inadequate lung inflation results in less response to iNO therapy
With significant parenchymal lung disease	Combination of HFOV and iNO results in best improvement in oxygenation because of improved lung inflation during HFOV that augments response to iNO by reducing intrapulmonary shunting and improving iNO delivery to pulmonary circulation
Without significant parenchymal lung disease	Combination of HFOV and iNO and iNO alone are more effective than HFOV alone
Congenital Diaphragmatic Hernia	
Routine use in CDH not recommended	CDH infants are poor responders to iNO Limited to CDH infants with suprasystemic PVR (after establishing optimal lung inflation and echocardiography determination of adequate LV function)
Late pulmonary hypertension in CDH infants	Late pulmonary hypertension is clinically evident when PVR becomes suprasystemic with right-to-left venoarterial admixture across the FO and/or ductus arteriosus measured on echocardiography
Use in ECMO/ECLS Centers	
Use to stabilize before cannulation for ECMO Use of iNO has not adversely affected outcome by delaying ECMO	Lower mortality rate for iNO-treated group than for infants not treated with iNO[95] iNO treatment associated with improved short-term pulmonary outcomes,[97] and decreased ECMO use is not associated with increased late-term morbidity[95,374]
Use in Non-ECMO/ECLS Centers and Transport with iNO	
If progressive deterioration in oxygenation occurs in centers without ECMO/ECLS, transport to ECMO/ECLS center without interruption of iNO therapy must be accomplished	Withdrawal of iNO to transport to an ECMO/ECLS center may result in acute and life-threatening deterioration

CDH, Congenital diaphragmatic hernia; *CLD/BPD,* chronic lung disease/bronchopulmonary dysplasia; *ECMO/ECLS,* extracorporeal membrane oxygenation/extracorporeal life support; *FDA,* Food and Drug Administration; *FO,* foramen ovale; *IVH,* intraventricular hemorrhage; *LOS,* length of stay; *LV,* left ventricular; *NIH,* National Institutes of Health; *PPHN,* persistent pulmonary hypertension of the newborn; *PVR,* pulmonary vascular resistance.

Modified from Kinsella JP. Inhaled nitric oxide in the term neonate. *Early Hum Dev.* 2008;84(11):709; Kinsella JP, Steinhorn RH, Krishnan US, et al. Recommendations for the use of inhaled nitric oxide therapy in premature newborns with severe pulmonary hypertension. *J Pediatr.* 2016;170:312; Data from Kinsella JP. Inhaled nitric oxide in the term neonate. *Early Hum Dev.* 2008;84(11):709.

Use of HFOV and iNO to treat PPHN has decreased the number of neonates meeting ECMO/ECLS criteria who subsequently require ECMO/ECLS treatment, has shortened length of hospital stay, and has decreased costs. However, a recent national survey of neonatal nurse practitioners (NNP) found that late rather than early use of iNO, only 35% of respondents knew the oxygen index at which iNO should be initiated and fewer than 20% knew that early initiation prevents progression to use of ECMO/ECLS. The surveyors concluded that more education of NNPs was necessary, especially related to the hazards of oxidative stress on neonates.[261] A quality improvement project using a shared baseline protocol improved evidence-based iNO use.[233]

Pharmacologic Therapy. **Surfactant replacement therapy is used when significant parenchymal lung disease (e.g., MAS) is the cause of PPHN.** Secondary surfactant deficiency also may exist in PPHN. Surfactant replacement in the early phase of PPHN significantly decreases the need for ECMO/ECLS in term newborns without increasing the risk for complications.[286] **In term and late-preterm**

infants with hypoxic respiratory failure, early use of surfactant and iNO improves outcomes (less mortality and ECMO use).[279,293]

Use of inotropic support (e.g., vasopressors) (Table 23.22) increases SVR, which decreases right-to-left shunting through the foramen ovale and ductus arteriosus. Cardiac output, cardiac contractility, and systemic blood pressure are all increased. A small study of newborns (n = 18) treated with iNO for PPHN (but with symptoms of circulatory failure [despite adequate fluids]) showed that IV norepinephrine improved lung function by decreasing the ratio between pulmonary and systemic artery pressures and improving cardiac performance.[528]

Systemic vasodilators (e.g., tolazoline, sodium nitroprusside, prostaglandin E1) have been used to decrease PVR. These medications have resulted in variable and unpredictable results and are associated with systemic hypotension, the need for volume expansion and fluid resuscitation, and an inability to achieve and maintain pulmonary vasodilation. When vasodilators are infused in dosages sufficient to decrease pulmonary hypertension, there is increased venous admixture as a result of right-to-left shunting of venous blood and pulmonary ventilation-perfusion mismatch. **Because of these adverse effects, use of systemic vasodilators is no longer recommended.**

From 40% to 50% of neonates do not respond to iNO therapy,[518] **so alternatives and synergistic agents are used for pulmonary vasodilation.** The reason for nonresponse to iNO is unknown, but a recent retrospective review found that infants receiving iNO with blood group A were poorer responders than those with B or O blood groups.[155] In poor or partial response to iNO, the need for ECMO is able to be predicted after 72 hours of iNO therapy.[534]

Phosphodiesterase inhibitors are used as an alternative, as a supplement, or for weaning from iNO in PPHN (Table 23.23).[8,293,340,493,495] **In term and late-preterm neonates with PPHN who are nonresponders or have a suboptimal response to iNO, use of IV milrinone results in improved clinical and ECMO changes.**[340] Intravenous (IV) milrinone improves oxygenation without compromising systemic blood pressure.[340] Use of sildenafil (1) is as effective as iNO in improving pulmonary vasodilation, (2) assists weaning from iNO, (3) improves oxygenation, (4) may or may

TABLE 23.22 VASOPRESSOR RESPONSE IN THE NEONATE

DRUG DOSE	DISADVANTAGE
Dopamine	
<4 mcg/kg/min: renal vasodilation, mesenteric and cerebral vasodilation (effects unknown) plus increase in cardiac output	May decrease systemic arterial pressure
5-20 mcg/kg/min: increase in cardiac output depending on myocardial norepinephrine	Loss of renal and mesenteric perfusion
>20 mcg/kg/min: systemic arterial pressure increases more than pulmonary artery pressure	Cardiac output may decrease Myocardial oxygen consumption increases Marked increase in left ventricular afterload Dysrhythmias noted
Dobutamine	
10 mcg/kg/min: increases cardiac contractility directly; cardiac output increases depending on myocardial catecholamine stores	No selective renal or mesenteric vasodilation Tends to increase skeletal blood flow at the expense of viscera Increase in pulmonary artery pressure
Isoproterenol	
0.05-1 mcg/kg/min: lowers pulmonary vascular resistance in pulmonary hypotensive and vascular disease in child and adult; lowers hypoxemia-induced pulmonary vascular resistance in animal models	Dysrhythmias No specific vasodilation effects
Nitroprusside	
0.4-5 mcg/kg/min: cardiac output increases because of decreased left ventricular afterload; systemic vascular resistance (indicated by blood pressure) decreases because of decreased left ventricular afterload	Systemic vascular resistance remains constant if CO_2 increases

Modified from Drummond W. The use of cardiotonic therapy in the management of infants with PPHN. *Clin Perinatol.* 1984;11(3):715.

TABLE 23.23 PHOSPHODIESTERASE INHIBITOR THERAPY FOR PPHN

DRUG	DOSE	COMMENTS
Milrinone[340]	Loading dose: 50 mcg/kg IV over 60 min Maintenance dose: 0.33–0.99 mcg/kg/ min for 24–72 hr Half-life: 4.1 hr Duration: 24–42 hr Clearance reduced in neonates and increases with age[178]	Improves oxygenation (increased PaO_2) Reduces FiO_2 Decreases oxygen index, MAP, and iNO dose Lowers inotrope score Improves base deficit and plasma lactate levels Monitor: blood pressure for transient systolic hypotension; heart and respiratory rate and rhythm; assess COP; fluid/electrolytes and renal function; platelet counts for thrombocytopenia Used in suboptimal or nonresponders to iNO ECHO: Lowers PA pressure Better right-to-left ventricular function Less right-to-left shunting
Sildenafil* [263]	0.3–1 mg/kg/dose per OG tube every 6–12 hr Peak concentration: 30–120 min Bioavailability: 40% Loading dose: 0.4 mg/kg continuous IV over 3 hr[495] Maintenance dose: 1.5 mg/kg/day continuous IV infusion[495]	Pulmonary vasodilation as an alternate, supplement, or weaning agent from iNO Concentrated in the presence of erythromycin, cimetidine, amlodipine Adverse effects: systemic hypotension, blood pressure lability, worsening oxygenation (decreased Pao_2)

*FDA issued a warning against the use of sildenafil for the treatment of pediatric pulmonary hypertension because of the higher risk of death with higher (3–6 mg/kg/day) versus lower doses. (From US Food and Drug Administration. Revatio [sildenafil]: drug safety communication—recommendation against use in children. Silver Spring, MD: US Food and Drug Administration; 2012.) FDA issued a clarification of the 2012 warning stating that use of sildenafil in children may be warranted when the benefits outweigh the risks, when other treatment options are limited, and when use of sildenafil can be closely monitored. (From US Food and Drug Administration. Revatio (sildenafil): drug safety communication—FDA clarifies warning about pediatric use for pulmonary arterial hypertension. Silver Spring, MD: US Food and Drug Administration; 2014.)

ECHO, Echocardiogram; *FiO_2,* fraction of inspired oxygen concentration; *iNO,* inhaled nitric oxide; *MAP,* mean airway pressure; *OG,* orogastric; *PA,* pulmonary artery; *PPHN,* persistent pulmonary hypertension of the newborn.

not decrease systemic blood pressure, (5) improves cardiac output, (6) is more effective when used together with iNO than either used separately, (7) is useful in resource-limited areas where iNO is unavailable, and (8) is safe, effective, and well tolerated with chronic use.[8,263,492,495] **RCTs are needed to establish the safety, efficacy, side effects, and long-term outcomes of sildenafil and milrinone use in PPHN.[263,400] Other drugs used to treat PPHN are listed in** Table 23.24.

Complications. **Follow-up at 18 to 24 months of age of the neonates in the NINOSG trial found no increase in neurodevelopmental or behavioral abnormality;** the children in the control group experienced a higher incidence of seizures after discharge than did the iNO-treated group.[374] Two other studies also showed no increase in adverse neurodevelopmental or pulmonary outcomes as a result of treatment with iNO and avoidance of ECMO treatment.[95,319] Other studies found high rates of neurodevelopmental impairment at 18 months of age[280] and a lower incidence of respiratory morbidity (26%) compared with the respiratory morbidity after ECMO treatment (37%) or CMV (56%).[229]

A follow-up study of 85 children (at 5 to 11 years of age) who had been treated for PPHN compared with a matched reference group found (1) sensorineural hearing loss (11%), (2) increase in chronic health problems (42% vs. 17%), (3) use of bronchodilators (21% vs. 8%), and (4) increased use of remedial education (19% vs. 5%).[159] Survivors of PPHN may have significant pulmonary and neurodevelopmental impairment, whether treated with conventional methods or with ECMO/ECLS, and should have long-term follow-up.

TABLE 23.24 OTHER DRUGS USED TO TREAT PPHN

DRUG	DOSAGE	COMMENTS
PGI_2 (iloprost ; treprostinil): Synthetic prostacyclin analog	Inhaled iloprost: 0.5–2 mcg/kg/dose	Selective pulmonary vasodilator; effects similar to iNO[265] More effective than oral sildenafil as alternative therapy for PPHN Benefits VLBW preterm infants with severe pulmonary hypertension[153,187]
Bosentan: Endothelin receptor antagonist	1 mg/kg every 12 hr PO by gastric tube[330]	Single-center RCT: improves oxygenation in PPHN without iNO use[348] Multi-center RCT: no additive effect as adjuvant therapy to iNO in PPHN[494] Mild systemic hypotension after initiation of therapy[330]

BID, Twice daily; *iNO*, inhaled nitric oxide; *kg*, kilograms; *mcg*, micrograms; *mg*, milligrams; *PGI_2*, prostaglandin I_2; *PO*, per os (by mouth); *PPHN*, persistent pulmonary hypertension of the newborn; *RCT*, randomized controlled trial; *VLBW*, very low birth weight.

APNEA

Pathophysiology. **The two major control mechanisms that regulate pulmonary ventilation are the neural and chemical systems. The cerebral cortex and brainstem are the governing agents for the neural control system, which regulates respiratory rate and rhythm.** The peripheral components of this system are found in the upper airway and lung. **The chemical control center is found in the medulla and is sensitive to changes in $PaCO_2$.** The peripheral portion of the chemical system lies in the carotid and aortic vessels and is sensitive to changes in $PaCO_2$. **Alveolar ventilation is controlled by the chemical system, and this system is the principal defense against hypoxia.** Neonates have a unique response to hypoxemia and carbon dioxide retention. Unlike adults, who have sustained increase in ventilation to hypoxemia, infants have a brief period of increased ventilation followed by respiratory depression.

Carbon dioxide responsiveness is less developed in the preterm infant, which may be the result of decreased sensitivity in the chemical center or mechanical factors that prevent an increase in ventilation. **Apnea is the cessation of breathing for 20 seconds or longer or cessation of breathing for 15 seconds with cyanosis and/or bradycardia. Apnea of prematurity or primary apnea is not associated with other specific disease entities. The younger the GA, the greater is the incidence of apnea, so at least 85% of preterms less than 34 weeks' gestation have apnea of prematurity.**[458] In one observational study, the incidence of apnea of prematurity was 28.6% in a cohort of late-preterm infants with 10.9% receiving caffeine therapy.[386] Apnea and bradycardia episodes usually begin within the first week after birth and spontaneously resolve at 36 weeks' PMA.[407] In infants born at 27 weeks' gestation or earlier, 58% to 60% have persistent apnea at 36 weeks' postconceptual age.[150] Apnea may be associated with hypoxemia, neuronal immaturity, sleep, catecholamine deficiency, and respiratory muscle fatigue.

Etiology. **Causes of apnea in the premature are characterized as *central apnea* (absence of breathing effort), *obstructive apnea* (breathing efforts occur but the airway is blocked), or, most commonly, *mixed apnea* (an initial central apnea followed by obstruction of the airway).** Various conditions may cause apnea in the premature infant by producing hypoxia and/or altering the sensitivity of peripheral or central chemoreceptors (Table 23.25). Neuronal immaturity is a plausible cause for apnea because respiratory efforts are more unstable at younger GAs. The decreased response appears to be the result of a general lack of dendritic formation and limited synaptic connections, thereby decreasing the excitatory drive. Another hypothesis is that apneic episodes are manifestations of synaptic disorders that occur without a motor component. Such phenomena have been confirmed on EEG. Infants depend on alternating excitation and inhibition to establish rhythmic breathing; therefore imbalances (e.g., hypoxia, hypoglycemia, hypocalcemia) may cause respiratory arrest.

Apnea is more frequent during sleep and especially during rapid eye movement (REM) or active sleep in both term and preterm infants.[527]

TABLE 23.25 CAUSES OF APNEA IN THE PREMATURE INFANT

CAUSE	SPECIFICS
Infection	Pneumonia, sepsis, meningitis
Respiratory distress	Immaturity of respiratory development, RDS, airway obstruction, CPAP application, postextubation, congenital anomalies of the upper airways
Cardiovascular disorders	Patent ductus arteriosus, congestive heart failure
Gastrointestinal disorders	Vomiting, necrotizing enterocolitis, deglutition syncope
Central nervous system disorders	Depressant drugs, intraventricular hemorrhage, seizure, elevated bilirubin levels, bilirubin encephalopathy/kernicterus, infection, tumors/ischemia
Metabolic disorders	Hypoglycemia, hypocalcemia, hyponatremia/hypernatremia
Environmental	Rapid increase of environmental temperature, hypothermia, vigorous suctioning, feeding, stooling, stretching/movement; fatigue/stress, prenatal exposure to maternal cigarette smoking, position, sleep state (e.g., active vs. quiet) Pain* First immunization (DTP/IPV/Hib): increase in apnea, bradycardia, and desaturations within 72 hours of immunizations
Hematopoietic	Polycythemia, anemia

*Oral sucrose relieves pain but does not decrease apnea and bradycardia.
DTP, Diphtheria-tetanus-pertussis; *CPAP*, continuous positive airway pressure; *Hib*, *Haemophilus influenzae* type B; *IPV*, inactivated polio virus; *RDS*, respiratory distress syndrome.

Apnea associated with sleep becomes more significant in premature infants, particularly those of less than 32 weeks' gestation, who spend 80% of their time asleep. Equally significant is the time spent in REM sleep, the predominant sleep state of premature infants. Apnea is uncommon in non-REM sleep, but periodic breathing may be observed. The effects of REM sleep are inhibition of spinal motor neurons, increase in brain activity causing increasing eye movements and muscular twitching, and changes in brain temperature and cerebral blood flow and CNS arousal, shown by EEG changes.

A premature infant has a more compliant chest cage and less compliant lungs, resulting in greater respiratory workload. Respiratory muscle fatigue occurs easily in the absence of fatigue-resistant fibers.

Secondary apnea may be associated with a particular disease entity or in response to special procedures. Many disorders leading to secondary apnea may exert their influence through hypoxemia and subsequent respiratory center depression.

The majority of cases of secondary apnea arise from four conditions. In RDS, apnea is related to the degree of parenchymal disease and may result from muscle fatigue. With CNS hemorrhage and seizures, apnea arises from asphyxia with subsequent hypoxemia and respiratory center depression or actual brain injury. Apnea is related to central depression in sepsis. In addition, carbon dioxide retention and hypoxemia associated with the left-to-right shunting of a PDA may cause apnea.

Iatrogenic causes of apnea include increased environmental temperature, sudden increases in environmental temperature, vagal response to suctioning of the nasopharynx or to a gavage tube, vomiting, and obstruction of the airway. **Reflex apnea occurs when foreign material (milk or secretions) is present in the oropharynx.** This laryngeal chemoreflex is protective in that it prevents inhalation of the substance into the airway and has been documented in preterm and hospitalized infants. **Obstruction may occur from improper neck positioning or aspiration.**

Cerebral blood flow (CBF) velocity decreases with apnea and bradycardia[402] and is directly correlated with the severity of bradycardia,[421] and an increase in CBF may occur on recovery.[325] Decreased oxygen saturation also correlates with the duration of apnea, regardless of type. Obstructive apnea is associated with significantly greater maximum fall in cerebral blood volume than central or mixed apneic episodes. **Because alteration of CBF may cause or exacerbate IVH, obstruction of upper airways with resultant apneic episodes should be prevented.**

Prevention. All infants assessed as being at high risk for apneic spells should be carefully monitored for at least 10 to 12 days. Impedance apnea monitors do not distinguish normal respiratory efforts from gasping movements associated with obstruction. **Both heart and respiratory rates should be monitored.** Alarm systems should be used at all times. A qualified observer is essential.

Apneic episodes are frequently associated with alterations in heart rate and oxygen saturation—the degree of these changes is related to the duration of apnea. Apnea generally precedes a drop in heart rate and oxygen desaturation. Changes in oxygen saturation are distinct from heart rate changes, so the desaturation cannot be predicted from changes in heart rate patterns. Because episodes of apnea and bradycardia are associated with a decrease in CBF and because oxygen desaturation (as little as 5% to 10%) is associated with alteration of cerebral circulation,[325] **oxygen saturation monitoring should accompany cardiorespiratory monitoring** (both in-hospital and home monitoring).

Pulse oximetry monitors may detect hypoxemic conditions that may lead to apneic spells. In a premature infant younger than 32 weeks' gestation, this type of apnea is common. Care should be organized to decrease stressful hypoxic episodes.

Apneic episodes may be prevented or decreased by several means. **Reducing environmental stress by providing adequate rest** has resulted in a faster rate of decline in apneic episodes.[525] **Gentle tactile stimulation** alone has been shown to be effective in decreasing and preventing apneic spells in most premature infants. Noxious stimuli such as shaking or banging on the incubator should be avoided. If tactile stimulus is ineffective and **temporary bag-and-mask ventilation is necessary,** attention should be paid to preventing undue pressure on the lower chin and neck so that the airway remains open. Bagging that is too vigorous also may stimulate pulmonary stretch receptors and induce apnea; therefore it should be avoided. **Waterbed flotation** may decrease the frequency of apnea but generally does not completely eliminate it. Systematic reviews have concluded that (1) prophylactic use of kinesthetic stimulation (e.g., waterbed, oscillating mattress) to reduce apnea or bradycardia cannot be recommended,[219] (2) prophylactic use of methylxanthine for prevention of apnea is not supported by data,[220] and (3) prophylactic use of methylxanthines increases the chances of successful extubation of preterm infants within 1 week.[218]

Increased environmental temperature and sudden changes in temperature have resulted in apneic episodes; prevention includes maintaining the environmental temperature at the lower end of the normal spectrum, particularly if an apneic episode already has occurred. **Incubator temperature may require a 0.5° to 1.0° C (1° to 2° F) decrease to counter the problem.** The frequency of apnea during active sleep is influenced by temperature: more apnea occurs in a warmer environment, whereas apnea is less frequent in cooler conditions.[527] **Phototherapy may provide sufficient radiant energy to increase an infant's temperature** and contribute to the incidence of apnea. **Care should be taken to avoid sudden changes in temperature.** An infant should not be placed on a cold scale; he or she should be placed in a prewarmed incubator or bed. Oxygen should be warmed and humidified before administration.

Careful attention must be paid to prevent airway obstruction. Small neck rolls under the neck and shoulders have been used to decrease neck flexion and prevent airway obstruction when in the supine position. Prone positioning improves lung mechanics and oxygenation, but with increasing gestation age (>32 weeks), the sudden infant death syndrome precautions of supine position for sleep need to be followed (see Chapter 13). A study comparing supine with prone positioning of preterm infants ($n = 21$) found no clinically significant increase in acid gastroesophageal reflux (GER) or obstructive apnea episodes associated with GER in asymptomatic convalescent preterms.[55] **Close monitoring should be done during procedures such as lumbar puncture in which accidental airway obstruction may occur.**

An RCT using olfactory stimulation with vanillin compared with no intervention was conducted in 36 preterm infants less than 2500 g at 2 days of age.[148] Compared with no intervention, the preterms exposed to a saturated vanillin solution had a significantly lower (3.1-fold) incidence of apnea, as well as arterial oxygen saturation and heart rates, during the study. In addition to calling for more research, the study authors speculated that vanillin might also be used to treat apnea of prematurity.[148]

Data Collection. Evaluation of apnea should include studies to rule out treatable causes.

History. Evaluation of the prenatal and birth history may give a clue to the causes and provide a basis for further study.

Physical Examination. A thorough physical and neurologic examination rules out grossly apparent abnormalities. **Observation and documentation of apneic and bradycardic episodes and any relationship to precipitating factors help differentiate**

primary from secondary apnea. A continuous, computerized analysis system to document apnea, bradycardia, and desaturation is more reliable in accurately capturing episodes.[547]

Laboratory Data. **A CBC and CRP assay assess for infection and anemia as causes of apnea. Measurements of serum glucose, calcium, phosphate, magnesium, sodium, potassium, and chloride levels assess metabolic causes. Arterial blood gas measurements assess hypoxemia and metabolic and respiratory contributions to apnea. Blood, urine, and cerebrospinal fluid (CSF) cultures rule out sepsis as the cause of apnea.** The CSF culture is usually performed only when other signs and symptoms of infection are present. **Chest x-ray examinations** assess cardiac and respiratory causes. The examinations may also rule out aspiration of gastric contents caused by vomiting or gastroesophageal reflux. **Ultrasonographic examination of the head and an EEG may be used to rule out IVH or other neurologic causes of apnea.**

Treatment. Treatment of secondary apnea is aimed at the diagnosis and management of the specific causes. In the treatment of **primary apnea (apnea of prematurity), initial efforts should begin with the least invasive intervention possible. Gentle tactile stimulation** is frequently successful, especially with early recognition and intervention. When infants do not immediately respond to external stimuli, **bag-and-mask ventilation** must be initiated. **Generally, an FiO_2 approximating that used before the spell but not exceeding a 10% increase will alleviate hypoxemia and avoid marked elevations in the arterial PaO_2.** The use of pulse oximetry monitoring allows closer evaluation of PaO_2 fluctuation and helps prevent complications of oxygen toxicity. Elevation in ambient oxygen concentrations, although decreasing the frequency of apnea, causes prolongation of apnea spells.

Apnea responds to low-pressure (3–5 cm H_2O) nasal CPAP.[409] Mechanical ventilation may be necessary if the infant fails to respond to lesser measures and continues to have repeated and prolonged apneic episodes. It also may be necessary in extremely immature, unstable, or debilitated infants. **Mechanical ventilation for apnea may be administered with nasal prongs or nasotracheal tube to avoid intubation.** SNIPPV is more effective than NIPPV or NCPAP in reducing apnea, desaturations, and bradycardia.[183]

An RCT of 36 preterm infants (mean GA 30.5 weeks ±3 weeks; mean birth weight of 1409 g ±450 g) with apnea of prematurity, bradycardia, and oxygen desaturations used **vibration-based therapy.**[483] The stochastic resonance (vibrating) mattress successfully reduced: (1) the number of apneic episodes by 50%, (2) bradycardia intensity reduced by 20%, and (3) the number, duration and intensity of oxygen desaturation episodes by 20% to 35%.[483]

Methylxanthines (e.g., caffeine, theophylline, aminophylline) are used to treat apnea of prematurity (Table 23.26). They are used only in primary apnea (i.e., when pathologic causes have been eliminated). Methylxanthines are potent cardiac, respiratory, and CNS stimulants and smooth muscle relaxers. **The effect on decreasing the frequency of apnea is related to central stimulation rather than to changes in pulmonary function.** Caffeine citrate is considered the drug of choice because (1) administration is once a day; (2) there is an earlier onset of action; (3) it has a wide therapeutic range, requiring fewer serum blood level evaluations; (4) there is no alteration of CBF; and (5) there are fewer side effects than with theophylline.[221,321] **Methylxanthines reduce the frequency of apnea and are associated with a decrease in the use of mechanical ventilation.**[218,220,221] A large (n = 2006 preterm with birth weight of 500–1250 g) multisite, international RCT of caffeine use for apnea of prematurity found that caffeine (1) reduced the incidence of CLD/BPD (36% in the treated group vs. 47% in the placebo group), (2) reduced the use of positive airway pressure by 1 week, and (3) temporarily (in the first 2 weeks of the study) reduced weight gain.[456] A recent RCT determined the frequency of intermittent hypoxia after caffeine therapy was discontinued and whether extended use of caffeine (to 40 weeks' PMA) reduced intermittent hypoxia with apneic episodes.[426] Extended use of caffeine reduced intermittent hypoxia (PO <90%) by 47% for preterms of 35 to 39 weeks' PMA.[426]

Caffeine is safe and efficacious when used for prophylaxis and/or treatment of apnea of prematurity.[321] Benefits of early administration include: (1) within 2 hours of life: improved BP and systemic blood flow[256]; (2) within the first 2 days of life: reduced rates of death, BPD/CLD, and PDA[327]; and (3) within the first week of life: reduced risk of acute kidney injury[210] and better lung function

TABLE 23.26 METHYLXANTHINES USED TO TREAT APNEA OF PREMATURITY

DRUG	DOSAGE	THERAPEUTIC LEVELS	SIDE EFFECTS
Caffeine citrate	Route: PO Loading: 20-40 mg/kg Maintenance: 5-8 mg/kg/day administered 24 hr after the loading dose Route: IV Dose: Cafcit 20 mg/mL Administer IV over 15-30 min to avoid cardiac dysrhythmias Half-life: 3-4 days with a range of 40-230 hours; inversely related to gestational age and postconceptual age	Afterload: 8-14 mcg/mL Maintenance: 5-25 mcg/mL Toxic: >40-50 mcg/mL	Administer orally with feedings: Administer in morning so infant's sleep pattern is less disrupted than evening administration Tachycardia (withhold dose if >180/min), dysrhythmias, diuresis, glucosuria, ketonuria, hyperglycemia, jitteriness, seizures, vomiting, hemorrhagic gastritis, NEC
Theophylline	Route: PO Loading: 4-6 mg/kg Maintenance: 1.5 mg/kg q 8 hr to 3 mg/kg q 12 hr IV: Aminophylline 4-6 mg/kg over 30 min	5-15 mcg/mL, although levels of 3-4 mcg/mL have been shown to be effective in decreasing apnea	See above Tachycardia more prevalent with aminophylline than with caffeine citrate[474] IV theophylline delays gastric emptying in VLBW infants Aminophylline is effective in preventing apnea that is associated with prostaglandin E_1 (PGE_1) injection in infants with ductal-dependent lesions[317]

IV, Intravenous; *NEC,* necrotizing enterocolitis; *PO,* per os (by mouth); *VLBW,* very-low-birth-weight.
Data from Young T, Magnum B. *Neofax 2008*. Raleigh, NC: Acorn Publishing; 2008.

at 11 years of age.[143] In preterm infants under 29 weeks' gestation, caffeine levels over 14.5 mcg mL are associated with a reduction in BPD/CLD, duration of ventilation, oxygen at discharge, and length of stay.[11]

Several recent studies have investigated the use of high- versus low-dose caffeine for apnea of prematurity. In an RCT the use of high (40 mg/kg/day loading; maintenance of 20 mg/kg/day) versus low (20 mg/kg/day loading; maintenance of 10 mg/kg/day) dose caffeine was studied in the first 10 days of life in preterm infants 32 weeks' GA or under.[349] **Those preterms receiving the higher dose of caffeine had less apnea of prematurity and less extubation failure without significant side effects.** A pilot study of high loading dose (80 mg/kg/IV) versus low loading dose (20 mg/kg/IV) in the first 24 hours of life in 74 premature infants (≤30 weeks' GA) found a higher incidence of cerebellar hemorrhage, hypertonicity, and alteration in early motor performance in the group receiving the higher loading dose.[342] Another study using high (loading 20 mg/kg/day; maintenance 15 mg/kg/day) versus low (loading 20 mg/kg/day; maintenance 5 mg/kg/day) dosing in preterms less than 32 weeks GA found **significantly less apnea in the high-dose group, as well as fewer extubation failures, without a significant increase in side effects or clinical outcomes.**[592]

Theophylline has been shown to significantly decrease CBF velocity. A recent RCT comparing theophylline with inhalation of (0.8%) CO_2 to treat apnea of prematurity found equal efficacy in decreasing the number and duration of apneic episodes, with fewer side effects and no alteration of CBF with the inhalation therapy.[9]

A systematic review of doxapram for use as therapy in apnea of prematurity showed that there are limited studies and levels of evidence about its safety and efficacy.[552] The reviewers recommend a large multicenter RCT before routine use of doxapram can be recommended.

Although gastroesophageal reflux is frequent in preterm infants because of lower esophageal sphincter relaxation, recent studies do not find an association between predischarge apnea and reflux.[55,138] Reflux events are unrelated to apneic events; apneic events are not a frequent marker of reflux, and when there is a temporal association, there is no effect on apnea duration, desaturation, or bradycardia.[138] Another study measured cardiorespiratory and GER event rates during prefeeding and postfeeding intervals and found that the frequency, height, and pH of GER are significantly altered by feedings in preterms but that apnea, bradycardia, and desaturations were not more prevalent after feeding.[482] A more recent study found that the feeding method (bolus versus slow infusion) does not reduce the number or duration of apneic episodes in preterm infants.[375]

For premature infants, the AAP recommends that GER is normal, resolves with age, usually resolves without treatment, and preterm infants older than 32 weeks' PMA should be positioned supine using safe sleep practices.[152] **Prokinetic agents to improve gastric emptying (e.g., metoclopramide, domperidone, and erythromycin) do not reduce GER symptoms in preterm infants.**[107,152] Histamine-2 (H_2) receptor blockers (e.g., ranitidine, famotidine) have not been studied for their efficacy in relieving GER symptoms. **These medications are associated with increased incidence of NEC, late-onset infections, and death, possibly due to intestinal microbiome alteration.**[152,197,201] **Proton-pump inhibitors (e.g., omeprazole, lansoprazole) are ineffective in relieving clinical signs of GER in infants and may have similar potential side effects as H_2 blockers.**[152] The AAP recommends that the **use of medications should be in moderation, if at all, because their efficacy is not supported with evidence and harm is associated with their use.**[152]

Complications. Side effects of xanthines include gastric irritation, hyperactivity (restlessness, irritability, wakefulness), myocardial stimulation (tachycardia, hypotension), and increased urinary output.

The prognosis for apnea arising from an underlying cause depends on the outcome of the disease process itself. The prognosis for apnea is generally good in infants who are otherwise well and healthy and for whom the apnea is not prolonged. **Delayed resolution of apnea (>36 weeks' PMA) and prolonged episodes of hypoxemia (>1 minute in duration) are associated with an increased risk for neurodevelopmental disturbance** at 13 months' postconceptual age[407] and at 18 months of age.[410] Long-term follow-up of the preterms in the randomized multicenter trial of caffeine use for apnea of prematurity (CAP) study found improved rates of survival without neurodevelopmental disability, reduced incidence of CP, and reduced BPD/CLD at 18 to 21 months of age among the caffeine-treated group.[458] The 11-year follow-up study of preterm infants in the CAP trial found a reduced risk of motor impairment in VLBW preterm infants given caffeine for apnea of prematurity but no significant reduction of the combined rate of academic, motor, and behavioral impairments.[457] More research is needed on the effects of caffeine on the developing brain, especially at the cellular/molecular levels, with administration of various doses and durations and the impact on the structure and function of the developing brain.[23]

PARENT TEACHING

Parental attachment to an infant with respiratory disease is especially difficult. It is made more difficult if the infant is also premature. Normal interaction is curtailed by the infant's condition and appearance, the environment, and the parent's reaction to these factors. An infant who is in an oxygen hood or receiving ventilation therapy to the lungs may give inadequate cues to arouse parental attachment and instead may arouse feelings of grief and loss (see Unit Six).

The goal of discharge planning is the best possible outcome with the least family disruption. Evaluation of parental readiness to care for their infant is essential to effective teaching and learning (Box 23.17). **Physical surroundings and preparations for the infant are assessed when possible by a home visit. Parental concerns at bringing home an infant with special care needs must be assessed and discussed.** The parents learn to be comfortable in handling and caring for their infant gradually throughout hospitalization. A specially designated or decorated room is used for family visiting and caregiving. Before discharge, the mother and/or father spends the night caring for the infant. Positive reinforcement and praise from the professional staff should be freely given to parents who

BOX 23.17 PARENT/CAREGIVER TEACHING IMPORTANT ASPECTS FOR PARENTS OF INFANTS WITH RESPIRATORY DISEASE

- Individualize parent teaching and evaluate parental readiness to care for an infant with ongoing respiratory care needs (e.g., home oxygen, tracheostomy, or ventilator care).
- Involve and teach parents care of their infant throughout hospitalization.
- Provide parents with written instructions for home care (e.g., tracheostomy care, suction, gastrostomy tube [g-tube] care).
- Provide parents with written instructions about all medications (dose, route of administration, side effects).
- Teach parents how to feed their infant, and encourage frequent feeding opportunities; teach parents how to feed with alternative feeding methods such as gastrostomy tube.
- Teach parents and other care providers how to perform cardiopulmonary resuscitation.
- Instruct parents in use of apnea monitors and other equipment for home use.
- Instruct parents to notify emergency personnel about their infant, posting emergency phone numbers.
- Instruct parents about the importance of follow-up care.

attend classes and successfully master the tasks of caregiving for their infant.

Special equipment such as oxygen tanks, NCs, a ventilator, and suction equipment for home use must be acquired before discharge. Sources, mode of delivery, and use of equipment must all be taught to parents before discharge. Pulmonary hygiene for infants with prolonged difficulty in handling secretions also must be taught. **Written protocols and instructions should be provided to parents, whenever possible. Parents must be informed of dosage, route of administration, side effects, and planned duration of use of all medications.**

Fluid and nutritional status is very important to any infant with a chronic condition, and nutritional information for parents is necessary. **Infants with tachypnea (CLD/BPD) often have difficulty with coordinating suck and swallow. Often smaller, more frequent feedings are necessary with use of supplemental oxygen.** Alternative feeding methods such as gavage or gastrostomy feeding may be necessary to safely provide enough calories with a minimum of work.

Apnea is especially distressing to parents because of their fears of recurrence once the infant goes home. If apnea is related to an underlying disease, treatment of the cause should result in resolution of the apneic episodes. Parents can be assured reliably that recurrence is unlikely unless the disease recurs. **With apnea of prematurity, assurance can be offered that infants do grow into a regular ventilatory pattern as their respiratory center matures, generally by 43 weeks' PMA.**[151] The AAP does not recommend the use of routine home monitors for preterm infants with resolved apnea of prematurity. However, home monitoring may be indicated for some preterm infants who have had an "unusually prolonged course of recurrent, extreme apnea," [151] and is usually discontinued after 43 weeks' PMA.

Before an infant needing a home monitoring system is discharged from the hospital, the parents must be given adequate support and instruction. Classes on the use of the apnea monitors must include demonstration of the equipment and return demonstrations. Minor equipment checks and repairs should be mastered before discharge.

Support by the primary care providers after discharge is essential. Parents must have telephone numbers of the medical facility and personnel they can call 24 hours a day in case of problems or equipment failure.

Anticipatory support includes discussion of potential stress factors related to having an infant on a monitor and/or oxygen at home. An apnea monitor in the home may provoke anxiety despite discussion and instruction. **When infants are discharged with apnea monitors, there is a marked increase in maternal fatigue 1 month after discharge** compared with a similar group discharged without monitors.[573] Increased fatigue interferes with activities of daily living and ability to parent and increases caregiver stress.[573] Interventions to alleviate fatigue after discharge may include spousal support, household help, child care for siblings, and opportunities for increasing sleep.

The parents of every infant who has apneic episodes or serious respiratory disease must be taught CPR. This set of skills is learned over the course of time by reading written materials and seeing and returning the demonstration. **Learning CPR cannot be done on the day of discharge but, rather, must be a staged process of individual and class instruction.** Supplying instructional

pamphlets written just for parents' aids in initial learning and provides a quick reference. If other family members or babysitters will provide child care during work or evening hours, they too must be able to resuscitate the infant.

Other emergency actions for which parents must be prepared include clearing the infant's airway, calling for help (having emergency phone numbers easily accessible), planning for an alternative communication source (e.g., neighbor's phone), and notifying the community rescue squad of the infant's presence in the home.

Parents must be taught how to recognize signs of illness or significant deterioration in the condition of their infant. In addition to information about special care needs, parents need information about normal newborn care. Developing realistic expectations and positive parenting skills is as important to these parents as it is to all new parents.

For the parents of an infant with special respiratory problems, the importance of continuous follow-up care must be emphasized. Follow-up visits should coincide with developmental stages, the natural course of the disease, and expected complications of the disease.

The parents whose child has special respiratory needs must learn a myriad of involved technical information. The primary care provider (frequently the primary nurse) is responsible for organizing, teaching, coordinating, and documenting the information. This nurse is also responsible for ensuring that the parents have not only been taught but in fact understand these concepts.

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RESOURCE MATERIALS FOR PROFESSIONALS AND PARENTS

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24 CARDIOVASCULAR DISEASES AND SURGICAL INTERVENTIONS

TARA SWANSON AND LORI ERICKSON

Congenital heart disease (CHD) is the most common life-threatening birth defect encountered in the neonatal intensive care unit (NICU). Although the incidence of these conditions has remained constant at approximately 1% of all infants born in the United States, the methods of diagnosis and treatment have undergone tremendous change over the past several decades.[8,40,99] It is the responsibility of the practitioner to recognize the presence of CHD and to provide accurate diagnosis and treatment. This chapter reviews the anatomy and physiology of the fetal and neonatal circulations, the pathophysiology of CHD, and the most current evidence-based treatments.

CONGENITAL HEART DISEASE: OVERVIEW

History

In 1892, Dr. William Osler wrote that CHD was of "limited clinical interest as in a large proportion of cases the anomaly is not compatible with life, and in others, nothing can be done to remedy the defect or even relieve the symptoms."[19] Dr. Maude Abbott, along with Dr. Helen Taussig and Dr. Alfred Blalock, suggested surgery to help these "blue babies."[97] This opened up the field of surgical treatment for cyanotic malformations of the heart. In 1938 Dr. Robert Gross was the first to successfully ligate a patent ductus arteriosus in a 7-year-old girl at Boston's Children's Hospital. The first successful adult heart transplant in the United States was done at Stanford University by Dr. Norman Shumway in 1968.[15] The first single-ventricle Fontan surgery was reported by Francis Fontan in 1971.[29,33] Remarkable progress has been made in the assessment and treatment of CHD in the subsequent decades. This is the direct result of advances in pediatric and fetal cardiology, cardiac surgery, neonatology, and neonatal intensive care nursing.

Incidence

Each year, approximately 40,000 babies born in the United States are diagnosed with CHD.[3,8] Highly sensitive echocardiography has led to the detection of more trivial forms of CHD, such as tiny ventricular septal defects. This inclusion has led to the higher incidence figures in recent years. The incidence of structural CHDs in liveborn infants is 4 to 10 per 1000 live births.[8,19] **Of these infants, approximately 25% will have *critical congenital heart disease* (CCHD) that results in death or requires cardiac surgery or cardiac catheterizations during the first year of life.**[8,37,67] Advances in diagnostic imaging, cardiac surgery, and neonatal intensive care have led to significant decreases in mortality rates. Infants with cardiac lesions that were once considered fatal are now surviving into adulthood.

Embryology

The heart is one of the earliest differentiating and functioning organs. **In human embryos, the heart begins to beat at about 22 to 23 days of life**

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and begins to effectively pump blood in the fourth week of life. The heart develops from the cardiogenic mesoderm and begins as a primitive heart tube. During the first few weeks of life, this primitive heart tube receives blood from three different venous systems (cardinal, vitelline, and umbilical) and supplies blood to six paired aortic arches. These veins and aortic arches must each regress or mature, and the primitive heart tube must undergo a complex process of looping, shifting, and septating to result in a normal heart with normal venous and arterial communications. **Cardiac development is almost complete by week 6 of gestation, which may be before a pregnancy is even recognized.**

Alterations in normal cardiac embryology result in a nonviable circulation (which leads to spontaneous fetal demise) or the abnormal but viable CHDs we see postnatally. Some cardiac lesions are viable in the setting of fetal circulation with a patent foramen ovale (PFO) and patent ductus arteriosus (PDA) but are not viable if these fetal connections close. **These congenital heart lesions require lifesaving treatment soon after birth, so a diagnosis must be made prenatally or within hours after birth to prevent cardiovascular collapse and death.**

Physiology

The physiologic changes that occur during the transition from intrauterine to extrauterine life have been well documented. To develop a clear understanding of the various congenital heart defects, knowledge of the basic principles of fetal circulation must be established.

FETAL CIRCULATION

Fetal circulation relies on the placenta for gas exchange, whereas postnatal circulation uses the lungs for gas exchange (Fig. 24.1). Highly oxygenated blood from the mother enters the fetal circulation through the vein in the umbilical cord. This blood enters the inferior vena cava via the ductus venosus. Blood from the inferior vena cava enters the right atrium (RA). Most of this blood is directed through the *foramen ovale* (a special fetal opening between the left and right atria) and into the left atrium (LA). Blood then passes through the mitral valve into the left ventricle (LV) and then through the aortic valve into the aorta. From the aorta, blood is first sent to the coronary arteries and brachiocephalic vessels. This results in **perfusion of the brain, the upper extremities, and the heart with the most highly oxygenated fetal blood. Only a small percentage of this blood will travel further in the aorta to supply the rest of the body.** After oxygen has been removed by the organs of the upper body, the blood returns to the right atrium through the superior vena cava. Some of the blood entering the right atrium stays on the right side of the heart, traveling through the tricuspid valve, right ventricle (RV), and pulmonic valve to eventually flow into the pulmonary artery.

Fetal lungs are not used for breathing. The work of exchanging oxygen and carbon dioxide is performed by the placenta. Because of high pulmonary vascular resistance (PVR), fetal circulation shunts most of the blood away from the lungs. Blood is shunted from the pulmonary artery to the aorta through a connecting fetal blood vessel called the *ductus arteriosus.*[72] Blood traveling through the ductus arteriosus has low oxygen content. This blood supplies the lower portion of the fetal body before returning to the placenta through the two umbilical arteries. Blood then enters the placental circulation and is resaturated.

TRANSITION FROM PRENATAL TO POSTNATAL CIRCULATION

In utero, systemic vascular resistance (SVR) is low, primarily because of low resistance in the placenta. Conversely, the PVR is high, with the constricted and hypertrophied pulmonary arterioles being relatively resistant to blood flow.

Both the labor process and the first few breaths of life begin the termination of fetal circulation and the transition to newborn circulation. **At birth, the placenta is removed from the circulation, thereby greatly increasing the SVR. The first few breaths inflate the lungs for the first time and also increase the oxygen content in the neonatal blood. Both of these changes cause a decrease in PVR, which leads to increased pulmonary blood flow.**

The *patent ductus arteriosus* (PDA) is extremely sensitive to oxygen levels in the blood. As the neonatal Pa_{O_2} rises, this fetal connection between the aorta and the pulmonary artery (PDA) is no longer needed and begins to close. Constriction of the PDA leads to functional closure of this vessel within the first few days of life. Permanent, fibrotic closure of the PDA usually

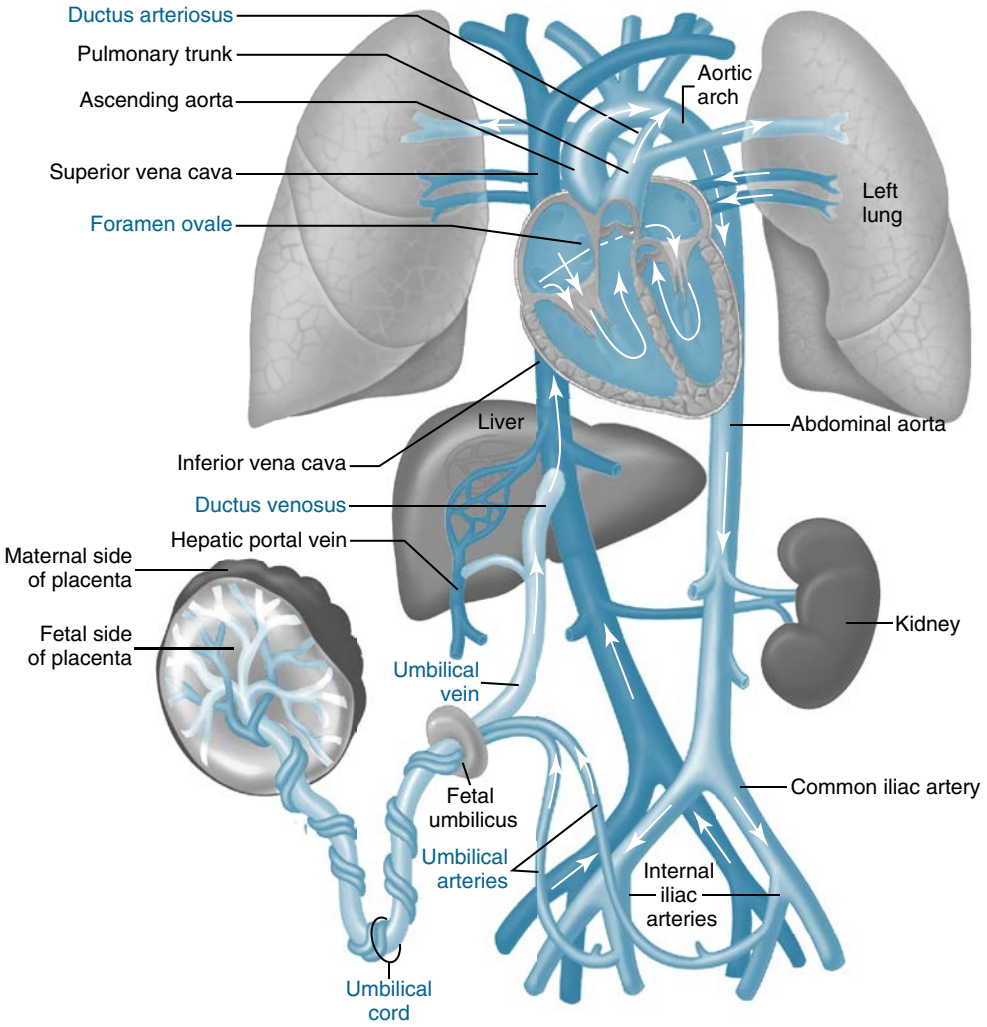

FIGURE 24.1 Fetal circulation. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle. (Modified from Patton KT, Thibodeau GA. *Anatomy and Physiology*. 7th ed. St. Louis: Mosby; 2010.)

occurs weeks to months after birth. As the PVR drops and the PDA closes, circulation to the lungs increases, resulting in increased blood return to the left atrium. This increased pressure in the left atrium causes the foramen ovale to close. **Anatomic closure of the foramen ovale can take months to years.** Finally, with the clamping of the umbilical cord, umbilical venous flow ceases, and the ductus venosus begins to close, with anatomic closure taking approximately 1 to 2 weeks.[74]

Once these changes occur, the newborn's circulation resembles that of an adult (Fig. 24.2). Deoxygenated blood returns to the heart by the inferior and superior venae cavae and enters the RA, RV, pulmonary artery, and pulmonary circulation, where oxygen and carbon dioxide are exchanged. Oxygenated blood then returns to the heart through the pulmonary venous system and enters the LA, LV, and ultimately the aorta and systemic arterial system. **However, PVR and pressures in the right ventricle and pulmonary system remain elevated in the neonate because of hypertrophy of the pulmonary vessels.** This hypertrophy slowly resolves so that PVR and right

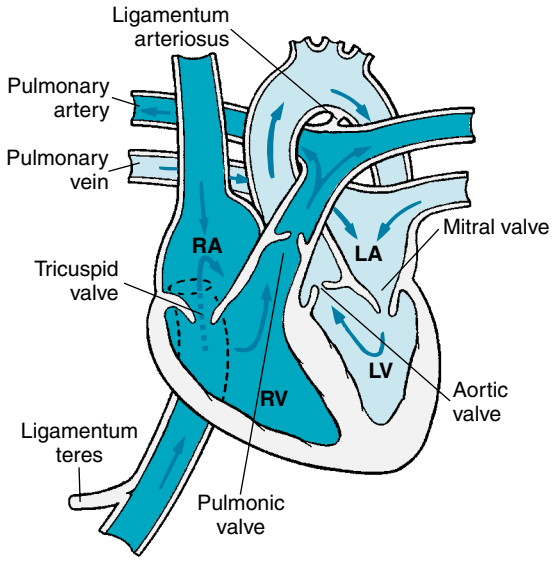

FIGURE 24.2 Postnatal circulation. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle. (Modified from Hockenberry MJ, Wilson D. *Wong's Essentials of Pediatric Nursing.* 8th ed. St Louis: Mosby; 2009.)

heart pressures decrease to lower levels between 1 and 2 months of age.

Etiology

In most cases, the cause of abnormal cardiac development is unknown. Traditionally, **the etiology of congenital heart defects is thought to be multifactorial, involving a complex interaction between genetic and environmental factors.** Some maternal factors contribute to the risk for CHD. For example, women with pregestational diabetes or women with excessive alcohol consumption are at increased risk of having an infant with a heart defect. Maternal phenylketonuria, maternal systemic lupus erythematosus, and maternal infections also increase the risk of CHD for offspring. The use of assisted reproductive technology also results in increased risk for a heart defect in fetuses conceived by these methods.*

However, **most CHD occurs in the absence of any identifiable maternal risk factors,** so most mothers should be reassured that they did not cause their child's malformation. Table 24.1 lists the most common maternal and familial risk factors for cardiac malformations.[96] Box 24.1 lists fetal risk factors associated with an increased incidence of cardiac defects that should be referred for evaluation by a fetal cardiologist.[23]

Recent studies suggest that the single greatest risk factor for CHDs is genetic. Table 24.2 shows the most common genetic abnormalities associated with CHDs. Children with chromosomal abnormalities such as trisomy 13, trisomy 18, and trisomy 21 often have significant CHD. At the level of the individual gene, there are well-established single-gene mutations that cause heart disease, such as mutations in *NOTCH-1* that cause aortic valve disease.[50] Smaller genetic abnormalities, such as deletions, duplications, and rearrangements, can also be closely associated with a high risk of structural heart disease. For example, 1p36 deletion syndrome is a microdeletion, with up to 71% of patients having a structural abnormality.[7] In familial CHD, there could be a 31% to 46% chance of identifying the genetic variant causing the defect in the known CHD genes.[10] With rapid advances in genetic testing capabilities, such as robust microarray testing and extremely rapid genome sequencing, new genetic causes of abnormal cardiac development are being identified daily.[93]

PRENATAL DIAGNOSIS

Because of the widespread use of antenatal ultrasound, it is increasingly common for the fetus to be diagnosed with CHD. Fetal echocardiography has proven to be a valid, reliable, and accurate tool in the prenatal diagnosis of CHD.[22] **The recommended timing for a fetal echocardiogram is between 18 and 20 weeks of gestation,** although detailed cardiac evaluation and accurate CHD diagnoses can be made as early as 12 weeks' gestation.[63]

Studies have shown that prenatal diagnosis of CHD can improve patient outcomes and survival after birth.[30,50] Being born at or near a hospital with pediatric cardiothoracic surgery services has also been shown to reduce neonatal morbidity and mortality rates.[64] **Some neonates with extremely critical CHD require cardiac intervention within the first minutes to hours of life;** these children have little chance of survival unless their heart disease is identified prenatally and their postnatal care providers are prepared for and capable of delivering emergency treatment in the delivery room.

An increased chance for survival of infants with CCHD is documented at greater than 38 weeks' gestation. A higher birth prevalence of

*References 6, 44, 48, 56, 75, 78, 79

TABLE 24.1 MOST COMMON MATERNAL AND FAMILIAL RISK FACTORS ASSOCIATED WITH CHD

	ASSOCIATED RISK, % LIVE BIRTHS	TIMING FOR FETAL EVALUATION AND COMMENTS
Maternal Factors		
Pregestational DM or DM noted in the first trimester	3-5	18-22 weeks for fetal echocardiogram; DM can be associated with numerous cardiac defects and ventricular hypertrophy in the third trimester with poorly controlled DM
Phenylketonuria	12-14	18-22 weeks for fetal echocardiogram
Lupus or Sjögren's syndrome if SSA/SSB autoantibody positive	1-5	16 weeks initially then frequently if heart block identified Maternal hypothyroidism or vitamin D deficiency may also increase risk
Maternal infections	1-2	18-22 weeks for fetal echocardiogram. Maternal rubella has been associated with CHD; parvovirus, coxsackievirus, adenovirus, and cytomegalovirus have been associated with fetal myocarditis
Teratogens: medication exposures	1-2	
Anticonvulsants	1.8	18-22 weeks for fetal echocardiogram
Lithium	<2	18-22 weeks for fetal echocardiogram
ACE inhibitors	2.9	18-22 weeks for fetal echocardiogram
Retinoic acids	8-20	18-22 weeks for fetal echocardiogram
Vitamin A (>10,000 IU retinol/day)	1.8	18-22 weeks for fetal echocardiogram
SSRIs	1-2	18-22 weeks for fetal echocardiogram, reports of associated risk for RVOT lesions
NSAIDs	1%-2% structural defects 5%-50% for ductal constriction	18-22 weeks for fetal echocardiogram With daily use rule out ductal constriction after exposure
Maternal and Family History		
Use of assisted reproductive technology	1.1-3.3	18-22 weeks for fetal echocardiogram Both IVF and IVF with ICSI seem to carry risk for CHD
Maternal structural cardiac disease	3-7 (all) 10-14 (atrial ventricular septal defects) 13-18 (aortic stenosis) <3 (TOF, d-TGA)	18-22 weeks for fetal echocardiogram
Paternal structural cardiac disease	2-3	18-22 weeks for fetal echocardiogram
Sibling with structural disease	3 Up to 8% for hypoplastic left heart syndrome	18-22 weeks for fetal echocardiogram
Second- and third-degree relatives with CHD	1-2	18-22 weeks for fetal echocardiogram

ACE, Angiotensin-converting enzyme; *CHD,* congenital heart disease; *DM,* diabetes mellitus; *d-TGA,* d-transposition of the great arteries; *ICSI,* intracytoplasmic sperm injection; *IVF,* in vitro fertilization; *NSAIDs,* nonsteroidal antiinflammatory drugs; *RVOT,* right ventricular outflow tract; *SSRIs,* selective serotonin reuptake inhibitors; *TOF,* tetralogy of Fallot.

CHD has been noted with very or extremely premature births compared with term births (7.4 per 1000 or premature births versus 1.5 per 1000 term births). Improved prenatal detection and referral to advanced maternal-fetal consultation is warranted to try to reduce the mortality and morbidity associated with a preterm infant with CHD.[18]

Unfortunately, less than half of children with CHD receive a prenatal diagnosis.[59] Even when routine prenatal ultrasound screening is performed during the pregnancy, one study showed that only 39% of CHD is detected.[71] Thus, access to medical care is not the only barrier to prenatal detection of heart lesions. Better screening methods are required, along with referral for a detailed fetal echocardiogram for any child at increased risk of having heart disease (see Box 24.1).[23] Even in the most experienced hands, fetal echocardiography is limited by technical and fetal factors that make some cardiac diagnoses impossible to detect before birth. **Box 24.2 lists CHDs that are often undetected by prenatal ultrasound evaluation.**

Extracardiac anomalies should prompt referral for intense cardiac evaluation because there is a high incidence of heart disease in children with even one other organ abnormality.[85] Conversely, children prenatally diagnosed with a congenital heart lesion should have a detailed evaluation of extracardiac structures to rule out associated anomalies.

BOX 24.1 FETAL RISK FACTORS FOR CONGENITAL HEART DISEASE THAT SHOULD BE REFERRED FOR FETAL ECHOCARDIOGRAM BY A FETAL/PEDIATRIC CARDIOLOGIST

Fetal Factors

- Suspected cardiac abnormality on obstetric ultrasound
- Rhythm abnormalities: tachycardia, bradycardia, complete heart block, irregular rhythm
- Identified noncardiac abnormality: central nervous, respiratory, gastrointestinal, genitourinary, musculoskeletal
- Known or suspected chromosomal abnormality
- Increased nuchal translucency on obstetric ultrasound
- Abnormality of umbilical cord, placenta, or intraabdominal venous anatomy
- Monochorionic twinning
- Hydrops fetalis

Data Collection

HISTORY

A detailed family history should be obtained because a parent or sibling with CHD increases the likelihood of CHD for a child.[23] Pregnancy details such as viral exposure during pregnancy (rubella, coxsackievirus B, and enteroviruses), maternal medications, and maternal ingestion of alcohol or illegal substances should be evaluated. Labor and delivery complications should be carefully examined for risk factors that could affect the cardiovascular system. For example, intrauterine hypoxia

TABLE 24.2 CHROMOSOMAL ABERRATIONS EVIDENT IN NEONATAL PERIOD THAT ARE ASSOCIATED WITH CONGENITAL HEART DISEASE

POPULATION	INCIDENCE OF CONGENITAL HEART DISEASE (%)	MOST COMMON LESIONS		
		1	2	3
Trisomy 21 syndrome	50	Ventricular septal defect, endocardial cushion defect	Atrial septal defect	Patent ductus arteriosus
Trisomy 18 syndrome	99+	Ventricular septal defect	Patent ductus arteriosus	Pulmonary stenosis
Trisomy 13 syndrome	90	Ventricular septal defect	Patent ductus arteriosus	Dextrocardia
Turner syndrome	35	Coarctation of the aorta	Aortic stenosis	Atrial septal defect
22q deletion syndrome (DiGeorge syndrome)	50	Interrupted aortic arch	Truncus arteriosus	Tetralogy of Fallot

and perinatal hypoxia are risk factors for the development of myocardial dysfunction or persistent pulmonary hypertension of the newborn (PPHN).

CLINICAL PRESENTATION OF INFANTS WITH SEVERE CARDIAC DISEASE

CHD is often not suspected until after birth when the newborn presents with one or more signs or symptoms (Box 24.3).[98] **The timing of presentation of signs or symptoms depends on the severity of the defect and alterations in cardiovascular physiology during transitional circulation (i.e., closure of the ductus arteriosus and the fall in PVR).** Despite the presence of many heterogeneous forms of heart disease, a limited number of signs and symptoms present in the neonate.

Murmurs. Heart murmurs are a common finding in neonates and can be normal. Closure of the PDA causes a murmur, so all neonates who go through the normal cardiac transition will have a murmur briefly as the ductus arteriosus closes. Although cardiac murmurs in the neonatal period do not necessarily indicate heart disease, they must be carefully evaluated. The absence of a murmur does not exclude severe, life-threatening cardiac anomalies.

Pathologic murmurs tend to appear at characteristic ages. Murmurs associated with semilunar valve stenosis and atrioventricular valve insufficiency tend to be noted very shortly after birth. In contrast, **murmurs caused by left-to-right shunt lesions (PDA, ventricular septal defect [VSD]) may not be heard until the second to fourth week of life.** The age of the neonate when the murmur is first noted gives an important clue about the nature of the cardiac defect. **The timing of the murmur during the cardiac cycle is important; diastolic murmurs are almost never innocent. The intensity (loudness), quality (harsh, vibratory), location, and radiation of the murmur in addition to other associated findings (click, rub, gallop) can all be used to help make a diagnosis.**

Cyanosis. Cyanosis (a bluish discoloration of the skin, nail beds, and mucous membranes) is one of the most common presenting signs of CHD in the neonate. Cyanosis occurs with CHD when deoxygenated venous blood abnormally shunts "right to left" within the heart and then enters the systemic arterial system again (without going through the lungs to pick up oxygen). **Depending on the underlying skin complexion, clinically apparent cyanosis is usually not visible until there is more than 3 g/dL of desaturated hemoglobin in the arterial system.**[28] Cyanosis depends on both the severity of hypoxemia (which determines the percentage of oxygen saturation) and the hemoglobin concentration. **True central cyanosis should be differentiated from acrocyanosis (blueness of the hands and feet only), which is a normal finding in the neonate.**

Cyanosis in the newborn must be differentiated between cardiac and noncardiac causes. Primary lung disease (see Chapter 23) is a common cause of labile cyanosis due to persistent pulmonary hypertension.[34] Central nervous system abnormalities can also cause hypoxia and result in cyanosis. Clinical cyanosis can occur without hypoxemia in a neonate with *methemoglobinemia* and *polycythemia*.

The *hyperoxia test* is beneficial in differentiating respiratory disease from cyanotic heart disease. This test is a sensitive and specific tool in the initial evaluation of the neonate with suspected CHD and is used

BOX 24.2 CARDIAC LESIONS OFTEN UNDETECTED BY FETAL ECHOCARDIOGRAPHY

- Small ventricular septal defect (VSD)
- Atrial septal defect (ASD)
- Persistent patent ductus arteriosus (PDA)
- Total or partial anomalous pulmonary venous return (TAPVR/PAPVR)
- Mild aortic or pulmonary stenosis
- Coarctation of the aorta

BOX 24.3 CRITICAL FINDINGS SEVERE CARDIAC DISEASE

- Cyanosis
- Respiratory distress
- Congestive heart failure
- Diminished cardiac output
- Abnormal cardiac rhythm
- Cardiac murmurs

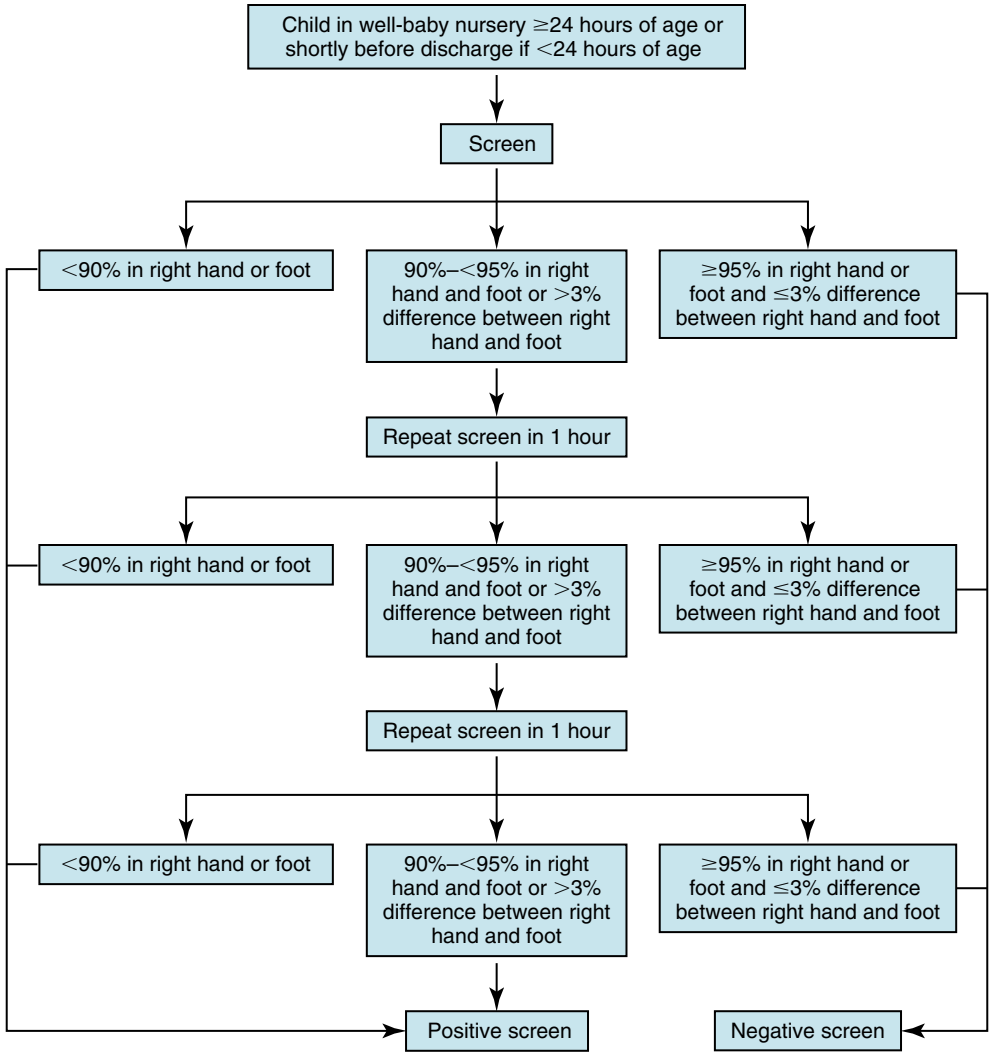

FIGURE 24.3 Screening for congenital heart disease. (From Kemper AR, Mahle WT, Martin GR, et al. Strategies for implementing screening for critical congenital heart disease. *Pediatrics.* 2011;128:e1–e8.)

to investigate the possibility of a fixed (intracardiac) right-to-left shunt. The hyperoxia test is performed by obtaining arterial blood gas measurements (preferably from the right radial artery) when the infant is in room air and then after the infant has been in 100% oxygen for 5 to 10 minutes. **If the Pa_{O_2} is greater than 150 mm Hg, the presence of a right-to-left shunt and CHD as the cause of cyanosis is unlikely.**[92]

Pulse oximetry screening is a simple and effective screening tool that has become mandated by many individual states in the United States to screen for CCHD. **Routine pulse oximetry is performed in asymptomatic newborns after 24 hours of life but before hospital discharge** (see Chapter 31).[57,58] **Utilization of routine pulse oximetry screening has found that infants with CCHD may have a low percentage of oxygen saturation before other clinical symptoms are noted** (Fig. 24.3).[49] Pulse oximetry completed after 24 hours of age has been shown to have a high sensitivity (76.5%) and specificity (99.9%) and a low false-positive rate (0.05%).[68] **An oxygen saturation (Spo2) of less than 92%**

and Spo2 differences of greater than 10% from preductal to postductal can be indicators of ductal-dependent cardiac disease.[34] Although all hypoxia found with pulse oximetry screening may not be caused by CHD (as noted with the false-positive results), infants with significant noncardiac hypoxia likely require NICU care.

Respiratory Distress. Most infants with cyanosis from CHD do not have respiratory distress (e.g., tachypnea, intercostal retractions, grunting, nasal flaring). Often the degree of cyanosis is not proportional to the degree of respiratory distress evaluated from the physical and chest x-ray examinations. If a cardiac lesion is present that allows a fixed right-to-left shunt, increasing inspired oxygen will have little effect on the arterial blood gases. However, if the cyanosis is caused by a diffusion defect in the lungs (pulmonary disorder), the degree of cyanosis often decreases with increasing inspired oxygen.

Respiratory distress most often occurs with CHD when the lungs become too "wet." This occurs when too much blood is pumped to the lungs (pulmonary overcirculation) or when the lung circulation cannot drain well due to pulmonary vein or left heart abnormalities. When there is too much blood in the lung circulation, fluid leaks into the lung tissues and causes pulmonary edema. This can affect the lungs' ability to exchange oxygen and carbon dioxide, and it is difficult for the lungs to expand when they are stiff due to excessive fluid. Signs and symptoms of respiratory distress include tachypnea, retractions, nasal flaring, head bobbing, and abdominal breathing. A chest x-ray identifies cardiomegaly and pulmonary edema, although it cannot determine whether the pulmonary edema is due to primary lung disease or a congenital heart lesion.

Congestive Heart Failure. CHF occurs when the heart cannot meet the metabolic demands of the tissues. Signs and symptoms of CHF reflect venous congestion and decreased tissue perfusion due to inadequate cardiac output. In the early stages, the neonate may be tachypneic and tachycardic with an increased respiratory effort, diaphoresis, hepatomegaly, and delayed capillary refill. If severe, CHF may present acutely with cardiorespiratory collapse and shock, particularly with obstructive defects. In less severe cases, CHF signs can be subtle such as feeding difficulties and growth failure. Edema caused by CHF is rarely seen in neonates. Birth asphyxia and anemia must also be considered as causes of CHF in neonates.

BOX 24.4 CRITICAL FINDINGS
CONGESTIVE HEART FAILURE

- Tachycardia
- Cardiac enlargement
- Tachypnea
- Gallop rhythm
- Decreased peripheral pulses and skin mottling in the extremities
- Decreased urine output and edema
- Diaphoresis
- Hepatomegaly
- Hypotension
- Decreased activity
- Failure to thrive and feeding problems
- Diminished cardiac output

The common symptoms associated with CHF (Box 24.4) can be understood using the physiologic principles previously outlined.

Tachycardia. The heart attempts to compensate for the decrease in cardiac output (CO) by increasing either the heart rate (HR) or the stroke volume (SV) (CO = HR × SV). The neonatal myocardium has fewer contractile elements and is poorly innervated by the sympathetic nervous system, thus limiting its capacity to increase stroke volume. Neonatal increases in cardiac output are achieved mainly by increasing the heart rate. In the sick neonate, a fast heart rate must be inspected closely to be certain it is a sinus tachycardia rather than an arrhythmia.

Cardiac Enlargement. Hypertrophy and dilation of the heart occur in response to a pressure or volume overload. This is referred to as *cardiomegaly.* This enlargement is evident on chest x-ray examination.

Gallop Rhythm. The gallop rhythm is an abnormal filling sound that can be present with CHF. It is heard as a triple rhythm on auscultation.

Decreased Peripheral Pulses/Poor Capillary Refill. Decreased cardiac output results in a compensatory redistribution of blood flow to vital tissues. Peripheral tissue

perfusion is decreased, which results in **decreased peripheral pulses and poor capillary refill.** A decrease in peripheral perfusion is often subtle, but it is an alarming sign of declining cardiac output and impending cardiovascular collapse. **Capillary refill and peripheral pulses are essential to monitor in the child at risk for decreased cardiac output.**

Decreased Urine Output and Edema. **Decreased renal perfusion results in decreased glomerular filtration. The body interprets this as a decrease in intravascular volume and begins to initiate compensatory mechanisms such as vasoconstriction and retention of fluid and sodium.** Neonates may manifest this as weight gain and periorbital edema. **Poor urine output can be a sign of poor central perfusion, and as such, urine output should be monitored closely.**

Diaphoresis. **CHF leads to an increase in metabolic rate and increased activity of the autonomic nervous system, resulting in diaphoresis.** This is representative of the increased workload of the heart in failure. In neonates, this is most concerning during feedings or other periods of increased metabolic demands.

Hepatomegaly. The right ventricle in CHF does not adequately empty. This leads to a backup of blood and elevated pressures in the RA central venous system, and hepatic system. ***Hepatomegaly* results from hepatic venous congestion and is an easily evaluated sign of systemic venous overload.**

Hypotension. **An infant with low cardiac output will exhibit systemic hypotension, which can be detected and monitored by invasive or noninvasive blood pressure measurements.** The causes of hypotension are complex and can stem from cardiac, respiratory, and endocrine abnormalities.[84] Short- and long-term complications are possible, including intraventricular hemorrhage, periventricular leukomalacia, poor long-term neurodevelopment, hepatic and renal injury, or death. These adverse events may be worse in preterm infants with hypotension.[14,43]

There are multiple causes of systemic hypotension, including pulmonary hypertension, arrhythmia, and structural heart disease. **Preload, contractility, and afterload all impact systemic blood pressure, and abnormalities can contribute to hypotension. Mean arterial pressure (MAP) should be followed, and normative values are impacted by gestational age.** Both systolic and diastolic hypotension can be a sign of impending cardiac failure.[43]

Decreased Activity and Exercise Intolerance. **The decreased perfusion to peripheral tissues and the increased energy needed by the heart in failure leave little energy for activities such as feeding and crying.** The infant in heart failure may sleep more than other infants.

Failure to Thrive/Feeding Difficulties. **The basal metabolic rate is increased in neonates with CHF,** and both the heart and lungs have a higher demand for energy due to their increased workloads and inefficiencies. However, tachypnea and easy fatigability compromise the infant's ability to feed. **Poor growth and failure to thrive occur from the mismatch between above-normal caloric needs and below-normal ability to eat.** Significant feeding support is often necessary. **Most infants require higher-calorie formula or expressed breastmilk supplemented with high-calorie additives.** Nasogastric (NG) or gastrostomy (G) feeding tubes may be required when caloric intake requirements cannot be met with oral feeding. **Supplemental feeding tubes also decrease the amount of work required to feed, so they can be beneficial to help augment the caloric intake and decrease the caloric needs of an infant.** Cardiac nutrition and dietary support are vital for infants with CHD and heart failure.

Dysrhythmias. Abnormalities of the cardiac rhythm and murmurs are discussed individually later in the chapter.

CARDIAC EXAMINATION

See Specific Conditions later in this chapter.

LABORATORY DATA

Blood Pressure/Four-Extremity Blood Pressure. Adequate blood pressure is vital to deliver enough blood to the body. **Hypotension is an alarming sign that may suggest worsening cardiac function and poor cardiac output.** An ill neonate may first show signs of peripheral vasoconstriction and poor perfusion, mechanisms that will maintain normal central blood pressure at the expense of peripheral tissue perfusion. **Neonates at risk for decreased cardiac output should have blood pressure evaluated frequently, as well as frequent monitoring of capillary refill and peripheral pulses.**

The measurement of blood pressure should be taken in both arms and both legs. A systolic pressure that is more than 10 mm Hg higher in

the right upper extremity compared with the lower body is abnormal and suggests coarctation of the aorta, aortic arch hypoplasia, or interrupted aortic arch. However, this is a highly specific test with low sensitivity; the lack of a systolic blood pressure gradient does not conclusively rule out aortic arch abnormalities. **After an aortic arch anomaly has been ruled out, routine blood pressure monitoring may be performed in a single extremity.**

Chest X-Ray Examination. Frontal and lateral views (if possible) of the chest should be obtained. In neonates, the size of the heart may be difficult to determine because of the overlying thymus. **Chest x-ray examination may be normal even in the presence of life-threatening CHD. However, the degree of pulmonary vascularity helps define the type of CHD present and is characterized as being increased, normal, or decreased. Pulmonary edema can also be assessed and can suggest pulmonary overcirculation or pulmonary venous congestion.** The heart size should be evaluated, and the cardiac silhouette can suggest which cardiac chamber may be enlarged.

Near-Infrared Spectroscopy. Near-infrared spectroscopy (NIRS) is a helpful, noninvasive tool to monitor cerebral and splanchnic oxygen saturations and can be used to infer details about regional hemodynamics in the critically ill newborn. **Downtrends in values may be an early indicator of low cardiac output before other clinical signs are noted.** NIRS monitoring is especially helpful for left-sided obstructive lesions, such as hypoplastic left heart syndrome and coarctation of the aorta, to monitor for early clinical indicators of low cardiac output.[39]

Arterial Blood Gases. The $Paco_2$ in cardiac disease is often normal unless primary pulmonary disease is also present. **In CHF and low cardiac output, metabolic acidosis may be present.** Frequent monitoring of blood gases may be necessary with CCHD that is ductal dependent to assess cardiac output and peripheral tissue perfusion. In general, **the acid-base balance should be monitored closely in neonates with critical CHD.**

Venous Blood Gases. Venous, capillary, and arterial blood gases can be used to assess acid-base status and guide ventilator and respiratory support. Mixed central venous saturations can provide important information about cardiac output and tissue oxygenation.[91]

Lactic Acid. Lactic acid production increases when there is poor tissue perfusion. An increased lactic acid level can indicate low cardiac output or insufficient systemic perfusion.

Basal Metabolic Panel. Electrolyte and renal function evaluation should be normal. **With low cardiac output, poor renal perfusion may lead to decreased renal function.** Renal function should be closely monitored, including blood urea nitrogen (BUN) and creatinine levels.

Hypoglycemia is not a primary effect of CHD, but it can result from poor feeding, genetic abnormalities associated with CHD, or medications used to treat the infant. **The glucose level should be closely monitored, and neonates should be maintained in a normal glycemic state.**

The use of diuretics for CHF can lead to electrolyte imbalances. Neonates taking diuretics may require electrolyte monitoring and supplementation to maintain normal balance. Sodium, potassium, and chloride depletions are most commonly noted with prolonged diuretic use.

Complete Blood Count. Significant anemia decreases the blood's oxygen-carrying capacity, increases the cardiac workload, and worsens hypoxemia in neonates with CHD. The desired hemoglobin level may be altered based on the infant's age and hypoxia because polycythemia is an expected and potentially helpful response to chronic cyanosis. Elevation of the white blood cell count is not expected with CHD and, if present, should prompt assessment for possible infection. Platelet levels should be normal in neonates with CHD.

Brain-Natriuretic Peptide. Although levels may vary in individual cardiac defects, following trends for **brain-natriuretic peptide (BNP) or N-terminal (NT)-Pro BNP levels may help to predict clinical outcomes and the degree of cardiac stress. These values are not reliable in the first few days of life as an indicator of CHD alone but can be used in the preoperative and postoperative management of simple and complex CHD.**[27]

Electrocardiogram. **A neonatal electrocardiogram (ECG) is most useful for evaluating cardiac dysrhythmias and less useful for evaluating structural heart disease.** An abnormal ECG can help define the type of structural heart disease, but **a newborn ECG is frequently "normal for age" despite significant structural defects** (e.g., transposition of the great arteries). Some structural heart defects are associated with abnormal development of the conduction system. **An ECG is essential to evaluate conduction system abnormalities, including sinus node dysfunction, heart block, or accessory pathways.**

Echocardiogram. **The echocardiogram is indispensable in the diagnosis of CHD.** Two-dimensional echocardiography can define cardiac anatomy and can assess cardiac physiology by estimating pressures and gradients and evaluating cardiac function.[17] **Supplemented with Doppler and color Doppler, the echocardiogram has become the primary diagnostic tool in pediatric cardiology.** During the procedure, close monitoring is recommended, with attention to vital signs, respiratory status, and temperature.

A noninvasive transthoracic echocardiogram is the most commonly used approach. Three-dimensional echocardiograms that offer real-time three-dimensional imaging have improved significantly and are becoming more clinically useful, especially for evaluating valve anatomy and function. Transesophageal echocardiography (TEE) is almost never used for infants outside of the operating room, but this imaging modality is routinely used for cardiac evaluation in the operating room immediately before and after surgical repair.

Computed Tomography. Sixty-four-slice multidimensional computed tomography (64-MDCT) can image some thoracic regions beyond the scope of an echocardiogram and can help define the spatial relationship and distance between thoracic structures when planning surgery. **Computed tomography (CT) currently requires significantly shorter scan times compared with cardiac magnetic resonance imaging,[86] so sedation is not usually required.** This benefit can be substantial when evaluating a sick, unstable neonate. **CT exposes the infant to radiation, but newer technologies and protocols are now applied to keep the radiation dosage as low as possible.[20]**

Magnetic Resonance Imaging. Like CT, magnetic resonance imaging (MRI) offers three-dimensional reconstruction and high-resolution images of the heart and great vessels. MRI is of particular use in evaluating extracardiac vascular abnormalities, such as arch anomalies, vascular rings, and pulmonary arteriovenous anomalies. **MRI provides high spatial resolution, excellent soft-tissue definition, and a large field of view, and it does not expose the patient to radiation. However, an hour or two may be required to perform the test, so sedation is often required and this may be contraindicated for an unstable patient.** In addition, MRI is expensive.[35]

General Treatment Strategy

Optimal management of infants with heart disease requires specialized expertise. **Infants require close monitoring for hypoxia, hypoglycemia, acidosis, CHF, and poor peripheral perfusion.**

The infant must be kept in an incubator or radiant heat warmer in which body temperature is maintained while color changes (pallor and increased cyanosis) may be observed. **A cardiorespiratory monitor is necessary for continuous cardiac monitoring to detect bradycardia, tachycardia, and dysrhythmias. Monitoring of oxygen saturations is mandatory** to determine the adequacy of pulmonary blood flow and/or increased need for supplemental oxygen. Pre- and post-ductal oxygen saturations may both be required, depending on the child's cardiac disease. **Respiratory effort should be frequently assessed** for tachypnea, shallow breathing, apnea, retractions, grunting, abdominal breathing, head bobbing, and nasal flaring. **Urine output, peripheral pulses, blood pressures, NIRS, and capillary refill should be monitored closely. Other signs of CHF should be documented, such as diaphoresis, hepatomegaly, decreased activity level, and poor feeding behavior.**

MANAGEMENT OF CONGESTIVE HEART FAILURE

The medical management of CHF attempts to reverse the outlined process and helps the heart compensate with increased cardiac output. **Maintaining the balance of pulmonary blood flow and systemic blood flow is the primary concept that is used to treat CHF in neonates.**

If CHF is due to a ductal-dependent cardiac lesion, prostaglandin infusion should be used after consultation with pediatric cardiology. If signs of low cardiac output are present, small-volume fluid boluses may be needed to increase preload to improve systemic blood flow. Continuous inotrope or vasoactive infusion may be needed with significant CHF and CCHD.

Digoxin acts primarily as a positive inotropic (improves contractility) agent (Box 24.5). This drug should be used with caution if acidosis, myocarditis, or obstructive lesions (e.g., tetralogy of Fallot, subvalvular pulmonary stenosis, asymmetric septal hypertrophy) are present. Diuretics such as furosemide (Table 24.3) decrease total body water (which is increased as a result of CHF), and they effectively decrease pulmonary edema, which helps to decrease the work of breathing. Medications that reduce afterload, such as captopril, enalapril, and milrinone, may be used to reduce the systemic blood pressure and encourage systemic perfusion. Chronic fluid restriction and low-salt diets are not commonly used in newborns or infants with CHF.

Hypotension is a late sign of CHF, but frontline volume resuscitation (5 to 10 mL/kg) can be used with caution. A decision to escalate treatment with inotropic support with intravenous (IV) agents such as dopamine, dobutamine, epinephrine, norepinephrine, and vasopressin should be made in conjunction with cardiology consultation. Evaluation of end-organ function and utilization of near-infrared spectroscopy may help to determine if advance support is necessary with the risk of possible side effects and the cause for CHF in each infant.[43]

Corticosteroids, such as hydrocortisone stress dosing, may be helpful for hypotension, especially in preterm infants.[14] Some studies on cortisol levels did not find a correlation between cortisol levels and gestational age or after treatment, so they may be used cautiously as a deciding factor for treatment in refractory hypotension.[84] **Hydrocortisone should be used cautiously over 2 to 3 days and weaned judiciously, with monitoring of blood pressures and stress-dosing intervals of every 6 to 12 hours, depending on gestational age.**[41]

Infants with CHF often have difficulty feeding. They may have trouble sucking, swallowing, and breathing simultaneously. They may have to rest frequently during a feeding, thus prolonging feeding times, and they may fall asleep exhausted before adequate caloric intake is achieved. **Caloric requirements are higher in infants with CHD; thus, the use of higher-caloric formulas may be necessary.** Adequate nutrition must be ensured by the following:

- **Observing the infant's ability to nipple feed.** A soft, free-flowing nipple offers the least resistance to sucking and helps the infant conserve energy. If necessary, alternative feeding methods such as gavage or continuous nasogastric drip may be required if the infant is sucking poorly.
- **Providing adequate calories for growth,** including higher-calorie formula or expressed breastmilk supplemented with a high-calorie additive
- **Anticipating the infant's hunger and offering feedings before the infant uses energy by crying**
- **Positioning the infant in a semierect position for feeding**

BOX 24.5 DIGOXIN DOSAGES AND COMMON SIDE EFFECTS

Digitalizing Schedule

Preterm Infant PO route: 20-30 mcg/kg total dose* **Term Infant** PO route: 25-35 mcg/kg total dose*	Total dose is usually divided into three doses giving one-half, then one-fourth, then one-fourth of the total dose q 8 hr. Check electrocardiogram rhythm strip for rate, PR interval, and dysrhythmias before each dose. Doses based on lean body weight and normal renal function for age.

Maintenance Schedule

Preterm Infant PO route: 5-7.5 mcg/kg/day* **Term Infant** PO route: 6-10 mcg/kg/day	Total dose should be divided BID. Allow 12-24 hr between last digitalizing and first maintenance doses. It takes about 6 days to "digitalize" a patient with maintenance doses alone. The sign of digitalis effect is usually prolongation of the PR interval. The first sign of digitalis toxicity is usually vomiting, dysrhythmia, or bradycardia. Drugs such as quinidine, amiodarone, and diuretics predispose to digoxin toxicity. The clearance of digoxin is directly related to renal function. Dosage must be reduced in patients with impaired renal function.

*Intravenous (IV) dose is 75% of oral (PO) dose.
BID, Twice daily; *PO,* per os, by mouth.
Data from Lexicomp Online. Digoxin. Accessed June 1, 2018.

TABLE 24.3 CARDIAC DRUGS

DRUG	ROUTE	DOSE	ONSET OF ACTION	COMMENTS
Adenosine	IV	0.05-0.1 mg/kg, increase by 0.05-0.1 mg/kg for nonresponsive SVT	Seconds	Slows the spontaneous heart rate and prolongs the PR interval; may cause transient complete heart block and hypotension; half-life is only 9.3 seconds, so its effects quickly dissipate
Amiodarone	IV PO	10-15 mg/kg/day in 1-2 divided doses 2.5-10 mg/kg/day daily maintenance dose	Hours 2-3 days	Should only be used with a pediatric cardiologist and electrophysiology consultation Hypotension, abnormal liver function, and abnormal thyroid function can occur
Atropine	IV	0.01-0.03 mg/kg/dose PRN (max 0.4 mg)	Seconds	May cause tachycardia, urinary retention, or hyperthermia
	ETT	Give 2-3 times the IV dose followed by NS flush	Minutes	May cause tachycardia
Calcium chloride (10% solution)	IV	10-20 mg/kg/ dose q 4-6 min PRN for hypocalcemia	Minutes	Slow infusion; must be IV; potentiates digoxin, bradycardia
Calcium gluconate (10% solution)	IV	200-800 mg/kg/day divided in 4 doses for hypocalcemia	Minutes	Slow infusion (over 10-30 min); must be IV; potentiates digoxin, bradycardia/dysrhythmias
Captopril (Capoten)	PO	Preterm and postnatal age <7 days: Initial dose: 0.01 mg/kg/dose q 8-12 hr Titrate: up to max 0.5 mg/kg/dose Term neonates >7 days: Initial dose: 0.05-0.1 mg/kg/day Titrate: up to 0.5 mg/kg/dose in 1-4 divided doses	15 min +	Hypotension, tachycardia, increased BUN and serum creatinine, hypercalcemia Monitor BP for 2 hours after first dose
Chlorothiazide (Diuril)	IV PO	5-10 mg/kg/day in 2 doses 20-40 mg/kg/day in 2 divided doses	15 min 2 hours	Hypotension, electrolyte disturbances
Dobutamine (Dobutrex)	IV	2-15 mcg/kg/min	Minutes	Do not use if IHSS or tetralogy of Fallot, may cause ventricular ectopy, tachycardia, or hypertension Incompatible with alkaline solutions
Dopamine (Intropin)	IV	1-15 mcg/kg/min	Minutes	Tachydysrhythmia, vasoconstriction, gangrene of extremities, anginal pain, and palpitations can occur; inactivated in alkaline solution
Enalapril	PO	0.1 mg/kg/day in 1-2 divided doses, increase to max of 0.5 mg/kg/day	Hours	Monitor for hypotension with initiation and dosage changes
Epinephrine (1:10,000)	IV/ETT	0.1-0.3 ml/kg/dose (max 5 ml/dose) q 3-5 min PRN	Seconds	May cause tachycardia, dysrhythmias, or hypertension; not effective if acidosis is present

Continued

TABLE 24.3 CARDIAC DRUGS—CONT'D

DRUG	ROUTE	DOSE	ONSET OF ACTION	COMMENTS
Esmolol (Brevibloc)	IV	*Initial dose:* 50-75 mcg/kg/min Continuous infusion: titrate 50-200 mcg/kg/min	Minutes	May cause bradycardia, hypotension, bronchoconstriction
Flecainide	PO	1-3 mg/kg/day in 3 divided doses	Hours	May cause ECG changes and hypotension
Furosemide (Lasix)	IV	1-2 mg/kg/dose	5-15 min	May cause metabolic alkalosis and hypokalemia; monitor electrolytes—may need KCl supplementation; renal calcification
	PO	1-4 mg/kg/dose	30-60 min	
Ibuprofen lysine (NeoProfen)	IV	10 mg/kg first dose; then 5 mg/kg second and third dose (q 24 hr)	Most effective in first 3 days of life	Monitor urine output and creatinine levels; discontinue drug if dramatic decrease in urine output Significantly fewer adverse effects (compared with indomethacin) on renal and mesenteric blood flow; less oliguria and increase in serum creatinine levels
Indomethacin (Indocin)	IV	0.1-0.2 mg/kg/dose; may be repeated q 8 hr for a total of 3 doses		Less effective if administered after 7 days of age; probably will have no effect after 14 days Monitor urine output and creatinine levels; discontinue drug if dramatic decrease in urine output Contraindications: severe renal impairment, active bleeding in the CNS or GI tract, and NEC
Isoproterenol (Isuprel)	IV	0.05-2 mcg/kg/min	30-60 seconds	May cause tachycardia/ventricular tachydysrhythmia; may also cause subendocardial ischemia
Lidocaine (Xylocaine)	IV	*IV bolus:* 1-2 mg/kg *IV drip:* 20-50 mcg/kg/min		May cause dysrhythmia, CNS agitation or depression
Milrinone (Primacor)	IV	*Loading:* 50 mcg/kg over 15 min *Maint.*: 0.25-1 mcg/kg/min	5-15 minutes	May cause ventricular dysrhythmias, ventricular fibrillation, or hypotension
Nitroprusside (Nipride)	IV	0.2-4 mcg/kg/min (protect from light; change solution q 4 hr)	Within 2 minutes	May cause hypotension and reflex tachycardia; may cause thiocyanate toxicity, especially if decreased renal function is present
Procainamide (Pronestyl)	IV	*Loading:* 7-10 mg/kg/dose over 5 min (max 100 mg) *Maint.*: IV 20-80 mcg/kg/min	1-5 min	May cause hypotension or lupus-like syndrome

TABLE 24.3 CARDIAC DRUGS—CONT'D

DRUG	ROUTE	DOSE	ONSET OF ACTION	COMMENTS
Propranolol (Inderal)	PO	Dysrhythmias: 0.25 mg/kg/dose TID-QID (max daily dose 5 mg/kg/day)	30-60 min	May severely decrease cardiac output
Prostaglandin E_1 (Prostin VR)	IV	*Initial dose:* 0.02-0.1 mcg/kg/min cont. IV infusion *Maint.:* 0.01-0.05 mcg/kg/min cont. IV infusion	30 min	May cause apnea, fever, or hypotension
Sotalol	PO	*Initial dose:* 1 mg/kg/dose q 12 hr Increase gradually as needed every 3-5 days until stable rhythm is maintained *Maximum dose:* 4 mg/kg/dose q 12 hr		Antiarrhythmic used to treat refractory ventricular and supraventricular tachyarrhythmias Proarrhythmia effects in first days of treatment; cardiorespiratory monitoring essential
Spironolactone (Aldactone)	PO	1-2 mg/kg/day	3-5 days	Hyperkalemia, drowsiness, GI upset

Standard Concentrations: Each institution's concentration may vary; NOT to exceed maximum concentration per pharmacy reference manuals. Neonatal Drug Guidelines. Updated May 7, 2002.

BID, Twice daily; *BP,* blood pressure; *BUN,* blood urea nitrogen; *CNS,* central nervous system; *ETT,* endotracheal tube; *GI,* gastrointestinal; *IHSS,* idiopathic hypertrophic subaortic stenosis; *IV,* intravenous; *IM,* intramuscular; *KCl,* potassium chloride; *maint.,* maintenance; *max,* maximum; *mcg,* micrograms; *mg,* milligrams; *min,* minutes; *NEC,* necrotizing enterocolitis; *NS,* normal saline; *PO,* per os, by mouth; *PRN,* as needed; *q,* every; *QID,* four times a day; *SVT,* supraventricular tachycardia; *TID,* three times a day.

Data from Lexicomp Online. Medication reference. Accessed June 1, 2018.

- **Maintaining oral feedings at 15 to 20 minutes** to minimize overexertion for the neonate
- **Burping the infant after every half ounce** consumed to help minimize vomiting
- **Medical treatment of gastroesophageal reflux**
- **Weighing the infant daily** to check for appropriate weight gain

Before discharge from the nursery, the infant should be feeding well and gaining weight appropriately.

Many infants gain weight very slowly because of their cardiac defects. **Poor nutrition has been associated with increased respiratory support, increased hospital stay, and mortality risk after cardiac surgery.**[62] However, adequate growth can be achieved with the use of fortified formula or breastmilk and an NG tube, and possibly G-tube, to supplement basic oral feedings. **Frequent monitoring of weight gain is necessary.** Cardiac nutrition experts and cardiology providers can work together to promote nutrition with standardized feeding guidelines in the high-risk cardiac population.[4]

The family of an infant in CHF needs support and teaching. **Explanation of the term *congestive heart failure* should be given early because it is a frightening term for parents.** The phrase "heart failure" is often interpreted as "heart attack" or "cardiac arrest." Parents must understand that saying an infant is in heart failure does not imply that the infant's heart will stop beating. **Describing heart failure as a condition in which the heart struggles to pump enough blood to meet all the needs of the body can help decrease anxiety for the family.**

SPECIFIC CONDITIONS

Patent Ductus Arteriosus

PHYSIOLOGY

The ductus arteriosus is a normal pathway in the fetal circulatory system and allows blood from the right ventricle and pulmonary arterial system to

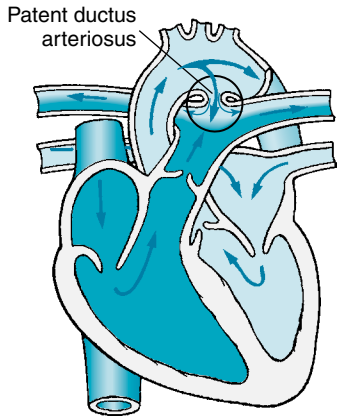

FIGURE 24.4 Patent ductus arteriosus. (Modified from Hockenberry MJ, Wilson D. *Wong's Essentials of Pediatric Nursing*. 8th ed. St Louis: Mosby; 2009.)

flow into the descending aorta for ultimate delivery to the placenta (Fig. 24.4). After birth, as a result of a decrease in the pressure of the pulmonary circulation and an increase in the pressure of the aorta, the blood flow through a PDA is predominantly from the aorta to the pulmonary artery (left-to-right shunt). **Functionally, the *patent ductus arteriosus* (PDA) closes within a few hours to several days after birth, but this closure is often delayed in premature infants.** The hemodynamic changes and the resultant clinical manifestations of a PDA depend on the magnitude of the pulmonary vascular resistance and the size of the ductal lumen.

DATA COLLECTION

History. Preterm birth, respiratory distress, inability to wean from a ventilator, labile blood pressures, feeding difficulties, necrotizing enterocolitis (NEC), intracranial hemorrhage, and increased oxygen (Fio_2) demand can all accompany a PDA.

Physical Findings. Increased flow to the pulmonary circulation often results in increased pulmonary edema and work of breathing.

Cyanosis. Generally, cyanosis is not present in an isolated PDA because the predominant shunt is from left to right. Oxygen saturation monitoring should have normal values.

Heart Sounds. Infants with a PDA may have an audible murmur as a result of the left-to-right shunting through the ductus arteriosus during systole. **The classic murmur from a PDA is a grade I to III/VI systolic murmur best heard at the upper left sternal border with radiation to the left axilla and faintly to the back.** Although this murmur occasionally may spill into diastole, the classical continuous machinery-like murmur is an unusual occurrence in the newborn period. It is often helpful to briefly disconnect the newborn from the ventilator before auscultation. **When a large PDA is present, there may be no audible murmur.**

Pulses. With a rapid upstroke and wide pulse pressure, the peripheral pulses are bounding. **Assessment of the pulses should include palpation of brachial, plantar, and femoral pulses. The presence of an easily palpated, hyperdynamic pulse in these areas suggests the presence of an aortic run-off lesion, which is most commonly a PDA.**

Congestive Heart Failure. With a volume overload of the left ventricle, the infant may show signs of CHF and pulmonary edema (see Congestive Heart Failure earlier in this chapter).

Laboratory Data

Arterial Blood Gases. Arterial blood gas values are usually normal. **A large PDA in a premature neonate may prevent adequate systemic blood flow and acidosis may result.**

Basic Metabolic Panel. **Electrolyte abnormalities may occur with the use of diuretics to manage pulmonary congestion.** Close monitoring to maintain normal electrolytes should be used. **Renal function should be monitored during medical treatment for the closure of a PDA.**

Chest X-Ray Examination. **Chest x-ray examination is normal in small shunts. Cardiomegaly is present with increased pulmonary vascularity in large shunts.** Pulmonary edema is present with CHF.

Near-Infrared Spectroscopy. Systemic NIRS monitoring may not be helpful in the preterm infant with hemodynamically significant PDA. Retrograde diastolic blood flow has not affected cerebral and renal NIRS measurements for infants <28 weeks of age.[90]

Brain Natriuretic Peptide. BNP values may be helpful to trend for each neonate and aid in deciding whether further intervention is recommended. BNP value cutoffs are difficult to generalize, especially in preterm infants. Medical treatment has been suggested for BNPs ranging from 250 to 800 pg/mL and surgery at levels higher than 2000 pg/

mL. Surgical intervention of preterm infants with hemodynamically significant PDA may be recommended if the NT-BNP value is >40,000 pg/mL.[52] NT-BNP should be used with caution if it is drawn less than 7 days before the physiologic decline.

Electrocardiogram. The ECG may be normal, demonstrate left ventricular hypertrophy, or demonstrate combined ventricular hypertrophy.

Echocardiogram. Echocardiographic imaging is the preferred method both to diagnose patency and to determine the significance of the ductus arteriosus. **An echocardiogram should be performed before medical or surgical closure of the PDA to rule out a ductal-dependent lesion or other associated anomalies.** Color-flow Doppler mapping allows visualization of the PDA and aids in determining the size and direction of the shunt across the PDA (i.e., left to right, right to left, bidirectional).

Cardiac Catheterization. Cardiac catheterization is usually not necessary for diagnosis. However, coil or device closure of a PDA by cardiac catheterization is highly successful later in infancy or childhood. **In a clinically symptomatic preterm infant with a moderate to large PDA, medical or surgical closure is preferred.**

TREATMENT

Medical Management. Asymptomatic infants with PDAs generally do not require medical management or surgical ligation. These infants should be monitored for evidence of CHF, failure to thrive, increasing oxygen requirement, or other complications. In extremely low-birth-weight (ELBW) infants less than 24 hours of age, prophylaxis for PDA closure with IV indomethacin should be considered with a high likelihood of severe intraventricular hemorrhage or pulmonary hemorrhage.[82]

Fluid restriction, watchful waiting, and ventilator support are frequently used as management strategies. However, severely symptomatic infants require ductal closure by either pharmacologic management or surgical ductal ligation. Indomethacin was first reported in the 1970s and became first-line therapy for the treatment of persistent PDAs. Ibuprofen lysine has also been shown to be effective.[67] Recently, **oral acetaminophen has been reported as a second-line treatment after indomethacin failure, with a 50% reduction in the need for surgical PDA ligation in preterm infants.**[95] Table 24.3 provides indomethacin and ibuprofen lysine doses, contraindications, and side effects. **Urine output and creatinine levels should be closely monitored with both medications. If urine output decreases dramatically, the drug should be discontinued.**

Surgical Treatment. Although surgical ligation of the ductus arteriosus through a lateral thoracotomy incision is a low-risk procedure when performed by an experienced surgical team, this should be reserved for those infants who cannot tolerate or have failed pharmacologic intervention. Questions have been raised about the long-term effects of surgical PDA closure in ELBW infants and the relationship between ligation and bronchopulmonary dysplasia (BPD), severe retinopathy of prematurity (ROP), and neurosensory impairment.[42,94]

COMPLICATIONS AND RESIDUAL EFFECTS

Complications and residual effects, although rare, include recanalization, recurrent laryngeal or phrenic nerve palsies, and false aneurysms. The surgical mortality rate in the neonatal period is generally less than 1%.

PROGNOSIS AND FOLLOW-UP

Asymptomatic infants have an excellent prognosis, although follow-up is necessary. If the ductus arteriosus remains patent beyond infancy, closure by interventional cardiac catheterization may be recommended.

Patent Foramen Ovale

A patent foramen ovale (PFO) is a communication in the atrial septum between the left and right atrium. Unlike an atrial septal defect, this is a flap-like opening with no deficiency of tissue. A PFO is needed before birth to allow blood to flow from the right atrium to the left atrium. After birth, increased pulmonary blood flow causes left atrial pressure to exceed right atrial pressure, and the flap opening shuts. A trivial left-to-right shunt often persists until permanent anatomic closure is completed. Approximately 20% of adults have a persistent PFO, but this rarely has clinical consequences.[36]

A PFO is considered a normal finding and requires no treatment or cardiology follow-up.

Atrial Septal Defect

PHYSIOLOGY

An atrial septal defect (ASD) may occur as an isolated anomaly or as part of a more complex cardiac disease. Only isolated ASDs are discussed in this section.

ASDs are common congenital heart lesions that are challenging to diagnose (Fig. 24.5). Prenatal diagnosis of an ASD rarely occurs because a natural atrial septal communication (patent foramen ovale) is always present before birth. **Neonates with ASDs are generally asymptomatic, so diagnosis often does not occur until later in life.**

Three types of ASDs exist, classified by location. A *secundum atrial septal defect* is most common and is located in the central portion of the atrial septum. A *primum atrial septal defect* is located close to the mitral and tricuspid valves and is often associated with a cleft mitral valve or atrioventricular septal defect. A *sinus venosus defect* is not a defect in the atrial septum, but it is often classified as an ASD due to its similar effects on the heart; this defect can be associated with partial anomalous pulmonary venous return. **Secundum ASDs can spontaneously close in the first few years of life, but primum ASDs and sinus venosus defects always require surgical closure.**

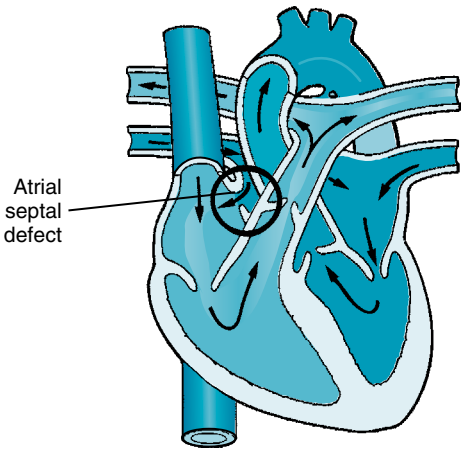

FIGURE 24.5 Atrial septal defect. (Modified from Hockenberry MJ, Wilson D. *Wong's Essentials of Pediatric Nursing.* 8th ed. St Louis: Mosby; 2009.)

DATA COLLECTION

Physical Findings

Cyanosis. An isolated ASD does not cause cyanosis because the predominant shunt is from the left atrium to the right atrium. Oxygen saturation monitoring is normal.

Heart Sounds. **Abnormal heart sounds are not usually appreciated during infancy.** In older children, fixed splitting of S_2 can be appreciated due to delayed closure of the pulmonary valve. S_1 is normal. **Flow across the ASD does not create a murmur.** However, when left-to-right atrial-level shunting is large, excessive flow across the pulmonary valve can create a systolic, ejection-type murmur that is indistinguishable from the murmur of mild pulmonary stenosis. Less commonly, excessive flow across the tricuspid valve can cause a low-pitched "diastolic rumble."

Congestive Heart Failure. CHF does not occur, even in the presence of a large ASD.

Laboratory Data

Arterial Blood Gases. Arterial blood gas values are normal.

Venous Blood Gases. Venous blood gas values are normal.

Basic Metabolic Panel. No major electrolyte abnormalities or renal dysfunction should be present related to an ASD.

Chest X-Ray Examination. A chest x-ray examination is normal. Later in life, right-sided heart dilation and cardiomegaly may be present.

Electrocardiogram. **The ECG in an infant with an ASD is usually normal.** As right-sided heart dilation occurs over the first few years of life, right atrial enlargement and right ventricular enlargement may be detected by ECG.

Echocardiogram. **A two-dimensional echocardiogram is diagnostic and can demonstrate the number, size, and location of atrial septal defects.** Right-sided heart enlargement may also be appreciated in older infants and children.

Cardiac Catheterization. A diagnostic cardiac catheterization is not necessary. (See Treatment section for discussion of interventional cardiac catheterization.)

TREATMENT

Medical Management. Medical management is not necessary because ASDs do not cause significant symptoms during childhood.

Cardiac Catheterization (Device Closure). **Device closure of a secundum ASD by interventional cardiac catheterization is often possible. This**

involves placing a device across the defect to plug the hole. Device closure is contraindicated if there are insufficient rims around the defect; the device must sandwich the atrial septum around the entire defect to avoid embolization of the device. Less commonly, device closure cannot be performed because the child's atria are too small to accommodate the appropriately sized device or the ASD is larger than commercially available devices. **This procedure is rarely performed in infants or toddlers.** Procedural risks are very low, but embolization of the device and erosion of the device through the heart are rare adverse events that can be life-threatening.

Surgical Treatment. Surgical treatment of an ASD is necessary for primum ASDs, sinus venosus defects, or secundum ASDs that cannot be closed by cardiac catheterization intervention. Surgery for isolated defects is rarely performed during infancy or the toddler years. Either primary suture closure or patch closure of the defect is performed through a median sternotomy incision.

COMPLICATIONS AND RESIDUAL EFFECTS

Complications or residual effects rarely occur but may include a persistent shunt (residual ASD) or rhythm abnormalities.

PROGNOSIS AND FOLLOW-UP

Eighty percent of neonatal secundum ASDs measuring 8 mm or less will close spontaneously within the first 2 years of life.[72] If spontaneous closure occurs, cardiology follow-up is not required. After surgical or device closure of an ASD, long-term cardiology follow-up is recommended.

Ventricular Septal Defect

PHYSIOLOGY

A VSD may occur as an isolated anomaly or as part of a more complex cardiac lesion. Only isolated VSDs are discussed in this section. **VSDs are the most common congenital heart defect.** VSDs can be located in various portions of the ventricular septum and are classified according to their anatomic position (Fig. 24.6). VSD types each have clinically important differences, such as the likelihood of spontaneous closure, possibility of affecting neighboring valve function, or complications that can develop with or without surgical repair.

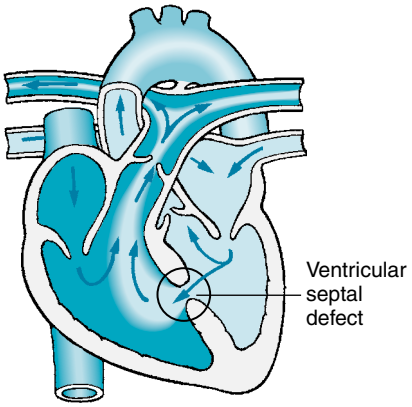

FIGURE 24.6 Ventricular septal defect. (Modified from Hockenberry MJ, Wilson D. *Wong's Essentials of Pediatric Nursing.* 8th ed. St Louis: Mosby; 2009.)

In addition to VSD type, the size of the defect also has an important role in clinical symptoms and treatment. A small VSD allows only a small amount of blood to shunt from the high-pressure LV to the lower-pressure RV. This small amount of left-to-right shunting is not enough to be clinically important or cause symptoms. Conversely, a large VSD allows a large amount of left-to-right shunting. Highly oxygenated blood returning from the lungs is shunted across the defect and back out to the lungs again. This pulmonary overcirculation results in CHF, pulmonary edema, respiratory distress, and failure to thrive.

Although the size of the VSD is of critical importance, the PVR also plays a role in how much blood shunts left to right across the ventricular septum. PVR is nearly systemic immediately after birth, so minimal blood travels across even a large defect. With minimal shunting, there are minimal symptoms and a minimal murmur. PVR usually rapidly falls in the first several days of life, then continues to fall more gradually over the next few months. **As PVR declines, more blood is shunted across the VSD, and symptoms gradually increase. Premature infants tend to have lower pulmonary vascular resistance at birth, allowing greater left-to-right shunting, and therefore may be symptomatic earlier.** Infants with severe lung disease (e.g., RDS, BPD, pneumonia) may have elevated PVR and therefore minimal left-to-right shunting and minimal symptoms.

DATA COLLECTION

Physical Findings

Cyanosis. Infants with isolated VSDs are rarely cyanotic because the predominant shunt is from the left ventricle to the right ventricle. Oxygen saturation values should be normal.

Heart Sounds. **Most infants with VSDs have a heart murmur. The time when this murmur is first audible depends on the PVR and the size of the defect.** The murmur is typically a grade II to III/VI harsh systolic murmur heard best at the lower left sternal border. A diastolic flow rumble at the apex indicates a large left-to-right shunt.

Congestive Heart Failure. A child with a moderate to large VSD will have increasing symptoms of CHF over the first few months of life as the PVR drops (see Congestive Heart Failure earlier in this chapter). CHF is unusual if the VSD is small and singular.

Laboratory Data

Arterial Blood Gases. Arterial blood gas values are normal.

Basic Metabolic Panel. Electrolytes are normal. If diuretics are used to treat CHF symptoms, electrolytes should be monitored, and electrolyte supplementation may be required.

Chest X-Ray Examination. A chest x-ray examination shows a normal to increased heart size with increased pulmonary blood flow.

Electrocardiogram. The ECG in an infant with a VSD is usually normal but may demonstrate left or biventricular hypertrophy.

Echocardiogram. **A two-dimensional echocardiogram can accurately diagnose even the smallest VSDs noninvasively.** The use of color-flow technology is particularly advantageous in identifying the presence of multiple VSDs and the direction of blood flow across a VSD.

Cardiac Catheterization. Cardiac catheterization is not necessary for diagnosis. Cardiac catheterization for intervention and device closure may be possible in older children and adults, depending on the type of VSD and associated cardiac issues.

TREATMENT

Medical Management. **Medical management of CHF associated with VSDs includes digoxin, diuretics, afterload reducers, and caloric supplementation** (see Congestive Heart Failure earlier in this chapter). Medical management may only be required temporarily as the child grows and the VSD becomes smaller. Spontaneous closure of the VSD later in life may also occur.

Surgical Treatment. **Failure to thrive despite maximum medical treatment is an indication for surgical repair of the defect.** Even if the defect is small, a VSD may require surgical repair due to the location of the defect (i.e., proximity to the aortic valve).

Surgical treatment of a VSD consists of either suture closure or patching (most commonly using a synthetic material such as Dacron). The surgical approach is through a median sternotomy incision. The defect is approached through the right atrium and tricuspid valve, thereby avoiding a right ventriculotomy.

If the infant is small (less than 2 kg) or if multiple muscular VSDs are present, it may be necessary to perform a palliative procedure called *pulmonary artery banding* to decrease pulmonary blood flow until the infant is older and can undergo debanding and closure of the VSDs. With improvements in surgical technique and technology, VSD closure can be performed safely and effectively in the younger pediatric population.[51]

COMPLICATIONS AND RESIDUAL EFFECTS

Complications or residual effects from surgery may include (1) a persistent shunt (residual VSD), (2) conduction abnormalities (right bundle-branch block and third-degree heart block), and (3) aortic or tricuspid insufficiency (less than 1%). The mortality rate from surgical repair of an isolated VSD is less than 1%,[32] although surgical correction in the neonatal period is rare and associated with a higher mortality rate.

PROGNOSIS AND FOLLOW-UP

Depending on the anatomic type, **small VSDs may close spontaneously in the first months of life, with reports of up to 84% closure with muscular VSDs.**[100] After spontaneous closure, complications have rarely been reported, and routine outpatient cardiology follow-up is generally not necessary.

If surgical repair is performed, long-term cardiology follow-up is recommended. If surgical repair is not performed and a large left-to-right shunt is persistent after 12 to 24 months of age, the child is susceptible to the development of

irreversible and life-limiting pulmonary vascular disease (Eisenmenger syndrome).

Coarctation of the Aorta

PHYSIOLOGY

Coarctation of the aorta is a localized constriction of the aorta that usually occurs at the junction of the transverse aortic arch and the descending aorta in the vicinity of the ductus arteriosus (Fig. 24.7). However, **coarctation can occur anywhere in the aorta. The precise location of the coarctation and the presence or absence of associated anomalies affect the clinical presentation.** Associated anomalies include PDA, VSD, and bicuspid aortic valve. **Coarctation is one of the more common CHDs, accounting for approximately 7% of cardiac lesions.**[25] Coarctation is observed in approximately 10% of infants with Turner syndrome.[24]

Coarctation of the aorta may only develop postnatally when the ductus arteriosus closes and causes constriction of the aortic periductal tissue. As such, coarctation of the aorta may not be able to be diagnosed before birth. **Neonates who had a fetal echocardiogram concerning for coarctation development may require a "coarctation watch" for the first few days after birth. This involves very close bedside monitoring of lower-extremity pulses, four-extremity blood pressures, urine output, and other measures of fetal well-being until postnatal echocardiogram confirms that the ductus arteriosus is completely closed.**

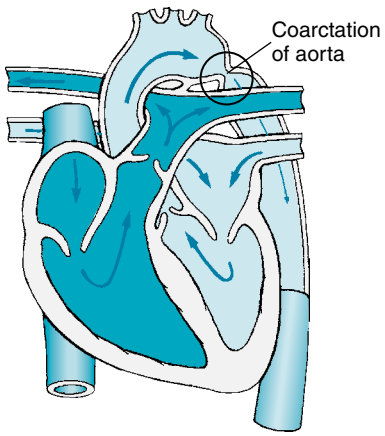

FIGURE 24.7 Coarctation of the aorta. (Modified from Hockenberry MJ, Wilson D. *Wong's Essentials of Pediatric Nursing.* 8th ed. St Louis: Mosby; 2009.)

DATA COLLECTION

Physical Findings. In utero, the majority of systemic blood flow to the lower body is via the ductus arteriosus. When ductal closure occurs after birth, the neonate with coarctation becomes critically ill because the left ventricle cannot pump the entire cardiac output past a significant point of obstruction. Newborns with critical coarctation of the aorta will have signs and symptoms of CHF and low cardiac output. **Severe coarctation of the aorta is a medical and surgical emergency. Untreated infants with severe coarctation often have a rapidly deteriorating clinical course that can progress to death unless prostaglandin infusion is started.**

Cyanosis. Generally, cyanosis is not present in the newborn with isolated coarctation of the aorta, but **an oxygen saturation difference may be found between the upper and lower extremities. Goal saturations should be greater than 92% unless another heart defect is noted.**

Heart Sounds. A **murmur heard only in the back is strongly suggestive of coarctation.** However, **a cardiac murmur may not be heard in isolated, severe coarctation of the aorta.** If other cardiac defects are present, murmurs from those anomalies will be heard. A gallop rhythm sometimes is present and is associated with CHF.

Pulses and Blood Pressure. **The blood pressure proximal to the area of obstruction is higher than the blood pressure distal to the area of obstruction. The most consistent physical finding in infants with critical coarctation of the aorta is a higher systolic blood pressure (greater than 10 mm Hg) in the right upper extremity than in the lower extremities.** This blood pressure must be measured with the appropriate-size cuff. **In addition, pulses are easily palpable in one or both upper extremities but are difficult to palpate or are absent in the lower extremities.** Pulses should be carefully evaluated in all extremities and blood pressures obtained in both arms and both legs.

Congestive Heart Failure. CHF is a common finding in infants with severe coarctation and is the result of pressure overload on the left ventricle (see Congestive Heart Failure earlier in this chapter).

Laboratory Data

Arterial Blood Gases. **Arterial blood gas values are normal until PDA closure causes severely decreased lower body perfusion. Metabolic**

acidosis due to peripheral tissue hypoxia then occurs.

Lactic Acid. An increased lactic acid level can be a sign of low cardiac output and should be monitored frequently.

Chest X-Ray Examination. Cardiomegaly may be seen on the radiograph. Pulmonary vascularity is normal unless associated anomalies are present.

Near-Infrared Spectroscopy. Systemic NIRS monitoring can help monitor for signs of low cardiac output.

Electrocardiogram. Right ventricular hypertrophy is frequently present. Left ventricular hypertrophy or combined ventricular hypertrophy is rarely seen in the newborn period. The ECG may be normal.

Echocardiogram. An echocardiogram is diagnostic; the area of coarctation can be visualized using two-dimensional techniques and color-flow mapping. However, interpretation of the findings may be difficult if a PDA is present.

Cardiac Catheterization. Cardiac catheterization is rarely necessary. Cardiac catheterization for balloon angioplasty of the coarctation is rarely performed because the results are usually only temporary for neonates.

TREATMENT

Medical Management. Medical management is used only for stabilization prior to surgery. **Medical management consists of continuous IV infusion of prostaglandin E1 (PGE1) to keep the ductus arteriosus open; dopamine and/or dobutamine for inotropic support; and correction of metabolic acidosis, hypoglycemia, and anemia.** CHF should be treated immediately and aggressively for stabilization before surgery. **Intractable CHF, acidosis, oliguria, and hypertension are indications for urgent corrective surgery.** (See General Treatment Strategy under Congenital Heart Disease earlier in this chapter.) Since the introduction of PGE1, emergency surgical repair is rarely necessary.

Surgical Treatment. The most common surgical procedure is resection of the coarctation with end-to-end anastomosis.[53] The area of the coarctation is resected, and the ends of the aorta reanastomosed. Coarctation repair is usually performed through a lateral thoracotomy incision and is highly successful in relieving coarctation and providing for the future growth of the aorta.

COMPLICATIONS AND RESIDUAL EFFECTS

Before surgery, significant lower-body ischemia puts neonates affected with this CHD at risk for NEC. After surgery, complications and residual effects include residual coarctation, persistent hypertension, chylothorax, phrenic nerve injury, and diaphragm paralysis. The overall operative mortality rate is low at less than 1%, but a higher mortality rate may apply if the neonate is medically unstable before surgery, weighs less than 2.5 kg,[25] or there are significant associated cardiac lesions.[88]

PROGNOSIS AND FOLLOW-UP

Infants with mild coarctation require minimal care initially. If these patients are medically managed, close follow-up is mandatory, and repair at a later date is likely. **Infants with severe coarctation require prompt medical and surgical treatment.** If this therapy is instituted early, the prognosis generally is favorable.

After surgical repair, frequent follow-up is necessary to ensure adequate coarctation repair. Cardiac catheterization may be necessary several months to years after the surgical procedure is completed if re-coarctation occurs. Balloon dilation and stent placement can be performed for re-coarctation. In adulthood, patients must continue to be monitored by a cardiologist for complications such as systemic hypertension and aneurysm formation at the coarctation site.

Critical Aortic Stenosis

PHYSIOLOGY

Obstruction of the left ventricular outlet may occur below the aortic valve, at the aortic valve, or above the aortic valve (subvalvular, valvular, or supravalvular aortic stenosis) (Fig. 24.8). **Valvular aortic stenosis is the most common type** and is discussed here. **Critical aortic stenosis is present if adequate blood supply to the body cannot get through the severely stenotic valve. In critical aortic stenosis, right-to-left shunting through the PDA helps supply blood to the body; with PDA closure, low cardiac output occurs and can be fatal.**

DATA COLLECTION

Physical Findings. Although most infants with aortic stenosis are asymptomatic in the neonatal period, **a neonate with critical or severe aortic**

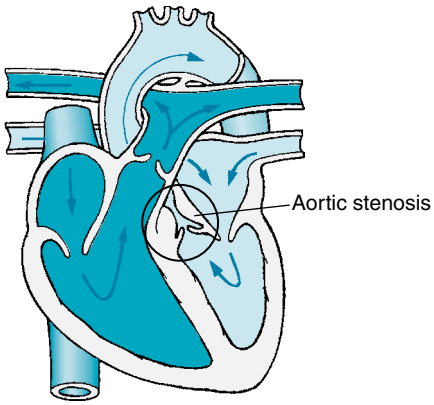

FIGURE 24.8 Aortic stenosis. (Modified from Hockenberry MJ, Wilson D. *Wong's Essentials of Pediatric Nursing*. 8th ed. St Louis: Mosby; 2009.)

stenosis needs emergent treatment. As the PDA closes, the infant with critical aortic stenosis will have signs and symptoms of CHF and low cardiac output.

Cyanosis. Cyanosis is generally not present in isolated valvular aortic stenosis. Oxygen saturation should be normal if the aortic stenosis defect is isolated.

Heart Sounds. A grade II to IV/VI harsh systolic murmur is typically heard at the upper right sternal border, radiating to the upper left sternal border and faintly to the neck. An ejection click may be heard at the apex. A suprasternal notch thrill is sometimes palpable.

Congestive Heart Failure. **Infants with critical aortic stenosis may have CHF caused by a pressure overload of the left ventricle** (see Congestive Heart Failure earlier in this chapter).

Laboratory Data

Arterial Blood Gases. Arterial blood gas values are generally normal unless PDA closure causes severely decreased cardiac output and body perfusion. Metabolic acidosis due to peripheral tissue hypoxia then occurs. Mixed venous gas values may be helpful in ensuring adequate cardiac output is being met.

Lactic Acid. An increased lactic acid level can be a sign of low cardiac output and should be monitored frequently.

Chest X-Ray Examination. A chest x-ray examination shows cardiomegaly with normal pulmonary vascularity.

Electrocardiogram. The ECG may be normal or demonstrate left ventricular hypertrophy. There is poor correlation between an electrocardiographic abnormality and the degree of aortic stenosis.

Echocardiogram. **A transthoracic echocardiogram is diagnostic.** The aortic valve is usually thickened and appears to open abnormally. Doppler interrogation can accurately estimate the systolic pressure gradient from the left ventricle to the ascending aorta and identify the level or levels of obstruction.

Near-Infrared Spectrometry. Systemic NIRS monitoring can be helpful for monitoring for signs of downtrends possibly indicating low cardiac output.

Cardiac Catheterization. Cardiac catheterization is not required for diagnosis but is the primary method of treatment.

TREATMENT

Medical Management. **Medical management consists of continuous IV infusion of PGE1 to keep the ductus arteriosus open; dopamine and/or dobutamine for inotropic support; and correction of metabolic acidosis, hypoglycemia, and anemia.** CHF should be treated immediately and aggressively for stabilization before cardiac catheterization intervention. **Intractable CHF, acidosis, and oliguria are indications for cardiac catheterization as soon as possible for critical aortic stenosis in the newborn** (see General Treatment Strategy earlier in this chapter).

Cardiac Catheterization. **Cardiac catheterization is performed to balloon dilate the aortic valve and improve aortic valve opening.** Dilation of the aortic valve often results in damage to the valve leaflets, resulting in valve regurgitation. Care must be taken to balance the desired improvement in aortic valve opening with the detrimental effect on aortic valve closing. Subsequent cardiac catheterizations for balloon valvuloplasty are often required during infancy and early childhood.

Surgical Treatment. Initial treatment with surgical aortic valvotomy is rarely required because balloon dilation of the valve in the cardiac catheterization laboratory is highly successful. However, repeated balloon valvuloplasties often result in significant aortic regurgitation, which can only be treated with surgical valve repair or valve replacement. **Newborns with critical or severe**

aortic stenosis often require surgical valve repair or replacement later in life.

COMPLICATIONS AND RESIDUAL EFFECTS

Complications and residual effects include aortic insufficiency and residual aortic stenosis. The mortality rate from aortic balloon valvuloplasty is low, and the procedure can be done safely even in premature infants weighing less than 2 kg. The newborn with critical obstruction has the highest risk.

PROGNOSIS AND FOLLOW-UP

All patients with critical aortic stenosis require lifelong follow-up. Further surgical or catheter intervention is almost always necessary.

Critical Pulmonary Stenosis

PHYSIOLOGY

In critical pulmonary stenosis, the flow to the pulmonary artery from the right ventricle is obstructed. The obstruction may occur below the valve in the infundibular area, at the valve, or above the valve (subvalvular, valvular, or supravalvular). In valvular stenosis, the orifice of the pulmonary valve is markedly narrowed (Fig. 24.9). The pulmonary artery distal to this area of stenosis may be dilated. The right ventricle is subjected to a marked increase in pressure and becomes hypertrophied. **Critical pulmonary stenosis is present if adequate blood supply to the lungs cannot get through the severely stenotic valve. In critical pulmonary stenosis, left-to-right shunting through the PDA helps supply blood to the lungs; with PDA closure, low cardiac output occurs and can be fatal.**

DATA COLLECTION

Physical Findings

Cyanosis. Cyanosis is generally not present in an isolated lesion but may occur in the presence of a right-to-left atrial shunt. Goal oxygen saturations are often greater than 85%.

Heart Sounds. A harsh grade II to III/VI systolic murmur is heard in the upper left sternal border, radiating to both axillae and faintly to the back. A murmur of tricuspid insufficiency (soft, systolic murmur at the lower left sternal border) may be heard. An ejection click also may be heard at the left sternal border.

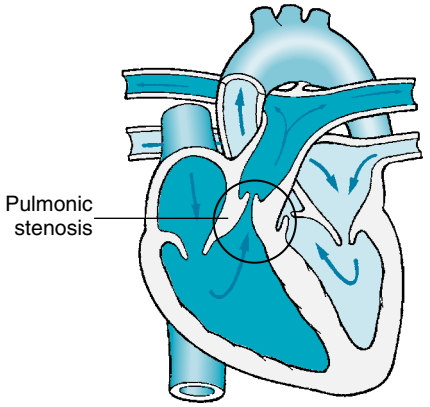

FIGURE 24.9 Pulmonic stenosis. (Modified from Hockenberry MJ, Wilson D. *Wong's Essentials of Pediatric Nursing*. 8th ed. St Louis: Mosby; 2009.)

Congestive Heart Failure. The infant with critical pulmonary stenosis typically has signs and symptoms of right-sided CHF resulting from excessive pressure overload (see Congestive Heart Failure earlier in this chapter).

Laboratory Data

Arterial Blood Gases. Arterial blood gas values generally are normal unless there is an atrial right-to-left shunt.

Venous Blood Gases. Venous blood gas values generally are normal.

Chest X-Ray Examination. The chest x-ray examination may be normal but usually demonstrates cardiomegaly with normal or decreased pulmonary vascularity.

Electrocardiogram. The ECG may be normal or demonstrate right ventricular hypertrophy.

Echocardiogram. A two-dimensional echocardiogram is diagnostic. Doppler interrogation and color-flow mapping can accurately estimate the systolic pressure gradient from the right ventricle to the pulmonary artery and identify the level or levels of obstruction.

Cardiac Catheterization. Cardiac catheterization is not required for diagnosis but is the primary method of treatment.

TREATMENT

Medical Management. PGE1 may be required to maintain the patency of the ductus arteriosus, thereby allowing adequate pulmonary blood flow until balloon dilation is performed. Oxygen saturations should be monitored as a sign

of adequate pulmonary blood flow before the cardiac catheterization procedure. CHF management including inotropic support is not usually required.

Cardiac Catheterization. **Catheter balloon valvuloplasty is the treatment of choice for this defect.** Successful balloon valvuloplasty is associated with excellent clinical results, although subsequent balloon dilation procedures may be necessary later in life. Pulmonary regurgitation often results from balloon valvuloplasty, but this rarely requires surgical pulmonary valve repair or replacement later in life.

Surgical Treatment. Surgical pulmonary valvotomy is rarely required because balloon dilation of the valve via a cardiac catheterization procedure is highly successful.

COMPLICATIONS AND RESIDUAL EFFECTS

Complications and residual effects include pulmonary insufficiency and residual pulmonary stenosis. The mortality rate for pulmonary balloon valvuloplasty is low, even in premature infants weighing less than 2 kg.

PROGNOSIS AND FOLLOW-UP

All patients with pulmonary stenosis require lifelong follow-up. Repeated catheterization procedures may be performed during infancy and childhood to treat residual or recurrent obstruction. The long-term prognosis is good.

Atrioventricular Septal Defect, Endocardial Cushion Defect (Atrioventricular Canal)

PHYSIOLOGY

An atrioventricular canal defect occurs when the endocardial cushions that form the central crux of the heart do not form normally. This results in an atrial septal defect, a ventricular septal defect, and one common atrioventricular valve (which should have separated into the tricuspid and mitral valves) (Fig. 24.10). **Nearly 70% of infants with a complete balanced atrioventricular canal had trisomy 21 (Down syndrome) in a single-site review conducted over 10 years.**[2]

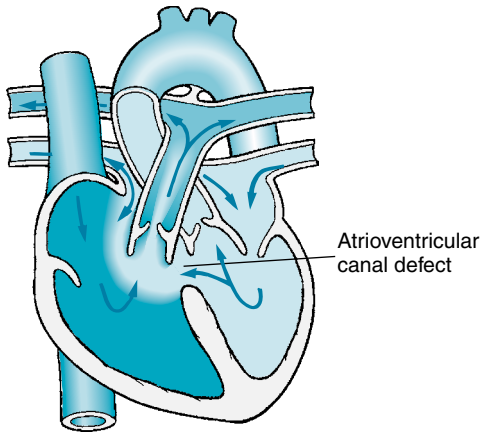

FIGURE 24.10 Atrioventricular (endocardial cushion) defect. (Modified from Hockenberry MJ, Wilson D. *Wong's Essentials of Pediatric Nursing.* 8th ed. St Louis: Mosby; 2009.)

These infants usually have a left-to-right shunt at both the atrial and ventricular levels. AV valve insufficiency also may be present. The symptomatology depends on the degree of shunting between the left and right sides and the amount of AV valve insufficiency present.

DATA COLLECTION

Physical Findings

Cyanosis. **There may be mild cyanosis, particularly in the immediate neonatal period before the pulmonary vascular resistance has fallen.** Goal oxygen saturations should be greater than 75% on room air.

Heart Sounds. **Often there is no murmur in the neonatal period.** If AV valve insufficiency is present, a blowing, holosystolic murmur best heard at the apex with radiation to the left axilla may be appreciated.

Congestive Heart Failure. **During the first few weeks of life, there are usually minimal cardiac symptoms due to elevated PVR. As the PVR falls, increasing left-to-right shunting causes infants to have increasing CHF symptoms.** AV valve insufficiency may also contribute to ventricular volume overload and may exacerbate the CHF (see Congestive Heart Failure earlier in this chapter). A minority of patients with trisomy 21 have persistent pulmonary hypertension and do not develop CHF symptoms. Oxygen saturations greater than 75% should be accepted because oxygen supplementation

can be detrimental and cause CHF through pulmonary overcirculation.

Laboratory Data

Arterial Blood Gases. The $Paco_2$ may be elevated if there is severe AV valve insufficiency and pulmonary edema. The pH and Pao_2 are usually normal.

Basic Metabolic Panel. Electrolytes are normal. With diuretic use for CHF symptoms, electrolytes should be monitored and replaced as necessary.

Complete Blood Count. Anemia may cause increased cyanosis and should be monitored in this cardiac defect. Inversely, chronic cyanosis may cause polycythemia.

Chest X-Ray Examination. The heart size may be normal or increased. The pulmonary vascularity is generally increased.

Electrocardiogram. An ECG with a left axis deviation, counterclockwise loop in the frontal plane, and superior axis suggests AV septal defect.

Echocardiogram. **A two-dimensional echocardiogram with Doppler and color-flow mapping is diagnostic** and demonstrates the ASD, VSD, common AV valve, and degree of AV valve insufficiency.

Cardiac Catheterization. Cardiac catheterization is generally not required.

TREATMENT

Medical Management. Medical management of CHF includes diuretics, digoxin, afterload reducers, and caloric supplementation. **Failure to thrive despite maximum medical treatment is an indication for surgical repair of the defect** (see Congestive Heart Failure earlier in this chapter).

Surgical Treatment. **Surgical repair is necessary. However, most centers do not perform surgery during the neonatal period.** Waiting until a few months of age has benefits, such as allowing the PVR to drop and allowing the child to grow bigger and stronger. The surgical procedure is performed through a median sternotomy incision and involves patch closure of the ASD and VSD and separation of the common atrioventricular valve into a mitral and tricuspid valve.

COMPLICATIONS AND RESIDUAL EFFECTS

Complications and residual effects include (1) persistent shunt (residual ASD or VSD), (2) mitral regurgitation, (3) tricuspid regurgitation, (4) left ventricular outflow tract obstruction, (5) conduction abnormalities (including third-degree heart block), and (6) dysrhythmias.

PROGNOSIS AND FOLLOW-UP

The prognosis after surgical repair is generally good, and future surgeries or cardiac interventions are rarely required. The prognosis is less favorable if early surgical repair was required, pulmonary hypertension persists after surgery, or surgical complications occur. Significant residual defects (shunt or AV valve regurgitation) may require subsequent surgical repair.

Ebstein Anomaly

PHYSIOLOGY

Ebstein anomaly is an uncommon heart defect with an abnormal tricuspid valve that is displaced down into the body of the right ventricle. The resultant right ventricular cavity is smaller than normal, and there is a varying degree of tricuspid regurgitation that affects the severity of symptoms.[69]

Right ventricular output is usually decreased and is dependent on the size of the RV cavity as well as the severity of tricuspid valve regurgitation. **Children with minimal tricuspid regurgitation generally have minimal symptoms and clinically do well.** However, **when severe tricuspid regurgitation is present, the right ventricle can only eject a trivial amount of antegrade flow into the pulmonary arteries. These neonates rely on the PDA to supply pulmonary blood flow and thus require prostaglandins to survive.** Infants with severe tricuspid regurgitation have significant shunting of deoxygenated blood from the right atrium into the left atrium through the foramen ovale, causing cyanosis. **Low right ventricular output in the neonate can improve with time as the PVR drops.**

DATA COLLECTION

Physical Findings

Cyanosis. **Varying degrees of cyanosis are present,** depending on the amount of right-to-left shunting at the foramen ovale and the amount of blood that enters the pulmonary circulation by the right ventricle. **In severe cases, the amount of**

pulmonary blood flow is markedly decreased, and these infants may be deeply cyanotic. Goal oxygen saturations should be greater than 75% and should be continuously monitored to ensure adequate pulmonary blood flow.

Heart Sounds. The second heart sound, S_2, is normal in the mildly affected infant, but the pulmonary component of S_2 may be diminished or inaudible in severely affected patients. The holosystolic murmur of tricuspid regurgitation is usually present at the cardiac apex and varies from a grade I/VI to a grade V/VI. Diastolic murmurs and triple or quadruple rhythms can also be heard.

Congestive Heart Failure. **Newborns with significant tricuspid regurgitation have CHF resulting from volume overload** (see Congestive Heart Failure earlier in this chapter).

Laboratory Data

Arterial Blood Gases. The Pao_2 may be normal to very low, depending on the amount of shunting at the atrial level. **Pao_2 values in the low 20s are not uncommon.**

Lactic Acid. Lactic acid levels should be normal. Elevated lactic acid levels can suggest a state of low cardiac output.

Chest X-Ray Examination. The chest x-ray examination shows cardiomegaly with decreased pulmonary vascularity. Massive cardiomegaly generally indicates severe tricuspid insufficiency.

Near-Infrared Spectrometry. NIRS monitoring is helpful to assess cerebral and splanchnic blood flow. Depression in NIRS can be a red flag for worsening cardiac output.

Electrocardiogram. An ECG shows abnormal P waves and can demonstrate various degrees of heart block. The QRS complex generally has a right bundle-branch block pattern. *Wolff-Parkinson-White* (WPW) (preexcitation) syndrome is frequently present, and dysrhythmias such as supraventricular tachycardia are common.

Echocardiogram. **A two-dimensional echocardiogram is diagnostic.** Doppler interrogation and color-flow mapping are very useful in evaluating the degree of tricuspid insufficiency, the amount of antegrade blood flow through the pulmonary valve, and shunting at the atrial level.

Cardiac Catheterization. Cardiac catheterization is not generally performed unless a question about the differential diagnosis exists (to rule out pulmonary atresia).

TREATMENT

Medical Management. Medical management is aimed at **supporting the neonate through the initial period of transitional circulation.** Because of elevated PVR, pulmonary blood flow may be severely limited, with profound hypoxemia and acidosis. **PGE1 may be required to maintain a patent ductus arteriosus. Providing a high level of supplemental oxygen, providing inhaled nitric oxide, and maintaining a mild respiratory alkalosis may help decrease PVR and promote antegrade pulmonary blood flow.** Sildenafil may also be helpful to reduce right ventricular afterload and improve forward flow of blood across the pulmonary valve.[1]

Ebstein anomaly is often associated with WPW syndrome and supraventricular tachycardia. Arrhythmia medications may be necessary to control rhythm abnormalities.

Surgical Treatment. Surgical treatment for Ebstein's anomaly is generally reserved for the severely symptomatic patient. The procedure, performed through a median sternotomy incision, involves repositioning the tricuspid valve and an annuloplasty to improve the competency of the valve. In addition, plication of the atrialized ventricle is often performed. Replacing the tricuspid valve may be necessary. In severe cases, a *Blalock-Taussig shunt* (BT shunt) is placed to provide pulmonary blood flow if prostaglandin infusion cannot be removed without causing severe cyanosis. This may lead a patient fully or partially down the single-ventricle pathway, with subsequent bidirectional *Glenn* and *Fontan* surgeries.

COMPLICATIONS AND RESIDUAL EFFECTS

Ebstein anomaly can be associated with pulmonary hypoplasia because the massively enlarged right heart in utero can prevent normal pulmonary development. Other complications include tricuspid insufficiency and dysrhythmias.

PROGNOSIS AND FOLLOW-UP

The prognosis usually depends on the severity of the tricuspid regurgitation (TR). The severity of the TR may improve in the early neonatal period as the PVR decreases and right ventricular output increases. The prognosis for mild Ebstein anomaly is favorable. Although surgery has been used successfully in the more severe forms of Ebstein anomaly, the prognosis is less favorable in

patients requiring surgical intervention. **The prognosis for neonates presenting with profound cyanosis caused by Ebstein anomaly is grave.** Long-term cardiology follow-up is necessary, and visits may be more frequent if arrhythmias are persistent.

Persistent Pulmonary Hypertension in the Newborn

PHYSIOLOGY

Infants with abnormally elevated PVR have persistent pulmonary hypertension of the newborn (PPHN) or persistent fetal circulation. These infants are generally hypoxic and acidotic but usually do not have severe pulmonary parenchymal disease or underlying cardiac disease. **These infants have a right-to-left shunt at the ductal and atrial levels.**

DATA COLLECTION

History. PPHN is usually associated with severe antepartum or peripartum conditions that involve hypoxia reflected by low Apgar scores (see Chapter 23). **These infants are generally term or late preterm and are symptomatic within the first hours after birth.** Associated findings may include polycythemia, hypoglycemia, or an anatomic abnormality such as a congenital diaphragmatic hernia.

Physical Findings

Cyanosis. The milder cases of PPHN have **minimal transient tachypnea and cyanosis associated with stress (crying or feeding). Severe cases demonstrate marked cyanosis, tachypnea, acidosis, and decreased peripheral perfusion.**

Heart Sounds. A loud pulmonary component of S_2 and occasionally the systolic ejection murmur of tricuspid regurgitation is heard.

Congestive Heart Failure. Infants with PPHN may have CHF because of pressure overload of the right ventricle (see Congestive Heart Failure earlier in this chapter).

Laboratory Data

Arterial Blood Gases. Arterial blood gas values demonstrate acidosis, hypoxia, and increased $Paco_2$. **If a blood gas measurement is obtained simultaneously from the right radial artery (preductal) and from the descending aorta with an umbilical artery catheter (postductal), the right-to-left shunt at the ductal level can be documented.** If blood gas measurements are repeated after intubation and pharmacologic intervention (see Treatment earlier in this chapter), the degree of hypoxia is often reduced.

Pulse Oximetry. Simultaneous preductal and postductal transcutaneous oxygen measurements may also be helpful to monitor.

Chest X-Ray Examination. The chest x-ray examination may demonstrate mild cardiomegaly with normal pulmonary vascular markings. The lung fields may be clear.

Electrocardiogram. The ECG frequently is normal but may demonstrate right ventricular hypertrophy.

Echocardiogram. An echocardiogram is helpful to rule out a cyanotic cardiac lesion. Evaluating the right ventricular and pulmonary artery pressures by Doppler interrogation and the degree of right-to-left shunting at the atrial and ductal levels is also helpful.

Cardiac Catheterization. Cardiac catheterization usually is not performed.

TREATMENT

Medical Management. See Chapter 23.

D-Transposition of the Great Arteries

PHYSIOLOGY

D-transposition of the great arteries (Fig. 24.11) is one of the most common forms of serious heart disease. **The aorta arises from the right ventricle, receives unoxygenated systemic venous blood, and returns this blood to the systemic arterial circulation. The pulmonary artery arises from the left ventricle, receives oxygenated pulmonary venous blood, and returns this blood to the pulmonary circulation. This creates a situation of "parallel circulations," which requires shunting of blood between the parallel circulations for survival. The only mixing of oxygenated and unoxygenated blood occurs in the presence of associated lesions** (e.g., patent foramen ovale, ASD, PDA, or VSD). The extent of the mixing depends on the number, size, and position of the anatomic communications; the pressure differential between the two systems; and changes in the systemic and pulmonary vascular resistance. A small percentage of patients with transposition have an associated VSD, which helps with preoperative mixing between the two circulations but adds complexity to the surgical

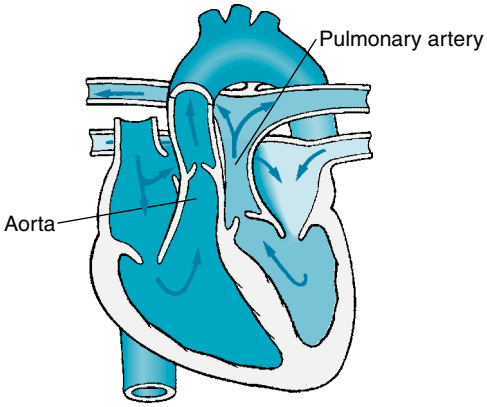

FIGURE 24.11 D-transposition of the great arteries. (Modified from Hockenberry MJ, Wilson D. *Wong's Essentials of Pediatric Nursing.* 8th ed. St Louis: Mosby; 2009.)

repair. The d-transposition anomaly can occur by itself or can be associated with other cardiac defects (e.g., pulmonary stenosis).

DATA COLLECTION

History. Transposition of the great arteries is more prevalent in males and is typically found in infants who are full term. The etiology of this congenital heart lesion is not well understood. Genetic defects are rarely associated, extracardiac anomalies are rarely present, and the pathogenesis is thought to be different from other conotruncal abnormalities.[89]

Physical Findings

Cyanosis. These infants are usually **cyanotic within the first hours of life, leading to their early diagnosis. Cyanosis is present in varying degrees, depending on the amount of intracardiac mixing present. Cyanosis may be mild if the mixing occurs through a significant VSD or PDA. Cyanosis is profound with an intact ventricular septum or a closing PDA.** Only a certain amount of oxygenated blood can reach the systemic circulation, and administration of additional oxygen does not improve this situation.

Cyanosis is exacerbated by neonatal stressors (crying, feeding, or exposure to cold temperatures). If the Pa_{O_2}, measured at rest in room air, is not greater than 35 mm Hg or if persistent metabolic acidosis is present, inadequate intracardiac mixing should be suspected. Initiation of PGE1 is mandatory. In addition, an emergency cardiac catheterization procedure to enlarge the interatrial communication may be lifesaving. Enlargement of the atrial communication is done by balloon septostomy (Rashkind procedure) and is performed to improve mixing between the two parallel circulations.

Oxygenation monitoring by pulse oximetry should reveal saturations greater than 75% due to a complete mixing lesion. Oxygen and ventilation support should be given to maintain this level of saturation.

Heart Sounds. The aorta arises from the anterior (right) ventricle, and the closure of the aortic valve is easily heard. The S_2 is single with an increased intensity. Murmurs, if present, are usually those of associated lesions.

Congestive Heart Failure. Congestive heart failure is usually not present.

Laboratory Data

Arterial Blood Gases. In neonates with transposition of the great arteries and an intact ventricular septum, **a very low Pa_{O_2} (15 to 20 mm Hg) with normal Paco2 and mild metabolic acidosis are often seen.**

Lactic Acid. Lactic acid levels should be normal if adequate intracardiac mixing is present preoperatively.

Basic Metabolic Panel. Electrolytes should be normal. Following renal function to ensure adequate preload and hydration can be important for ensuring hemodynamic stability with this mixing lesion.

Complete Blood Count. Anemia can worsen hypoxemia with mixing cardiac lesions. Intermittent evaluation of hemoglobin and hematocrit should be performed, and aiming for a higher baseline is clinically helpful.

Chest X-Ray Examination. The chest x-ray examination may be normal or demonstrate either decreased or increased pulmonary vascularity. The classically described "egg on a string" cardiac silhouette may be present; however, this finding is not diagnostic.

Electrocardiogram. The ECG may be normal or demonstrate right ventricular hypertrophy.

Echocardiogram. The echocardiogram is diagnostic. Special attention is directed to the size of the ASD, the size of the PDA, associated lesions, and the coronary arteries.

Near-Infrared Spectrometry. NIRS monitoring is used to assess cardiac output and is especially helpful in the setting of a critical mixing lesion.

Cardiac Catheterization. Cardiac catheterization may be necessary to perform a balloon atrial septostomy to improve intra-atrial mixing. A catheterization to delineate the coronary artery anatomy is not usually required because this can be accurately evaluated by transthoracic echocardiogram.

TREATMENT

Medical Management. **Serial venous and arterial pH measurements should be obtained to rule out the presence of a persistent metabolic acidosis that would suggest inadequate intracardiac mixing. PGE1 infusion is used to maintain ductal patency.**

Surgical Treatment. The *arterial switch procedure* is the treatment for d-transposition of the great arteries. This procedure, performed through a median sternotomy incision, involves transection of the main pulmonary artery and the aorta above the respective valves.[65] The pulmonary artery is anastomosed to the right ventricle, and the aorta is anastomosed to the left ventricle (the aortic valve becomes a functional pulmonary valve, and the pulmonary valve becomes a functional aortic valve). The coronary arteries are resected with a button of surrounding tissue and reanastomosed to the supravalvular area of the ascending aorta.[70] Additional defects are also repaired, including closure of atrial or ventricular defects and ligation of the PDA. **Surgery is usually performed in the first week of life.**

COMPLICATIONS AND RESIDUAL EFFECTS

Complications and residual effects of the arterial switch procedure include (1) dysrhythmias, (2) myocardial ischemia and infarction, and (3) aortic or pulmonary supravalvular stenosis.

PROGNOSIS AND FOLLOW-UP

After successful arterial switch operation, the long-term prognosis is good. Lifetime cardiology follow-up is mandatory to monitor for common longer-term problems, such as progressive valvar regurgitation.

Tetralogy of Fallot

PHYSIOLOGY

Tetralogy of Fallot is the most common cyanotic CHD (Fig. 24.12). The four components of tetralogy of Fallot are a VSD, an overriding of the ascending aorta, obstruction of the right ventricular outflow tract, and right ventricular hypertrophy. Although these patients have a large VSD, they traditionally do not have symptoms of CHF because their pulmonary circulation is protected from overcirculation by the right ventricular outflow tract obstruction.

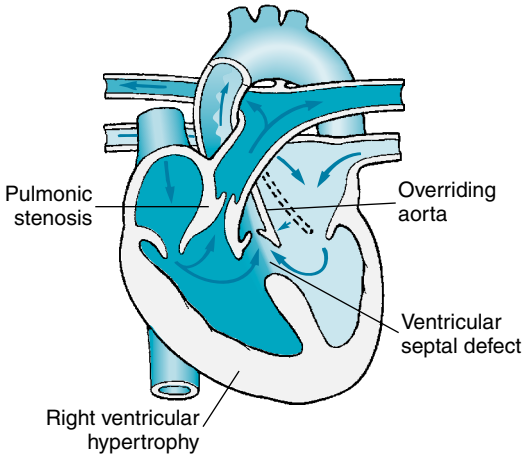

FIGURE 24.12 Tetralogy of Fallot. (Modified from Hockenberry MJ, Wilson D. *Wong's Essentials of Pediatric Nursing*. 8th ed. St Louis: Mosby; 2009.)

The degree of right ventricular outflow tract obstruction can vary significantly. A minority of children have too much pulmonary blood flow due to minimal right ventricular outflow tract obstruction. CHF will develop over time, much like a child with a simple large VSD (see Ventricular Septal Defect earlier in this chapter). **A child with minimal right ventricular outflow tract obstruction is sometimes called a "pink tet" and will not be cyanotic. On the other end of the spectrum, a child with severe right ventricular outflow tract obstruction may have too little pulmonary blood flow. In this case the ductus arteriosus may be vital to augment blood flow to the lungs, and the child may need prostaglandins and neonatal surgery.** Most children fall somewhere in the middle of the spectrum and have sufficient pulmonary blood flow but no CHF symptoms.

DATA COLLECTION

Physical Findings. Symptomatology in these infants relates to the degree of right ventricular outflow tract obstruction. **Newborns who are symptomatic usually have severe right ventricular outflow tract obstruction.**

Cyanosis. **The predominant intracardiac shunt is usually right to left; therefore, most infants with tetralogy of Fallot are cyanotic.** Varying degrees of cyanosis are present, depending on the amount of right-to-left intracardiac shunting and the amount of blood that enters the pulmonary circulation by the right ventricle. In severe cases, pulmonary blood flow is markedly decreased, and these infants are deeply cyanotic. However, if the right ventricular outflow obstruction is only mild or moderate, the intracardiac shunt can be left to right, and the infant will not be cyanotic.

Infants with tetralogy of Fallot are at risk for hypercyanotic (or "tet") spells. These spells consist of severe and intractable cyanosis, irritability, pallor, tachypnea, flaccidity, and possibly loss of consciousness. These spells are thought to be secondary to a transient increase in the obstruction of the right ventricular outflow tract, resulting in minimal or no pulmonary blood flow. See Medical Management later in the chapter for information on treatment. **True hypercyanotic spells rarely occur, but one significant spell should prompt early surgery because such spells can be life-threatening.**

Baseline oxygen saturations should be obtained before discharge from the neonatal intensive care unit. Oxygenation monitoring at home may be used if a BT shunt is placed before discharge.

Heart Sounds. A grade II to IV/VI harsh systolic murmur at the mid- to upper left sternal border is usually present but is diminished or absent during a hypercyanotic spell. The S_2 is usually loud and single (representing aortic closure).

Congestive Heart Failure. CHF is uncommon in tetralogy of Fallot. In rare "pink tet" cases, as described earlier, clinical symptoms will resemble a simple large VSD, and CHF will develop over time.

Laboratory Data

Arterial Blood Gases. The $Paco_2$ and pH are normal. The Pao_2 is normal if the pulmonary stenosis is mild and there is little right-to-left shunting at the ventricular level. If the pulmonary stenosis is more severe, the amount of right-to-left shunting is substantial, and the Pao_2 will be low.

Complete Blood Count. **Anemia can worsen hypoxemia with mixing cardiac lesions. Intermittent evaluation of hemoglobin and hematocrit should be performed, and aiming for a higher baseline is clinically helpful.**

Chest X-Ray Examination. The classic chest x-ray examination suggesting tetralogy of Fallot is a "boot-shaped heart" without cardiomegaly. However, this classic chest x-ray pattern described is not common in the newborn. Pulmonary vascularity is usually either normal or decreased.

Electrocardiogram. The ECG demonstrates right ventricular hypertrophy.

Echocardiogram. **An echocardiogram is diagnostic.** Doppler interrogation helps define the degree and level of pulmonary stenosis. Color-flow mapping can help delineate the size of the VSD and the direction of blood flow across the atrial and ventricular septa.

Cardiac Catheterization. Cardiac catheterization is not generally required.

TREATMENT

Medical Management. Immediate medical management is not generally required. Most infants with tetralogy of Fallot are stable and require no interventions or medications. **Neonates with severe right ventricular outflow tract obstruction may require PGE1 infusion to keep the ductus arteriosus open.**

Medical management of hypercyanotic (or "tet") spells includes **knee-chest positioning, oxygen, morphine, and fluid boluses.** If at home, parents should be instructed to calm the infant quickly and bring the infant's knees to his or her chest. A beta blocker (propranolol) and systemic vasopressor may also be tried. Rarely, emergent surgery is needed when medical management is insufficient.

Surgical Treatment. Total correction of tetralogy of Fallot involves intracardiac repair with patch closure of the large VSD and relief of the right ventricular outflow obstruction performed through a median sternotomy incision. A patch across the pulmonary valve annulus is often necessary. Contraindications include small size of the infant, anomalous left anterior descending coronary artery, and hypoplastic pulmonary arteries.

Total surgical repair of tetralogy of Fallot is not usually carried out in the neonatal period. Surgery is usually performed electively within the first year of life.[46,47] If surgical intervention in infancy is warranted (i.e., the infant is severely hypoxic because of inadequate pulmonary blood flow), a systemic-to-pulmonary

shunt (Blalock-Taussig (BT) shunt) is performed to provide adequate pulmonary blood flow until complete surgical repair at a later date.

COMPLICATIONS AND RESIDUAL EFFECTS

Surgical repair of tetralogy of Fallot often requires a patch across the pulmonary valve annulus. This makes the pulmonary valve dysfunctional and leaves the child with no functional valve in the pulmonary position. "Free" pulmonary regurgitation can be tolerated for decades with minimal symptoms, but right ventricular dilation gradually occurs, and right ventricular function can eventually be affected.[47] Pulmonary valve replacement is being performed earlier in life (teenage years), and advancements are moving toward performing pulmonary valve replacements by a cardiac catheterization procedure and tissue bioengineered valves that may one day grow with the patient.

PROGNOSIS AND FOLLOW-UP

The prognosis after surgical repair is good, although most children are left without a pulmonary valve. Severe pulmonary regurgitation can cause functional limitations in activities of daily living for some patients, and the right ventricular dilation secondary to severe pulmonary regurgitation can lead to ventricular arrhythmias and sudden death. Long-term follow-up after corrective surgery is necessary, and most children require a future surgery or intervention for pulmonary valve replacement.[77]

Pulmonary Atresia With Intact Ventricular Septum

PHYSIOLOGY

Pulmonary atresia is characterized by complete agenesis of the pulmonary valve. This lesion produces severe signs or symptoms soon after birth and is not compatible with life unless there is an associated interatrial communication and an additional pathway of entry for blood into the pulmonary circulation (through a PDA or collateral blood flow). **Because flow to the lungs usually depends on a PDA, death occurs when this structure closes.** The right ventricle is usually hypoplastic but may be normal or dilated, depending on the degree of tricuspid insufficiency present. The presence of sinusoidal connections between the right ventricle and the coronary arteries is associated with poorer long-term survival.[19]

DATA COLLECTION

Physical Findings

Cyanosis. **Cyanosis is always present due to reduced pulmonary blood flow and atrial right-to-left shunting.** Acceptable oxygen saturations are greater than 75% on room air when on PGE1 infusion.

Heart Sounds. The S_2 is single, and a soft systolic murmur may be heard as a result of either the PDA or tricuspid insufficiency.

Congestive Heart Failure. CHF is not present unless there is significant tricuspid insufficiency (see Congestive Heart Failure earlier in this chapter).

Laboratory Data

Arterial Blood Gases. The pH and $PaCO_2$ are usually within the normal range. **The PaO_2 is usually very low (20 to 30 mm Hg) unless there is a large shunt at the ductal or bronchial collateral level.** In some cases, the amount of pulmonary blood flow is insufficient, causing a low pH due to metabolic acidosis.

Complete Blood Count. **Anemia can worsen hypoxemia with mixing cardiac lesions.** Intermittent evaluation of hemoglobin and hematocrit should be performed, and aiming for a higher baseline is clinically helpful.

Chest X-Ray Examination. Heart size is normal unless tricuspid insufficiency causes cardiomegaly. Pulmonary vascularity is either decreased or normal, depending on the amount of shunting through the PDA or collateral blood flow.

Near-Infrared Spectrometry. NIRS can be helpful for monitoring in the immediate stabilization period, especially if the defect was not prenatally diagnosed.

Electrocardiogram. The ECG is usually normal but may demonstrate left ventricular hypertrophy.

Echocardiogram. A two-dimensional echocardiogram is diagnostic. Color-flow mapping can suggest the presence of coronary artery sinusoids.

Cardiac Catheterization. Cardiac catheterization may be performed if intervention to open the pulmonary valve is possible. Catheter intervention on the pulmonary valve is not possible if right-ventricle–dependent coronary sinusoids are present or if the

pulmonary valve annulus is extremely small. Balloon atrial septostomy may be performed at the time of catheterization but is rarely needed.

TREATMENT

Medical Management. **PGE1 is used to maintain the patency of the ductus arteriosus until surgical intervention** (see General Treatment Strategy earlier in this chapter).

Surgical Treatment. When the right heart structures are adequately sized, cardiac catheterization to balloon dilate the pulmonary valve may be the only intervention required in the neonatal period. However, if the pulmonary valve dilation is not possible or if it does not create enough pulmonary blood flow, a systemic-to-pulmonary shunt such as the Blalock-Taussig operation is performed. In cases where the right ventricle and tricuspid valve are not severely hypoplastic and coronary artery sinusoids are not present, a pulmonary valvotomy or right ventricular outflow tract reconstruction may also be performed in addition to a shunt. This establishes an open pathway through the pulmonary valve area and establishes blood flow through the right ventricle and pulmonary artery to promote the growth of the right heart. The pulmonary valvotomy and pulmonary outflow patch procedures are performed through a median sternotomy incision.

COMPLICATIONS AND RESIDUAL EFFECTS

Complications and residual effects of the Blalock-Taussig operation include CHF from a large shunt, inadequate pulmonary blood flow due to a too small shunt, shunt stenosis, and sudden death due to sudden shunt obstruction. The mortality rate in infants is 25% or higher as children go through long-term surgical and medical follow-up.[5,83]

PROGNOSIS AND FOLLOW-UP

Pulmonary atresia is fatal without surgical intervention. The size and function of the right ventricle and tricuspid valve determine if a child can eventually have a two-ventricle repair (where the right side of the heart functions independently and performs its normal job) or end up with single-ventricle physiology (where the right side of the heart is functionless and the left side of the heart does all the work) or something in the middle. The long-term prognosis depends on the original anatomy and the surgeries performed.[1] Multiple surgeries and long-term cardiac follow-up are always necessary.

Total Anomalous Pulmonary Venous Return

PHYSIOLOGY

Total anomalous pulmonary venous return (TAPVR) occurs when all the pulmonary veins do not drain normally into the left atrium. Instead, the pulmonary veins drain into an abnormal vein (or veins) connecting to the systemic venous system (superior vena cava [SVC], inferior vena cava [IVC], or coronary sinus). The systemic veins drain to the right atrium, so the oxygenated pulmonary venous blood ends up on the right side of the heart. The four main varieties of TAPVR are as follows:

- Supracardiac (most common) (Fig. 24.13), in which the four veins join behind the heart, travel superiorly, and the drainage is to the SVC
- Infracardiac, in which the four veins join behind the heart, pass inferiorly through the diaphragm, and connect to the portal venous system or IVC
- Intracardiac, in which the pulmonary veins drain into the coronary sinus or directly into the RA
- Mixed, in which at least two of the previous types of anomalous pulmonary drainage occur in the same child (e.g., right pulmonary veins return to the SVC, and left pulmonary veins drain to the coronary sinus)

Each of the various types of anomalous drainage can occur with or without obstruction along the pulmonary venous pathway. The presence or absence of obstruction profoundly affects the clinical course. **Because all pulmonary venous return (oxygenated blood) ultimately enters the RA (as opposed to the LA), a right-to-left shunt at the atrial level is necessary to sustain life.**

DATA COLLECTION

Physical Findings

Cyanosis. **Infants with TAPVR are frequently cyanotic, with saturations lower than 80% if obstructed venous return is present.** Obstructed TAPVR causes pulmonary venous congestion,

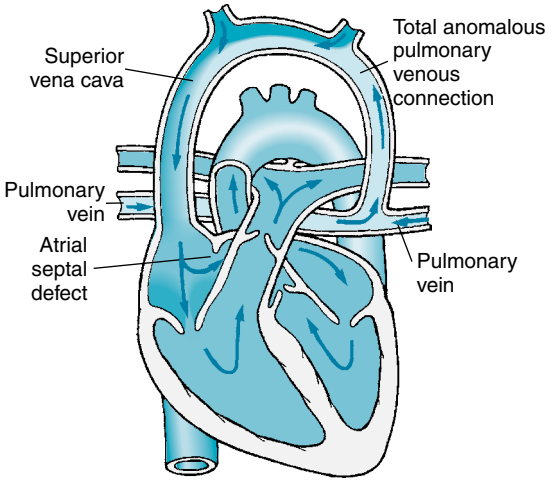

FIGURE 24.13 Total anomalous pulmonary venous return. (Modified from Hockenberry MJ, Wilson D. *Wong's Essentials of Pediatric Nursing.* 8th ed. St Louis: Mosby; 2009.)

which leads to reduced pulmonary blood flow and pulmonary edema, both of which also contribute to cyanosis.

Heart Sounds. **Murmurs are rarely heard in infants with TAPVR.**

Congestive Heart Failure. Infants with **unobstructed TAPVR usually show signs of CHF** (see Congestive Heart Failure earlier in this chapter). Infants with obstructed TAPVR have pulmonary venous congestion that can be life-threatening.

Laboratory Data

Arterial Blood Gases. The pH and $PaCO_2$ are usually normal. The PaO_2 is usually low but may be within the normal range if there is a large amount of pulmonary blood flow (always associated with severe congestive heart failure). If pulmonary venous obstruction is present, pulmonary blood flow is reduced, and the PaO_2 is low.

Chest X-Ray Examination. If the TAPVR is obstructed, the chest x-ray examination will demonstrate pulmonary venous congestion without cardiomegaly. If the TAPVR is unobstructed, the chest x-ray examination will demonstrate a marked increase in pulmonary vascularity and cardiomegaly.

Electrocardiogram. An ECG may demonstrate right axis deviation, RV hypertrophy, and RA enlargement.

Echocardiogram. **TAPVR is easily diagnosed by echocardiogram.** In two-dimensional imaging, an extravascular structure is seen behind the small left atrium. Color-flow mapping is helpful to trace the abnormal pulmonary venous connection to the SVC, coronary sinus, IVC, or mixed locations. The right-to-left shunting across the atrial septum can also be demonstrated.

Cardiac Catheterization. Cardiac catheterization is not usually required.

TREATMENT

Medical Management. **Obstructed TAPVR is a surgical emergency.** Nonobstructed TAPVR is usually stable enough to await elective surgery and rarely requires medical management.

Surgical Treatment. Surgical correction of TAPVR depends on the variety. The supracardiac and infracardiac varieties require surgical reimplantation of the common vein into the LA. Intracardiac TAPVR can usually be surgically repaired by realigning the atrial septum during closure of the ASD and directing the anomalous veins to the left atrial side.[37] All repairs are performed through a median sternotomy incision.

COMPLICATIONS AND RESIDUAL EFFECTS

Complications and residual effects include pulmonary venous obstruction and dysrhythmias. The mortality rate varies from 10% to 25% in infancy.[45]

PROGNOSIS AND FOLLOW-UP

Infants with nonobstructed TAPVR generally do well if the lesion is recognized early and early corrective surgery is performed. The prognosis for obstructed TAPVR is less favorable despite early surgical intervention. Pulmonary vein stenosis is a rare but frequently a progressive and lethal development that can also occur over time.

Tricuspid Atresia

PHYSIOLOGY

In tricuspid atresia, there is complete agenesis of the tricuspid valve, with no direct communication between the right atrium and right ventricle. Systemic venous blood entering the

right atrium is shunted through a patent foramen ovale or ASD into the left atrium. If a large VSD is present, the RV and pulmonary arteries may be normal in size. If the ventricular septum is intact but a large PDA is present, the right ventricular cavity is usually hypoplastic, but the pulmonary arteries may be slightly decreased or normal in size (Fig. 24.14). About 30% to 50% of these infants will have other associated anomalies, such as transposed great arteries and coarctation of the aorta.[87]

DATA COLLECTION

Physical Findings

Cyanosis. **Cyanosis is always present, although the degree of cyanosis varies. Newborns will have marked cyanosis if the pulmonary blood flow is compromised.** Oxygen saturations should be greater than 75% due to complete mixing of the oxygenated and deoxygenated blood within the heart.

Heart Sounds. Murmurs of associated shunts or lesions (VSD, PDA, pulmonary stenosis, etc.) may be present.

Congestive Heart Failure. CHF may be present with a large shunt (PDA or VSD) (see Congestive Heart Failure earlier in this chapter).

Laboratory Data

Arterial Blood Gases. The pH and $Paco_2$ usually are normal. The Pao_2 may vary from near normal if there is a large VSD or PDA to extremely low if there is limited shunting into the pulmonary system.

Complete Blood Count. Anemia can worsen hypoxemia with mixing cardiac lesions. Intermittent evaluation of hemoglobin and hematocrit should be performed, and aiming for a higher baseline is clinically helpful.

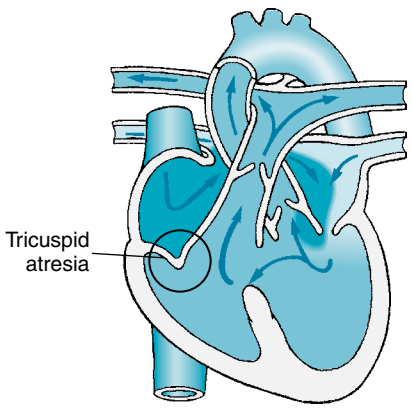

FIGURE 24.14 Tricuspid atresia. (Modified from Hockenberry MJ, Wilson D. *Wong's Essentials of Pediatric Nursing.* 8th ed. St Louis: Mosby; 2009.)

Chest X-Ray Examination. A chest x-ray examination may show a normal heart size or cardiomegaly. Pulmonary vascularity may be normal, decreased, or increased, depending on the amount of pulmonary blood flow.

Electrocardiogram. An ECG usually demonstrates left axis deviation with a counterclockwise loop, a superior axis in the frontal plane, and LV electrical dominance.

Echocardiogram. **Two-dimensional echocardiography is the gold standard for diagnosing tricuspid valve atresia,** as well as any associated anomalies. Color-flow mapping can identify the right-to-left shunt at the atrial level and the presence of a VSD, PDA, or valve stenosis.

Cardiac Catheterization. Cardiac catheterization is rarely required unless balloon atrial septostomy is necessary to improve intra-atrial mixing.

TREATMENT

Medical Management. **Immediate medical management is aimed primarily at maintaining adequate pulmonary blood flow.** In the usual case of severely limited pulmonary blood flow, **PGE1 infusion maintains pulmonary perfusion via the ductus arteriosus.**

Surgical Treatment. Complete repair of this heart defect is not possible because the mitral and tricuspid valves are necessary to achieve a two-ventricle circulation. Instead, **the single-ventricle palliative surgeries are necessary to allow the single left ventricle to perform all the work of the heart.** This palliative route may start with a systemic-to-pulmonary shunt (such as the Blalock-Taussig operation) if there is insufficient pulmonary blood flow, a pulmonary artery band placement if there is excessive pulmonary blood flow, or no surgery if there is a balanced circulation. Two subsequent staged surgeries are required, the *bidirectional Glenn* and *Fontan* procedures. Any associated defects are also repaired.

COMPLICATIONS AND RESIDUAL EFFECTS

If a BT shunt is required for pulmonary blood flow, interstage complications can include shunt occlusion and possible sudden death. Long-term

single-ventricle complications and residual effects include heart failure, chronic pleural effusions, renal or liver failure, persistent shunts, conduit obstruction, dysrhythmia, plastic bronchitis, and protein-losing enteropathy.[80] Survival through all three palliative surgeries depends on institutional experience and the specifics of each individual case, but the survival rate is generally up to 85% with a single-left-ventricle anatomy.[21]

PROGNOSIS AND FOLLOW-UP

The short-term prognosis for tricuspid atresia is guarded. Longer term, it is not known how long children can live with only a single ventricle performing all the work of the heart. Heart transplantation may eventually be performed. Long-term cardiology follow-up is a necessity.

Truncus Arteriosus

PHYSIOLOGY

Truncus arteriosus is characterized by one great artery arising from the left and right ventricles and, usually, an overriding VSD. This common artery has one valve and gives rise to (in order) the coronary arteries, the pulmonary arteries, and the brachiocephalic arteries. A second semilunar valve is not present. A coexisting VSD is present in more than 98% of cases. Truncus arteriosus is classified into three types, depending on the origins of the pulmonary arteries:

1. Type I—a short, main pulmonary artery arises from the common trunk that bifurcates into the right and left pulmonary arteries.
2. Type II—the right and left pulmonary arteries arise directly from the posterior surface of the common trunk.
3. Type III—the right and left pulmonary arteries arise directly from the lateral walls of the common trunk (Fig. 24.15).

In truncus arteriosus, the common trunk receives a mixture of unoxygenated blood from the RV and oxygenated blood from the left ventricle. Blood flow to the lungs varies with the type of truncus but is usually increased and at systemic-level pressure.

The ductus arteriosus is usually absent. A right aortic arch may be present. Extracardiac anomalies are present in 20% to 40% of cases, and 35% to 40% of neonates with truncus arteriosus have 22q11 deletion syndrome.[23]

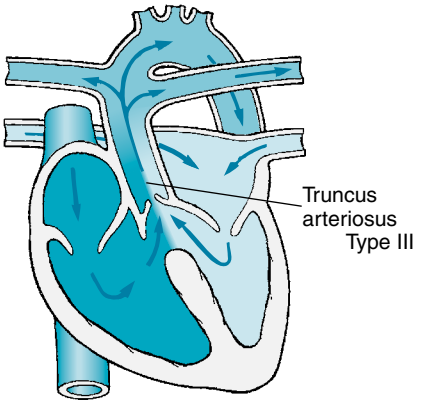

FIGURE 24.15 Truncus arteriosus type III. (Modified from Hockenberry MJ, Wilson D. *Wong's Essentials of Pediatric Nursing.* 8th ed. St Louis: Mosby; 2009.)

DATA COLLECTION

Physical Findings

Cyanosis. **Cyanosis may be present at birth but varies in intensity according to the amount of pulmonary blood flow.** Minimal cyanosis indicates adequate pulmonary blood flow.

Heart Sounds. The first heart sound, S_1, is normal, but the S_2 is single and loud because of the single valve of the common trunk. A loud systolic ejection click is frequently heard.

A loud pansystolic murmur maximal at the lower left sternal border that radiates to the entire precordium is commonly heard. A mid-diastolic rumble may be present. If the truncal valve is insufficient, a blowing diastolic murmur may be heard. A wide pulse pressure is often present.

Congestive Heart Failure. The presence of CHF depends on the amount of pulmonary blood flow. **Persistently high pulmonary arteriolar resistance in the first few weeks of life limits excessive pulmonary blood flow, and CHF may not be present until the PVR drops.** However, if the truncal valve has significant stenosis or regurgitation, CHF develops earlier due to pressure or volume overload (see Congestive Heart Failure earlier in this chapter).

Laboratory Data

Arterial Blood Gases. The pH and $Paco_2$ are usually normal. Pao_2 may be near normal if there is

adequate pulmonary blood flow (usually associated with severe CHF).

Complete Blood Count. Anemia can worsen hypoxemia with mixing cardiac lesions. Intermittent evaluation of hemoglobin and hematocrit should be performed, and aiming for a higher baseline is clinically helpful.

Chest X-Ray Examination. Cardiomegaly, displaced pulmonary arteries, and increased vascular markings are typical findings on the chest x-ray examination.

Electrocardiogram. Combined ventricular hypertrophy is most often seen on an ECG. Left atrial enlargement is also commonly found.

Echocardiogram. **A two-dimensional echocardiogram is diagnostic.** Particular attention is paid to the number of truncal valve leaflets, the presence of truncal valve insufficiency or stenosis, and the location of the bilateral branch pulmonary arteries.

Cardiac Catheterization. A cardiac catheterization is rarely necessary.

TREATMENT

Medical Management. **Medical management of these infants consists of stabilizing and treating CHF when present.** Calcium should be closely monitored because of the possibility of 22q11 deletion syndrome.

Surgical Treatment. Repair of truncus arteriosus consists of separating the pulmonary arteries from the common trunk, closing the VSD with a patch that dedicates the common trunk to the LV, and inserting an RV–to–pulmonary artery valve conduit. The use of homograft conduits for the repair of truncus arteriosus is common. Total repair of truncus arteriosus is performed through a median sternotomy incision.

COMPLICATIONS AND RESIDUAL EFFECTS

Complications and side effects include pulmonary vascular disease, residual shunts, truncal valve insufficiency or stenosis, and RV-PA conduit obstruction. The mortality rate is 10% to 20% and is dependent on the anatomy and severity of truncal valve abnormality.[61,73]

PROGNOSIS AND FOLLOW-UP

The longer-term outcome depends on the competency of the truncal valve. Severe truncal valve regurgitation or stenosis after truncus arteriosus repair is not well tolerated and may require reintervention.[16,81] Associated extracardiac anomalies or genetic abnormalities also significantly affect prognosis. Lifelong follow-up is always required.

Hypoplastic Left Heart Syndrome

PHYSIOLOGY

Hypoplastic left heart syndrome (HLHS) represents a clinical spectrum that includes severe coarctation of the aorta, severe aortic valve stenosis or atresia, LV hypoplasia, and severe mitral valve stenosis or atresia (Fig. 24.16). **Blood flow to the body is dependent on right-to-left shunting through the PDA. Ductal closure results in poor systemic perfusion and death. An atrial septal communication is also required to allow oxygenated pulmonary venous blood to shunt from the LA into the RA; a restrictive atrial septal defect can be life-threatening and require emergent cardiac catheterization intervention.**

DATA COLLECTION

Physical Findings

Cyanosis. **These infants are cyanotic, with a goal oxygen saturation in the range of 75% to 85%.** Blood flow to the lungs and systemically is in a delicate balance, so too much blood flow to the lungs results in poor systemic perfusion. This results in high oxygen saturations but marked poor perfusion, vasoconstriction, poor urine output, and CHF. **Too little blood flow to the lungs through the PDA can cause pulmonary undercirculation and low oxygen saturations.**

Heart Sounds. A nonspecific systolic murmur is heard in some infants with HLHS. A single S_1 and S_2 may be appreciated.

Congestive Heart Failure. CHF is present as a result of RV volume and pressure overload (see Congestive Heart Failure earlier in this chapter).

Laboratory Data

Arterial Blood Gases. **The arterial blood gas may represent the single best indicator of hemodynamic stability. Low arterial saturation (75% to 80%) with normal pH indicates an acceptable balance of systemic and pulmonary blood flow with adequate peripheral perfusion. Elevated**

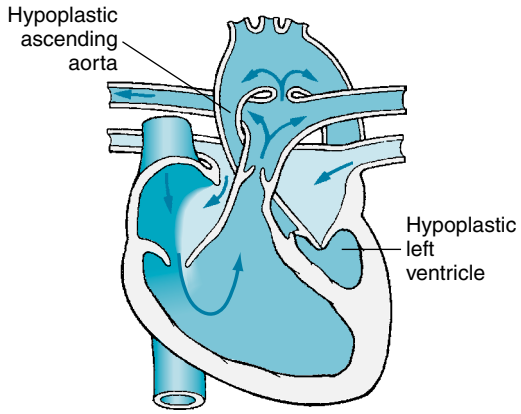

FIGURE 24.16 Hypoplastic left heart syndrome. (Modified from Hockenberry MJ, Wilson D. *Wong's Essentials of Pediatric Nursing.* 8th ed. St Louis: Mosby; 2009.)

oxygen saturation (greater than 90%) with acidosis represents significantly increased pulmonary and decreased systemic flow.

Complete Blood Count. Anemia can worsen hypoxemia with mixing cardiac lesions. Intermittent evaluation of hemoglobin and hematocrit should be performed, and aiming for a higher baseline is clinically helpful.

Brain-Natriuretic Peptide. BNP values may be helpful to differentiate respiratory or cardiac instability in neonates with HLHS. Values should be followed for trends rather than individual markers.

Chest X-Ray Examination. Cardiomegaly with increased pulmonary vascularity and pulmonary edema is seen on the x-ray examination.

Electrocardiogram. An ECG frequently demonstrates right axis deviation and right ventricular hypertrophy. However, the ECG may be normal.

Echocardiogram. An echocardiogram is diagnostic with a small left ventricular cavity and ascending aorta, mitral and aortic valve atresia or hypoplasia, and a dilated right ventricle. **Adequate atrial septal defect, patent ductus arteriosus, myocardial function, and degree of tricuspid regurgitation are essential parts of the echocardiogram.**

Near-Infrared Spectrometry Monitoring. NIRS monitoring is recommended to evaluate cerebral and systemic perfusion and monitor for low cardiac output.

Cardiac Catheterization. Cardiac catheterization carries a high risk in infants with hypoplastic left heart syndrome and is usually not necessary unless the atrial septal defect is not adequate for intra-atrial mixing. A balloon atrial septostomy and atrial septal stent placement can be performed if necessary.

TREATMENT

Medical Management. Pharmacologic maintenance of ductal patency with PGE1 with continuous infusion is required. Institutional practices vary, but the goal is a balanced pulmonary and systemic circulation by the use of volume expansion, inotropic support, and intubation. Maneuvers such as hypoventilation to increase PVR and redirect cardiac output to the body have been used. This may be a sign that cardiac surgery is necessary in an urgent manner due to an inability to balance the systemic and pulmonary circulation.

Surgical Treatment. Palliative cardiac surgeries are required for survival and occur over the first few years of life.[26] The *Norwood procedure* is performed in the neonatal period, consisting of enlargement of the atrial septal defect, ligation of the PDA, Damus-Kaye-Stansel (DKS) anastomosis of the pulmonary artery to the ascending aorta, aortic arch reconstruction, and creation of an aortopulmonary shunt (BT shunt) to provide pulmonary blood flow. Some centers use a hybrid approach with a PDA stent and bilateral pulmonary artery bands as a stage I palliation.[12,31] In the second stage, a *bidirectional Glenn* (anastomosis between the superior vena cava and the pulmonary arteries) is performed, and the aortopulmonary shunt is removed; this is usually performed at 5 to 9 months of age. The final stage is the *Fontan procedure,* which connects the inferior vena cava to the pulmonary arteries; this is generally done at 3 to 5 years of age.[26] Cardiac transplantation is an alternative surgical option, although infant donor hearts are rarely available. In some centers, the Norwood procedure is performed as a bridge to transplantation, allowing the infant to survive until a donor heart is available.

PROGNOSIS AND FOLLOW-UP

The longer-term outcome is variable and depends on associated factors such as a restrictive atrial septum, lung disease, genetic syndromes, and extracardiac anomalies. Turner syndrome, trisomy 13, trisomy 18, Holt-Oram, Smith-Lemli-Opitz, partial

trisomy 9, Jacobsen syndrome, and many others have been associated with HLHS. Since 2008 there has been an increased focus on improving interstage mortality after discharge from stage I Norwood (BT shunt) to stage II (Glenn), but this is still a high-risk time for infants with HLHS. There are advances with mobile technology (mHealth) during the interstage period, with reduced mortality and morbidity when compared with traditional interstage monitoring.[9] Current expectations are that up to 65% to 70% of newborns born today will survive all three palliative surgical procedures, but longer-term survival is not easily achieved.[21] Recently there have been case reports of HLHS patients having regenerative cellular strategies with autologous umbilical cord blood–derived cells at the second stage (Glenn surgery).[13] Although this research is in early phases without large clinical trials, the results are promising in feasibility trials. The results are encouraging for longer-term right ventricular function after cell-based therapy.

Heart Transplantation in Infants

For infants born with cardiomyopathy or uncorrectable CHD, heart transplantation may offer the only chance of long-term survival. Heart transplantation in infancy is severely limited by donor availability. There is a scarcity of donor hearts in this age and size group, so many infants on transplant lists die while waiting for donors. It is also important that families understand that heart transplantation requires lifelong medications, cardiac biopsies, hospitalizations for rejection of the organ or suspected infection (in the setting of the immunosuppression required after transplantation), and likely re-transplantation in the future.

Dysrhythmias

When evaluating an infant with a dysrhythmia, it is essential to assess simultaneously the electrophysiology and hemodynamic status. A neonate with poor perfusion and hypotension should first be treated for shock. A 12-lead ECG can then be done for definitive diagnosis of the type of dysrhythmia. When analyzing the ECG for the mechanism of dysrhythmia, a notation should be made in three main areas: (1) atrial and ventricular rates, (2) rhythm, and (3) QRS morphology.

PHYSIOLOGY

The development of the cardiac conduction system continues after birth, with a steady increase in the sympathetic innervation of the heart. This accounts for the observed heart-rate variability and the high frequency of benign dysrhythmias in the newborn. Premature ventricular beats (Fig. 24.17), premature atrial beats, brief episodes of ectopic atrial rhythms, wandering atrial pacemakers (Fig. 24.18), and even brief episodes of sinus arrest are all frequently seen in the newborn period. **The majority of these dysrhythmias do not require immediate treatment;** however, if they persist, the presence of CHD, sepsis, drug toxicity, persistent hypoxia, adrenal insufficiency, disorders of electrolyte and acid-base balance, hypoglycemia, and hypocalcemia should be considered.

All cardiac tissue is capable of generating a spontaneous depolarization. However, the sinoatrial (SA) node, atrioventricular (AV) node, and His-Purkinje system consist of specialized conductive tissue with rapid spontaneous depolarization. The SA node, located in the RA, is the normal pacemaker of the

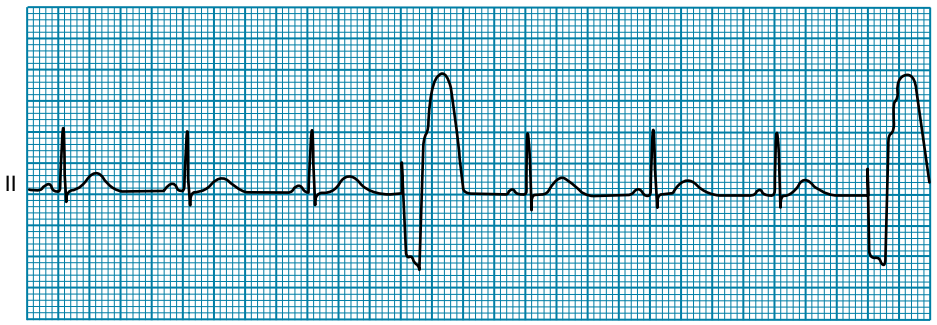

FIGURE 24.17 Premature ventricular beats.

heart because it has the fastest rate of spontaneous depolarization. If, however, the spontaneous depolarization of the SA node is delayed or slower than normal, an escape rhythm is generated by either the AV node or His-Purkinje system. These rhythms are called *nodal escape* or *ventricular escape,* respectively, and the heart rate set by these secondary pacing systems is slower than that of the SA node. Dysrhythmias also can originate from an automatic "ectopic" pacemaker located anywhere in the heart. These **ectopic pacemakers become more active in the presence of hypoxia, acidosis, digoxin toxicity, abnormal sympathetic nervous system stimulation, increased wall tension (CHF), or altered electrolyte balance.**

Drug therapy for dysrhythmias is based on the ability of certain medications to alter the electrophysiologic properties of cardiac tissue. One class of antidysrhythmic drugs directly increases the automaticity of certain cardiac fibers. Examples of such drugs are procainamide and lidocaine (see Table 24.3). Other drugs directly or indirectly affect the activity of the autonomic nervous system. Propranolol is a beta-adrenergic blocker and works in this fashion.

BENIGN DYSRHYTHMIAS: SINUS BRADYCARDIA, SINUS TACHYCARDIA, AND SINUS DYSRHYTHMIA

Of normal premature infants, up to 40% have brief episodes of sinus bradycardia (Fig. 24.19), sinus tachycardia, or sinus dysrhythmia (Fig. 24.20) that are benign and require no treatment. Healthy premature and term infants may have heart rates that range from 90 to 200 beats/min. Sustained heart rates (longer than 15 seconds) above or below this range should be evaluated with a 12-lead ECG and rhythm strip. The bedside monitor display is often contaminated with artifact that makes the accurate interpretation of dysrhythmias impossible. A 12-lead ECG provides necessary information that cannot be obtained from the bedside monitor alone.

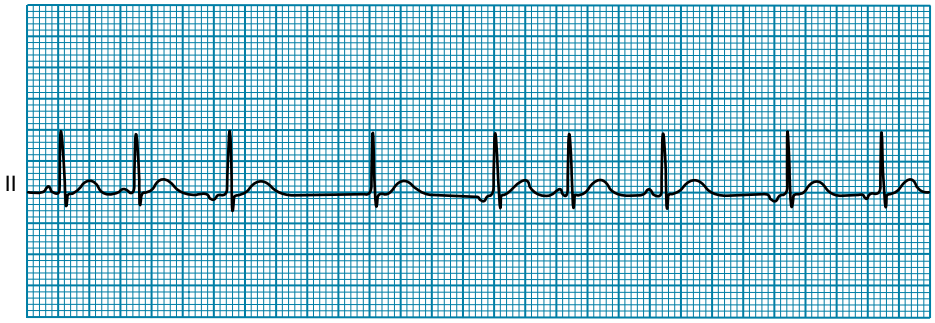

FIGURE 24.18 Wandering atrial pacemaker with junctional escape (fourth complex).

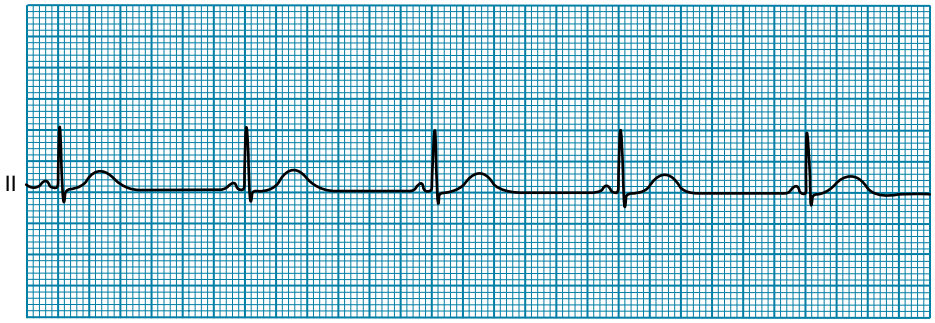

FIGURE 24.19 Sinus bradycardia.

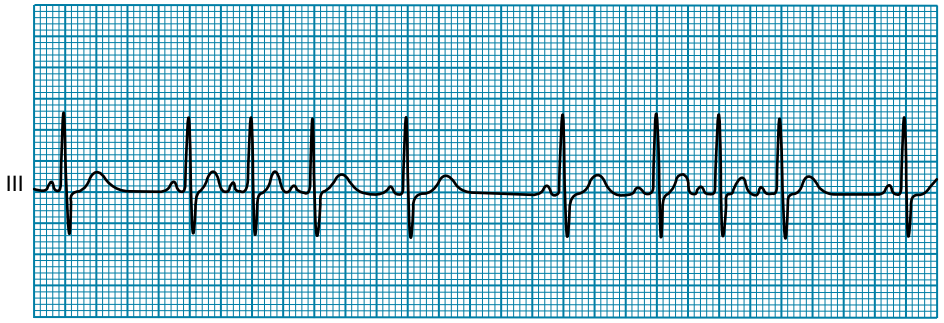

FIGURE 24.20 Sinus dysrhythmia.

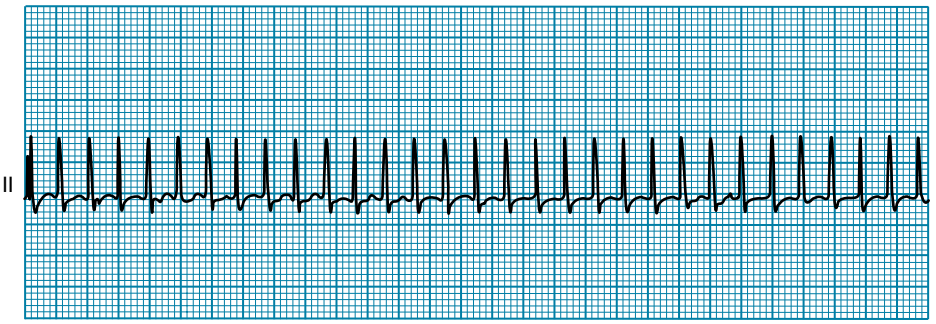

FIGURE 24.21 Supraventricular tachycardia.

SUPRAVENTRICULAR TACHYCARDIA

Supraventricular tachycardia (SVT) (Fig. 24.21) is the most common tachydysrhythmia in the newborn period. SVT can result from dual AV nodal pathways, rapid conduction through an accessory bundle (WPW syndrome), or the existence of an ectopic atrial pacemaker. SVT is occasionally associated with specific heart diseases, such as Ebstein anomaly of the tricuspid valve, cardiomyopathy, or myocarditis. These lesions are present in up to 25% of infants with SVT and should be excluded by evaluation with an echocardiogram.

Criteria for SVT include (1) persistent ventricular rate over 200 to 220 beats/min, (2) a fixed and regular R-R interval, and (3) little variability in heart rate with various activities (e.g., crying, feeding, apnea). The QRS complexes are most often narrow-complex, and P waves may be absent. **Newborns with SVT often have a history of restlessness, tachypnea, irritability, and poor feeding.** These symptoms may start abruptly with SVT initiation or may develop after 12 to 24 hours of SVT as ventricular function worsens. Prolonged tachycardia can be associated with CHF symptoms. **Without treatment, prolonged SVT can result in cardiovascular collapse, shock, and death.**[38]

Treatment. Various maneuvers may be used to attempt to convert the infant to normal sinus rhythm (NSR). Vagal maneuvers such as carotid occlusion and ocular compression should *never* be used. However, **stimulation of the diving reflex using an ice bag applied to the infant's face may be attempted and is the first line of treatment in the hemodynamically stable neonate with SVT.** Caution must be used with this procedure to ensure adequate ventilation for the infant. **Adenosine, a purinergic agonist, is an especially effective antidysrhythmic drug for the treatment of SVT** (see Table 24.3). Adenosine slows the sinus rate and produces a transient AV block, which can interrupt some types of SVT. Adenosine must be administered as a rapid bolus through an IV line to be effective, so venous access must be available to use this medication. Overdrive atrial pacing has been successful in converting SVT to NSR. However,

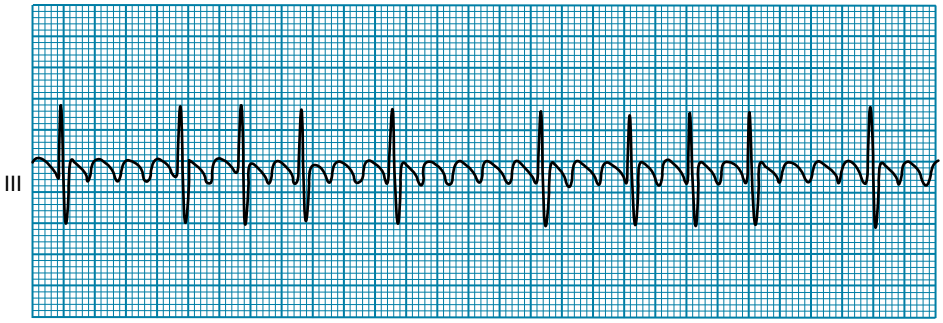

FIGURE 24.22 Atrial flutter.

direct-current (DC) cardioversion (1 to 2 watt-seconds/kg) is the most effective and rapid therapy and is the treatment of choice for a hemodynamically unstable neonate with SVT. The defibrillator must always be in the synchronous mode. If cardioversion is successful, maintenance drug therapy should be initiated with the consultation of pediatric cardiology.

For infants without WPW syndrome, digoxin or propranolol is often used for initial maintenance therapy. Digoxin should not be used in WPW syndrome, so this disorder should be ruled out before digoxin is used. Propranolol can be used for infants with SVT caused by WPW syndrome in the absence of CHF. Beta-blocking agents may inhibit circulating catecholamines, which are needed for the maintenance of adequate cardiac output in the face of CHF. In premature infants, propranolol may cause apnea and hypoglycemia. Esmolol is another beta-blocking agent that can be administered intravenously for SVT (see Table 24.3).

If the SVT fails to convert using the methods outlined previously, other drugs such as amiodarone, flecainide, or procainamide may be necessary. After conversion to NSR, maintenance drug therapy should be continued for 6 to 12 months or longer based on pediatric electrophysiology recommendations. **Relapses during the first 48 hours are common (70%) and should be anticipated.**

Fetal SVT is uncommon but, when present, can be associated with severe CHF and hydrops fetalis. Fetal SVT requires aggressive management, including conversion with maternally administered digoxin, flecainide, sotalol, or other antiarrhythmic medication. A favorable outcome usually can be expected for fetal SVT. Failure to control the fetal SVT in the presence of fetal hydrops is an indication for delivery if the fetus is of viable gestational age. The likelihood of SVT becoming a persistent problem after birth and cardioversion depends on the type and etiology of the fetal SVT.

ATRIAL FLUTTER AND FIBRILLATION

The presence of atrial flutter (Fig. 24.22) is often suggestive of a serious organic heart disease (endocardial fibroelastosis, Ebstein anomaly of the tricuspid valve, or complex heart defect). Atrial flutter is diagnosed when (1) the atrial rate is greater than 220 beats/min; (2) the P waves are very regular; and (3) there is a characteristic saw-tooth pattern, indicating a flutter wave. The ventricular rate will vary depending on the degree of AV block present. **Atrial fibrillation is extremely rare and almost always indicates a serious organic heart disease.** The prognosis for atrial flutter and fibrillation tends to be less favorable than those for SVTs caused by an accessory pathway or ectopic atrial pacemaker. However, **some cases of atrial flutter have been found in infants receiving broad-spectrum antimicrobials or those with an intracardiac catheter causing mechanical irritation of the right atrium.**[66] Atrial flutter is more difficult to treat in utero, more likely to be associated with structural heart defects, and more likely to develop hydrops fetalis.

Treatment. The treatment of atrial flutter or fibrillation is DC cardioversion or overdrive atrial pacing with pediatric electrophysiology consultation. In many cases, the neonate with atrial flutter will require a single cardioversion and then not require medication therapy to

prevent further episodes. However, maintenance therapy with an antidysrhythmic medication may be indicated and initiated by an electrophysiology specialist.

VENTRICULAR TACHYCARDIA

Ventricular tachycardia is relatively rare and is usually seen with severe medical illnesses such as hypoxemia, shock, electrolyte disturbances, and digoxin toxicity. Ventricular tachycardia is recognized by its characteristic wide QRS complexes, although it can be difficult to differentiate ventricular tachycardia from a supraventricular tachycardia with aberrant ventricular conduction. **A wide-complex tachycardia should always be assumed to be ventricular tachycardia until proven otherwise.** The presence of ventricular tachycardia is always alarming because the etiology is rarely benign, it can abruptly start and cause rapid hemodynamic instability and clinical deterioration, and it can be challenging to treat.

Treatment. Ventricular tachycardia is best treated with immediate DC cardioversion. Lidocaine may be used as a bolus (1 to 2 mg/kg intravenously) or as a continuous IV infusion of 20 to 30 mcg/kg/min. After conversion, maintenance therapy should be initiated using propranolol, lidocaine, procainamide, or amiodarone (see Table 24.3).

COMPLETE ATRIOVENTRICULAR BLOCK

In complete heart block, the SA node functions normally and sends out a depolarization impulse to the atria, but the AV node is dysfunctional and does not transmit this signal to the ventricles. As the ventricles receive no signal to depolarize from the atria, they depolarize on their own but at a much slower rate than the atrial rate. **The result is that atrial and ventricular depolarizations are completely independent of each other.** The ECG demonstrates P waves at a normal heart rate for age, but QRS complexes that occur at a much slower rate and are completely dissociated from the P waves.

Complete heart block can be seen in infants with specific structural cardiac defects, myocarditis, or endocardial fibroelastosis. **There is a strong association between congenital heart block and maternal collagen diseases such as systemic lupus erythematosus.** Often these mothers have no signs or symptoms of lupus, but laboratory confirmation is often possible.

Treatment. No treatment is immediately required unless the neonate is hemodynamically unstable due to significant ventricular bradycardia. Cardiac output is directly dependent on the ventricular rate; isoproterenol may be used temporarily to increase the ventricular rate until a pacemaker is placed. **If the ventricular rate is consistently below 55 beats/min, signs or symptoms of low cardiac output, or an associated congenital heart defect, pacemaker placement is indicated.** In most cases, the pacemaker will be set to listen to the child's normal SA node activity and will transmit these depolarization signals to the ventricles (the normal role of an AV node).

SICK SINUS SYNDROME

Sick sinus syndrome (SSS) is a broad term used to describe dysrhythmias resulting from abnormal sinus node function and includes a wide array of bradydysrhythmias, including sinus bradycardia, sinus pause/arrest, sinoatrial exit block, and slow escape rhythms, including junctional bradycardia. Although **most commonly acquired during surgical repair for CHD** (because of the proximity to the sinus node), **SSS may also be found congenitally in the neonatal period.** Mutations in the cardiac sodium channel gene *SCN5A* can result in congenital SSS.[99] **Treatment of SSS requires pacemaker placement,** but treatment is not always indicated.

PARENT TEACHING

The diagnosis of CHD in their child—whether given prenatally or postnatally—is a frightening experience and causes much distress to parents. Parents may grieve over the loss of the healthy newborn they had anticipated and experience shock, denial, guilt, anger, despair, or confusion.[28] **Comprehensive teaching, reassurance, and support are essential for the well-being of both the infant and the family** (Box 24.6).

If the diagnosis of CHD is made prenatally by fetal echocardiography, parent education

BOX 24.6 PARENT/CAREGIVER TEACHING

Key Points for Parents of Newborns with Heart Disease

- Refer to a pediatric facility experienced with infants with heart disease.
- Reassure and support the family for understanding that "this is not their fault."
- Explain all tubes, monitors, and equipment to decrease anxiety.
- Help parents accept and understand their infant's diagnosis.
- Encourage parental bonding with their infant and participation in care.
- Detail home care, including medications, signs and symptoms, and when to call the physician.
- Encourage normal activity.
- Explain the necessity of subacute bacterial endocarditis protection.
- Supply parents with resource information—booklets, brochures, Internet resources.

begins before the birth of the infant. Expectant parents should be referred to a pediatric facility experienced in providing complex medical and surgical care for infants with CHD. Arrangements should be made for parents to meet with key members of the medical and surgical team and tour the intensive care units. A multidisciplinary approach with providers and support staff from cardiology, cardiac surgery, the intensive care team, social work, chaplaincy, genetic counseling, and the palliative care team should be used.

Understanding the heart defect aids in decreasing anxiety, as well as allowing parents to provide good care for their child. Explain the infant's heart defect to the parents. Draw or show a picture of the heart defect, explaining the normal circulation of the heart in simple terms and how their infant's heart differs from normal. This explanation should be repeated often for parental understanding and retention. Careful explanation of all tubes, monitors, equipment, and procedures in the nursery also helps decrease parental anxiety.

Heart defects are not visible lesions. Infants with CHD can appear quite normal and healthy. It may be difficult for some parents to accept that their infant has a cardiac defect. In addition, parents are under great emotional and sometimes physical stress (from labor and delivery), which decreases their ability to hear new information and retain details. Patience and repetition of information are important.

Some parents may initially be unable to respond to their newborn with a heart defect. **Health care providers should facilitate bonding by encouraging interaction with the infant and enabling parents to participate in their infant's care.** Parental participation enables opportunities for parents to practice under the guidance of professionals and enables professional assessment of parental competencies. Parents should be encouraged to assist with diaper changes, positioning, and oral care and provide comfort measures even during the critical phase of illness. **During the postoperative and convalescent phase of hospitalization, parents should assume more of the infant's care, such as feeding, care of the incision, and medication administration.** Before discharge, parents should be encouraged to room with and completely care for their infant, with nursing assistance available as needed. Parents must feel comfortable caring for their infant and must demonstrate their ability to do so before discharge from the hospital.

Teaching home care of the infant before discharge should be detailed and include medications, signs to observe, and guidelines for care. It is critical that these be written instructions that can be referred to often. All medications should be explained in detail, including their purpose, action, and administration. Parents should be made aware of the potential adverse effects (side effects) of all of their infant's medications. **Parents should be observed giving medications in the nursery before the infant is discharged.** Parents should be instructed to telephone their physician if the infant demonstrates red flags such as (1) any behavior or bodily change that worries parents; (2) fevers; (3) poor weight gain; (4) increased work of breathing or stopping to breathe during feeds; (4) feeding difficulty, increased sweating during feeds, or excessive spitting up; (5) new or changed vomiting or diarrhea for a 12- to 24-hour period; (6) decreased activity level or irritability; (7) low oxygen saturations if home monitoring was prescribed; or (8) low number of wet diapers in a day.[66] Provide information about the infant's prognosis and follow-up care

and anticipatory guidance about special growth and development considerations.

Cyanotic heart disease is particularly disturbing to parents because their infant's skin color is "blue." Parents should be cautioned that their infant will appear blue, especially around the mouth, mucous membranes, hands, and feet, and that the blueness will increase with activity such as crying, feeding, and bowel movements. **Single-ventricle anatomy after the first stage of surgery requires that the discharged infant be followed closely with oxygen saturation checks twice a day or more, and parents should understand their child's expected oxygen saturation and how to contact their primary cardiac team for changes and concerns.** The neonates with the highest-risk cardiac anatomies will have a specialized follow-up in cardiology clinic for cardiology, nutrition, and family support.[9]

Normal Newborn Care and Maintenance

Many parents will develop a narrow, disease-oriented focus. **Emphasize to parents that their infant should be treated as normally as possible. It is often difficult for first-time parents to differentiate "normal baby problems" from cardiac-related problems.** It is important to have open communication among the family, primary care provider, and cardiologist. Parents should be encouraged to call medical personnel as needed for support, answers to questions, and reassurance. Support groups can also provide information, empathy, and practical tips to parents caring for children with CHD.

The trip home should occur in an **appropriate car seat, and a car seat screen is recommended to ensure oxygen saturations are maintained while restrained. Infection prevention strategies,** such as handwashing before handling the infant, avoiding ill contacts, and avoiding large crowds, are especially important to teach parents. Discharge planning should include normal newborn procedures if possible, including standard pediatric immunizations, hearing screen, and circumcision if permitted by the cardiac team. If there is a medical reason to delay these procedures, this should be discussed with parents, and future plans for these procedures should be made.

Infectious Endocarditis Protection

Infants with CHD are at increased risk for developing adverse outcomes associated with infectious endocarditis (IE), also known as bacterial endocarditis (BE). The American Heart Association's Endocarditis Committee extensively reviewed published studies and found no conclusive evidence to link gastrointestinal or genitourinary tract procedures with the development of IE in most patients with congenital heart defects.[11] **Antibiotic prophylaxis with dental procedures is recommended only for patients with cardiac conditions (e.g., prosthetic valves, previous endocarditis, cardiac transplant) associated with the highest risk for adverse outcomes from endocarditis. Antibiotic prophylaxis is also recommended for the following categories of CHD: (1) unrepaired cyanotic CHD, (2) completely repaired CHD with prosthetic material for the first 6 months after the procedure, (3) repaired CHD with residual defects adjacent to prosthetic material, (4) prosthetic cardiac valves, and (5) cardiac transplant recipients with valve regurgitation.**[11] Parents are encouraged to speak with their pediatric cardiologist regarding any questions related to IE antibiotic prophylaxis.

Activity

Normal newborn activity is encouraged after discharge. **There are no activity restrictions for infants with heart disease because infants "self-limit" according to their capacity. However, special precautions may be indicated for handling the infant.** Parents should avoid picking the infant up under the arms until the sternal wound and underlying structures are healed. If discharge occurs soon after surgery, there may also be special instructions for bathing the infant.

Supporting Ongoing Development

Infants with CHD are at risk for neurodevelopmental disorders, disability, or developmental delay for a number of reasons, including that the incidence of brain abnormalities is higher in children with CHD than in the general population. **Inform parents about their infant's increased risk for developmental delay, review normal developmental milestones, and provide pragmatic strategies**

to maximize infant development. These may include simple interventions such as prone placement ("tummy time") after the sternotomy has healed and continued oral stimulation if a G-tube is required. Referral to early intervention programs and cardiac neurodevelopmental clinics for developmental surveillance, screening, and evaluation throughout childhood may allow for later academic, behavioral, psychosocial, and adaptive functioning to maximize the child's potential development.[60]

Parenting an infant with CHD requires coping, adaptation, and evolution—from diagnosis to discharge from the hospital and through caretaking and parenting at home. Parents have reported feelings of posttraumatic stress associated with caring for infants with the most complex single-ventricle anatomies.[76] Consultation with a mental health professional may enable the family to recognize and build on strengths that will help them cope with this enormous challenge.

FUTURE RESEARCH

Improvements in the diagnosis, understanding, and treatment of CHD have drastically reduced the morbidity and mortality rates associated with these defects. Children with critical CHD that was once considered fatal are now living into adulthood, thanks to innovations in cardiac surgery, cardiology, anesthesia, intensive care, and nursing practices. However, we still have much to discover. The etiology of CHD is still poorly understood or completely unknown. Cardiac genetic research is focusing on similar cardiac anatomy and how genetic involvement may play into the development of CHD, but without an understanding of true CHD etiology, the prevention of CHD is almost impossible. Future developments are needed to promote earlier and widespread prenatal detection of CHD, as well as improvements in current fetal catheter and surgical interventions to intervene in defective cardiac development during fetal life. **Advanced screening methods are also necessary to promote early postnatal detection of CHD and avoid the morbidity and mortality risks that can occur at home from undiagnosed CHD.**

Medical, catheter-based, and surgical treatments for CHD continue to exponentially advance. Clinical practice guidelines are increasingly being used to standardize care and evaluate best practices.[65] Valve replacement without surgery is a rapidly developing reality, and the development of a tissue-engineered valve that will grow with a child is expected in the near future. Although we have much left to learn, the future is exciting and will bring improved care and health for children with CHD.

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RESOURCES FOR PARENTS

American Heart Association: Children with congenital or acquired heart disease: http://www.americanheart.org.
Congenital Heart Information Network: http://www.tchin.org.
Kids with Heart National Association for Children's Heart Disorders: http://www.kidswithheart.org.
Little Hearts, Inc., national nonprofit organization: http://www.littlehearts.org.
Sisters by Heart: Hypoplastic Left Heart Syndrome: http://www.sisters-by-heart.org.

25 NEONATAL NEPHROLOGY

MELISSA A. CADNAPAPHORNCHAI, DANIELLE E. SORANNO, TERRI J. BISIO, ROSANNE WOLOSCHUK, AND MEGAN KIRKLEY

In utero, the fetal kidney is not necessary for toxin removal or fluid and electrolyte homeostasis; rather, the placenta performs these functions. By contributing to amniotic fluid, the fetal kidney instead has an essential role in the normal development of the fetus. **After birth, as the infant adapts to the external milieu, the kidney gradually assumes its role as regulator of fluid and electrolyte homeostasis.** At birth, renal function changes dramatically, complicating clinical assessment. Assessment of renal function is an even greater challenge in the premature infant. The more complicated an organ is in its development, the more subject it is to maldevelopment. In this aspect, the kidney outranks most other organs. **Abnormalities of the genitourinary system constitute up to 30% of all anomalies diagnosed prenatally.**[146,188] Some anomalies may be readily apparent in the neonatal period, whereas others remain undiagnosed until later life.

Although renal disease can clearly affect the health of the newborn, it may also contribute to lifelong renal pathology. **Congenital renal dysplasia, renal obstructive disorders, and cystic diseases account for a substantial percentage of patients with end-stage renal failure.** Furthermore, a growing body of **data supports a link between prenatal and neonatal events and later hypertension and renal insufficiency in adolescents and adults.**[22,115,116]

NORMAL DEVELOPMENT OF THE KIDNEY

The mammalian embryo progressively develops three sets of excretory organs, all of which might be termed the "embryonic kidney."[188] The pronephros and mesonephros regress in the human but induce the metanephros, which is the direct precursor of the adult kidney (Fig. 25.1). The pronephros, a solid mass of cells along the nephrogenic cord, is located at the cervical level at approximately 3 weeks' gestation. Degeneration of the pronephros begins soon after its formation, and regression has completely occurred by week 5. The pronephros has no excretory function but plays an important role in the formation of the mesonephros. The primitive ureter of the pronephros forms the *Wolffian, or mesonephric, duct* via fusion of the pronephric tubular buds. The mesonephric duct then induces the formation of the second kidney, *the mesonephros,* at approximately 4 weeks' gestation. The mesonephros develops from the nephrogenic cord and forms 40 pairs of thin-walled tubules and glomeruli with excretory function. Portions of the mesonephric duct system are retained in the male fetus and form the *ducts of the epididymis, the ductus deferens, and the ejaculatory duct*. The remainder of the mesonephric duct system in the male infant has degenerated by the fourth month of gestation as the metanephric kidney develops. In the female, near-complete degeneration has occurred by the third month of gestation.

The *metanephros* appears at 4½ to 5 weeks' gestation. The metanephric kidney is the product of a series of inductive interactions between the metanephric mesenchyme and epithelial ureteric bud. Initially, the ureteric bud grows from the mesonephric duct into the mesenchymal portion of the urogenital ridge; concomitantly, the metanephric mesenchyme changes, becoming histologically distinct from the surrounding tissue. When the metanephric mesenchyme and ureteric bud make contact, a condensation of cells begins along the

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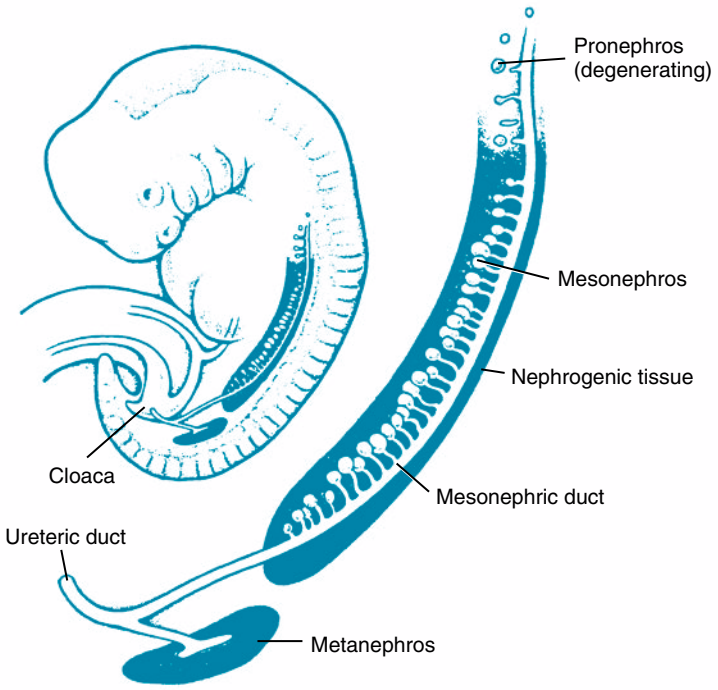


FIGURE 25.1 Schematic representation of overlapping stages in embryogenesis of human kidney. See text for detailed description. (From Holliday MA. Developmental abnormalities of the kidney in children. *Hosp Pract.* 1978;13(6):101. http://www.informahealthcare.com.)

surface of the bud. These cells are the beginnings of pretubular aggregates that undergo mesenchymal-to-epithelial transformation to become the segmented nephron. The condensed mesenchyme is also thought to produce a number of stem cells, which remain undifferentiated and proliferative. These cells serve to maintain a supply of precursor cells until the completion of nephron development. Thus, the epithelial portion of the adult kidney is derived from both the metanephric mesenchyme, via the stem cells ultimately responsible for individual nephron formation, and the ureteric bud, whose migration and division determine the pattern of formation of the urinary collecting system via its pretubular aggregates. **The ureteric bud migrates to the most caudal end of the nephrogenic cord and finally to the lumbar region by week 8 of gestation. The ureteric bud also rotates 90 degrees medially along the longitudinal axis. Abnormalities in ascent or rotation can lead to pelvic kidneys, horseshoe kidneys, or crossed fused ectopia.** Because of the complex interaction of metanephric mesenchyme and ureteric bud, anomalies of the kidney often accompany anomalies of the collecting system. **Congenital anomalies of the kidney and urinary tract (CAKUT) are a family of diseases with a diverse anatomic spectrum of kidney anomalies (agenesis, hypo/dysplasia, multicystic kidney dysplasia) and other urinary tract anomalies (duplex collecting system, megaureter, vesicoureteral reflux, posterior urethral valves).**[154,184] CAKUT is mostly considered polygenic at the current time, but recent studies have identified several causative single-gene mutations, including hepatocyte nuclear factor 1 beta (HNF1β) mutations, which account for up to 30% of CAKUT.[94,187] **CAKUT commonly cause progressive chronic kidney disease and constitute the most frequent cause of end-stage kidney disease and renal replacement therapy in childhood.**

Vascular system development occurs in concert with nephron formation. The surrounding major vessels and neural ganglia grow into the metanephros to complete the remaining cell types, and vessel architecture is similar to the newborn kidney

by 15 weeks of gestation. **The process of forming the adult complement of approximately 600,000 (range 250,000 to 2,000,000) nephrons in each kidney is complete by 34 to 36 weeks of gestational age (GA). In general, nephron development continues after birth in premature infants but at a slower rate than during gestation; thus, preterm infants are at higher risk for decreased nephron number compared with term infants.**

Physiologic Development of the Kidney

Although newborn kidneys are usually described as "immature," they are perfectly suited to their usual responsibilities.[37,138] During the latter part of gestation, their primary role is the maintenance of amniotic fluid volume. This requires a large volume of urine with a relatively high concentration of sodium. **Thus, fetal urine output is on the order of 10 mL/kg/hr of sodium-rich urine.** Fetal fractional excretion of sodium (FENa; i.e., the fraction of sodium in glomerular filtrate that appears in urine) is especially high, approximately 15%. This compares to less than 1% in a growing infant born after a full-term pregnancy.

The next major responsibility of the newborn kidney occurs during the first week of life. **Fetuses have a large amount of extracellular fluid (ECF) compared with older children and adults.** ECF as a percentage of body weight progressively diminishes throughout gestation, at approximately 65% of body weight at 26 weeks of gestation, 40% at full term, and 25% by 1 year of age. **Most of the postnatal reduction occurs in the first week of life and is the primary reason that body weight may decrease by up to 10% in breastfed term infants and even more in premature infants.** The healthy newborn kidney can handle this challenge without difficulty. Finally, in subsequent weeks, the kidney must retain the electrolytes needed for growth and the production of dilute urine to accommodate the large water load presented by breast milk. Growth itself is a powerful homeostatic ally. A substantial portion of carbohydrates, electrolytes, and nitrogenous wastes from protein absorbed from breast milk are never presented to the kidney for excretion but are instead incorporated into the growing body.

Only when the otherwise healthy neonatal kidney has to cope with unexpected derangements of water, electrolyte, or acid-base status secondary to premature birth or illness does its relative lack of ability to concentrate urine, excrete sodium and potassium loads, conserve sodium (in preterm infants), and regulate acid-base status become problematic. In older children and adults, normal kidneys can correct for substantial errors in clinical judgment in water and electrolyte administration or creation and/or correction of acid-base abnormalities. This is not so with neonatal kidneys, especially in smaller preterm infants. With that in mind, it is helpful to review specific aspects of neonatal renal function.

Glomerular Filtration Rate

The *glomerular filtration rate* (GFR) is the rate at which filtrate of renal plasma appears in proximal renal tubules.[1,15,175] For the fetus, the placenta serves to maintain fluid and electrolyte composition and clearance of metabolic wastes. Thus, renal arterial blood flow is approximately 5% of fetal cardiac output, compared with 25% in later life. This rapid increase in blood flow correlates with an increase in GFR from approximately 20 to 80 mL/min/1.73 m^2 by 6 months of age. GFR continues to improve over the first 2 years of life, typically reaching adult norms (when corrected for body surface area) by about 19 months of age. Table 25.1 shows glomerular filtration rates in healthy infants as measured by inulin clearance.

Tubular Function

Urine flow depends on both GFR and tubular reabsorption.[56,85,147] **Oliguria is ordinarily defined as urine output of less than 1 mL/kg/hr. However, urine output may transiently decrease immediately after birth to less than 1 mL/kg/hr because tubular reabsorption of water increases due to an increase in fetal antidiuretic hormone (ADH) during labor.** Nevertheless, **50% of full-term infants void by 12 hours, 92% by 24 hours, and 99% by 48 hours of life.** Causes for prolonged failure to void include true or perceived decreased effective circulating volume, primary renal dysfunction, and obstruction to urine flow. After transient oliguria/anuria, the urine flow rate increases as the newborn excretes the physiologically expanded fetal extracellular fluid volume as described earlier.

The **newborn has a limited capacity to concentrate urine.** Several factors account for this

TABLE 25.1 GLOMERULAR FILTRATION RATES* IN HEALTHY INFANTS AS MEASURED BY INULIN CLEARANCE

AGE	MEAN GFR (SD)
Preterm	
1-3 days	14.0 (5.0)
1-7 days	18.7 (5.5)
8-14 days	35.4 (13.4)
1.5-4 months	67.4 (16.6)
Term	
1-3 days	20.8 (5.0)
3-4 days	39.0 (15.1)
6-14 days	54.6 (7.6)
1-3 months	85.3 (35.1)
4-6 months	87.4 (22.3)
7-12 months	96.2 (12.2)

*Glomerular filtration rate (mL/min/1.73m^2).
GFR, Glomerular filtration rate; *SD,* standard deviation.
Adapted from Schwartz G, Furth SL. Glomerular filtration rate measurement and estimation in chronic kidney disease. *Pediatr Nephrol.* 2007;22(11):1839.

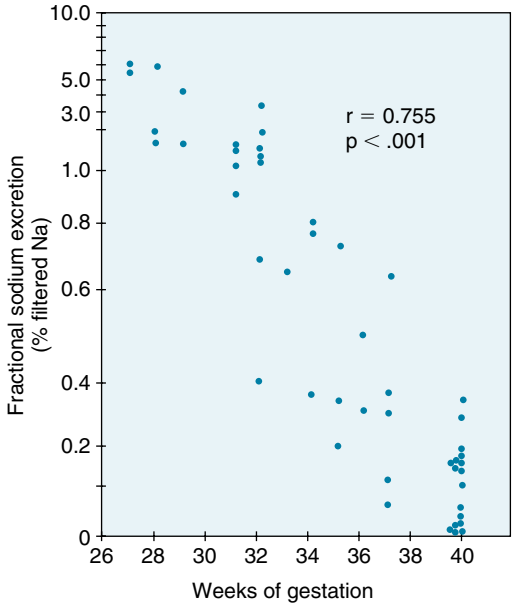


FIGURE 25.2 A decrease in fractional excretion of sodium occurs with increasing postconceptual age. *Na,* Sodium. (From Siegel S, Oh W. Renal function as a marker of human fetal maturation. *Acta Paediatr Scand.* 1976;65(4):481.)

observation. The concentration of osmotically active solutes in the urine is low during the first few weeks of life in association with high water and low protein content of breast milk and infant formulas, and ingested protein is preferentially used for growth rather than urea synthesis, leading to impairment of the countercurrent concentrating mechanism. Neonates also demonstrate resistance to ADH with decreased expression of collecting duct aquaporin-2 water channels, which normally enhance tubular water reabsorption. **These factors result in an increased risk of intravascular volume depletion when fluid intake is limited.** High-protein diets or urea supplementation can increase urinary urea excretion in newborn infants, thus enhancing urinary concentrating ability.

Proximal Tubular Function

The proximal tubule is responsible for reabsorbing glucose; amino acids; and most of the bicarbonate, sodium chloride, uric acid, and water in glomerular filtrate.[20,47,73,167] In smaller preterm infants, tubular transport mechanisms are insufficient to prevent spillage of each of these in varying degrees.

SODIUM

Physiologic diuresis in the first week of life is accompanied by physiologic natriuresis. The kidney is then responsible for conserving sufficient dietary sodium for growth.[91] **This is a challenge for preterm infants (Fig. 25.2), who often require extra sodium intake to compensate for obligatory sodium wasting.** Conversely, in the presence of a sodium load (e.g., from administration of large amounts of sodium), the neonatal kidney cannot compensate with a rapid increase in fractional excretion of sodium. The result is edema and possibly circulatory overload.

POTASSIUM

The kidney is an important site for regulation of potassium balance.[83,158] In the adult, it is responsible for maintaining zero balance. In contrast, **to sustain the neonate, the kidney must maintain positive**

potassium balance. In this context, it is less surprising that mechanisms for potassium excretion are underdeveloped at birth. **Serum potassium concentrations tend to be high in neonates (5.5 to 6 mEq/L) relative to older children and adults.** The levels are not of pathologic significance and perhaps play a role in supporting growth.

ACID-BASE BALANCE

By adult standards, serum bicarbonate concentrations are low in full-term newborns (19 to 21 mEq/L) and even lower in premature infants (16 to 20 mEq/L).[147,151] **Lower serum bicarbonate concentrations reflect limited ability to cope with the acid load from high protein intake and the acid generated by the formation of new bone.** The capacity of the neonatal **proximal tubule to reabsorb filtered bicarbonate is one third that of an adult.** Proximal tubular bicarbonate reabsorption is further compromised if ECF is overexpanded with crystalloid solutions; because proximal tubular sodium and bicarbonate reabsorption are closely linked, bicarbonate is wasted as sodium reabsorption decreases to rid the body of excess sodium chloride. **The capacities of ammoniagenesis and of the collecting duct to secrete hydrogen ions are also limited.** The net result is a limited capacity to correct metabolic acidosis. **This limitation is particularly evident in the setting of pathologic metabolic acidosis as may be seen in acute kidney injury.** However, the ability to achieve minimal urine pH values is usually intact. That is, **if serum bicarbonate is low enough (e.g., 14 to 15 mEq/L), the kidney can completely reabsorb the smaller amount of filtered bicarbonate and achieve a urine pH of 5.** Serum bicarbonate concentrations increase to adult levels of 24 to 26 mEq/L by the end of the first year.

URIC ACID

Serum uric acid concentrations are elevated in the newborn because production from nucleotide breakdown is increased just after birth, especially in premature infants.[170,177] This is accompanied by increased uric acid excretion. **High urinary uric acid concentrations may leave pink or red uric acid crystals in the diaper, which are often mistaken for blood (i.e., "brick-dust urine"). A microscopic urinalysis is helpful to exclude true hematuria in this setting.**

CLINICAL ASSESSMENT OF RENAL DISEASE IN THE NEONATE

History

A complete family history of renal disease or syndromes that involve the kidneys is important to obtain. Prenatal exposures to maternal infection, drugs, toxins, or medications are risk factors for neonatal renal disease. Paternal smoking and advanced age may also be associated with an increased risk for urinary tract anomalies.

The quantity of amniotic fluid is an indicator of fetal renal function because fetal urination is responsible for most of the amniotic fluid volume beginning in the second trimester of pregnancy. Normally, amniotic fluid volume increases during gestation, peaking at 34 weeks' gestation. **Any fetal renal condition associated with significant impairment in function with markedly diminished urine output can be associated with oligohydramnios.** With worsening oligo-/anhydramnios, a *Potter* sequence can be observed, in which the fetus develops pulmonary hypoplasia, a flattened nose, a recessed chin, low-set ears, and limb compression.[144,145] Serial amnioinfusion during pregnancy has been utilized to support lung development in this setting, although such intervention does not improve kidney function. Severe urinary concentrating defects (e.g., diabetes insipidus and Bartter syndrome) may be associated with polyhydramnios.

A review of the perinatal history should identify risk factors for renal ischemia. Special attention to the composition of administered parenteral fluids can help to identify iatrogenic contributions to fluid/electrolyte derangements. **Several potentially nephrotoxic medications are commonly used in the neonatal period, including diuretics, aminoglycosides, and nonsteroidal anti-inflammatory drugs (NSAIDs).**

Signs and Symptoms

Physical findings that are indicators of genitourinary tract abnormalities are outlined in Table 25.2. Although lower urinary tract and renal anomalies are seldom the presenting features of chromosomal disorders, they frequently form part of a multisystem malformation syndrome

TABLE 25.2 PERINATAL INDICATORS SUGGESTIVE OF ABNORMALITIES OF THE GENITOURINARY TRACT

FINDING	SUSPECTED ABNORMALITY
Oligohydramnios	Any congenital renal lesion associated with significant impairment in function
Polyhydramnios	Diabetes insipidus, Bartter syndrome
Enlarged placenta (>25% of infant birth weight) or >10-fold increase in maternal serum AFP	Congenital nephrotic syndrome—Finnish type
Velamentous insertion of umbilical cord	Increased congenital anomalies
Asphyxia neonatorum	Acute tubular or cortical necrosis
Physical Examination	
Hypertension	See text
Skin	
Hemangioma	Hemangioma of kidney or bladder
Edema	Congenital nephrotic syndrome
Head	
Encephalocele	Meckel-Gruber syndrome (polycystic kidneys)
Cleft lip and palate	Urinary tract anomalies
Macroglossia	Beckwith-Wiedemann syndrome (nephromegaly, cysts, structural urinary tract anomalies, nephrocalcinosis); Johanson-Blizzard syndrome (hydronephrosis, dysplasia); orofacial-digital syndrome (renal cystic disease)
Eyes	
Phakoma	Tuberous sclerosis
Retinitis pigmentosa	Nephronophthisis/renal ciliopathy
Cataracts	Lowe syndrome, WAGR, congenital rubella
Aniridia	WAGR
Ears	
Low-set or malformed	Increased risk for renal abnormalities, Potter syndrome/sequence
Ear tags	Branchio-oto-renal (BOR) syndrome
Preauricular pits	Structural renal disease
Skeleton	
Hemihypertrophy	Wilms tumor
Spina bifida	Neurogenic bladder
Arthrogryposis	Potter syndrome/sequence
Dysplastic nails	Nail patella syndrome
Vertebral anomalies	VATER/VACTERL syndrome
Polydactyly	Meckel-Gruber; renal ciliopathies
Limb anomalies	VACTERL syndrome

TABLE 25.2 PERINATAL INDICATORS SUGGESTIVE OF ABNORMALITIES OF THE GENITOURINARY TRACT—CONT'D

FINDING	SUSPECTED ABNORMALITY
Cardiac	
Congenital heart disease	Increased risk for renal abnormalities in association with multiple syndromes
Abdomen	
Absence of abdominal musculature	Prune-belly syndrome
Single umbilical artery	Increased congenital anomalies of the urinary tract
Umbilical discharge	Patent urachus
Abdominal mass	See Table 25.6
Hepatomegaly	Storage diseases, Beckwith-Wiedemann, Zellweger syndrome
Pulmonary	
Spontaneous pneumothorax	Oligohydramnios, Potter sequence
Pulmonary hypoplasia	Oligohydramnios, Potter sequence
Genitourinary—Male	
Undescended testes	Prune-belly syndrome, Noonan syndrome, Lawrence-Moon-Biedl syndrome, Denys-Drash syndrome
Congenital absence of vas deferens	Renal agenesis or ectopia
Hypospadias	Increase in renal anomalies
Abnormal urinary stream	Bladder dysfunction or urethral outlet obstruction
Genitourinary—Female	
Enlarged clitoris	Adrenogenital syndrome
Cystic mass in urethral region	Ectopic ureterocele, paraurethral cyst
Abnormal urinary stream or dribbling	Bladder dysfunction, urethral obstruction, urethral vaginal fistula
Common cloaca	Urinary tract abnormalities, obstructive uropathy
Urinalysis	
	See text
Rectal	
Abnormal anal sphincter tone	Neurogenic bladder dysfunction
Dilated prostatic urethra	Posterior urethral valves, prune-belly syndrome
Masses	Tumor, polycystic kidney disease, hydronephrosis, multicystic kidney disease
Anal atresia	VATER/VACTERL syndrome

AFP, Alpha-fetoprotein; *VATER/VACTERL,* vertebral defects, imperforate anus, cardiac disease, tracheoesophageal fistula, and limb anomalies; *WAGR,* Wilms tumor, aniridia, genitourinary anomalies, retardation.

Modified from Retik AB. Genitourinary problems in children. *Hosp Pract.* 1976;11(10):133.

caused by chromosomal anomalies. Renal disorders seen with chromosomal disturbance can include fused kidneys, duplication defects, renal agenesis or hypoplasia, hydronephrosis and hydroureter, renal dysplasia or cystic disease, hypospadias, micropenis, and cryptorchidism. The overall pattern of malformation with individual chromosomal disorders is usually sufficient for diagnosis; however, variation can be seen from one individual to another, even for patients with aneuploidy. Although **certain renal anomalies are characteristic of certain chromosomal disorders, no one renal malformation is unique to any particular chromosomal disorder.** A detailed description of chromosomal disorders associated with renal anomalies can be found elsewhere.[97]

Laboratory Data

SERUM CREATININE CONCENTRATION

Serum creatinine concentration is generally used to monitor renal function in the newborn. Cystatin C has been proposed as an alternative marker of renal function, but values can vary widely in the neonate.[1,8] **Serum creatinine is elevated at birth, reflecting maternal renal function, but rapidly declines to a stable level of around 0.4 mg/dL by 1 to 2 weeks of age in the term infant.** In the otherwise normal, very premature infant, there is a transient increase in serum creatinine (due to tubular reabsorption of creatinine in the setting of total body fluid loss and intravascular volume contraction) with a peak around day 4 of life, followed by a progressive decrease to normal neonatal values within 3 to 8 weeks of birth. **In general, the more premature the infant, the higher the serum creatinine and the longer it takes to normalize.**

Under ideal steady-state conditions (which are not always met by the ill neonate), **serum creatinine concentrations should provide an accurate indirect indication of GFR (see Table 25.1),** thus eliminating the need for timed urine collection or nuclear GFR scans. Creatinine is produced at a relatively constant rate. In a steady state, creatinine excretion in urine is equal to creatinine production and likewise constant. **As a general guideline, rising or stable serial serum creatinine concentrations, or an isolated value exceeding 0.5 mg/dL in a term infant, after 1 week of age indicate renal dysfunction.**

URINALYSIS

Specific Gravity. Urine specific gravity is a measure of the concentration of solutes in the urine, specifically the ratio of urine density compared with water density. Specific gravity in term infants ranges from <1.005 to 1.020. Specific gravity has been shown to have a good correlation with urine osmolality in neonates, although the relationship of these variables is somewhat different than in adults, likely due to decreased neonatal renal tubular reabsorption of low-molecular-weight proteins and other small molecules.[111] **It is, however, useful as an indicator of the ability of the kidney to concentrate and dilute.** It can be altered by the presence of glucose, protein, and urinary contrast agents. In such cases, osmolality must be measured directly.

Glucosuria. Trace quantities of glucose may be found occasionally in the urine of term infants and more frequently in premature infants. Even minor elevations of plasma glucose concentrations may cause glucosuria. Large glucose loads may cause osmotic diuresis.

Urinary pH. Urinary pH is typically around 6, although most neonates can achieve a urine pH of 5. Urine pH is frequently 7 or greater with distal tubular acidification defects.

Hematuria. A positive dipstick test for blood can be seen with hematuria, hemoglobinuria from hemolysis, or myoglobinuria from muscle breakdown, usually from perinatal asphyxia. Thus, a microscopic urinalysis is necessary to confirm the **presence of true hematuria, which is defined as >5 red blood cells (RBCs)/high-power field (hpf). Hematuria may occur if the kidneys are traumatized during delivery,** especially with an enlarged kidney (e.g., polycystic kidney disease or large hydronephrotic kidney). **Hematuria is also common in perinatal asphyxia.** Other conditions associated with hematuria include renal vein or artery thrombosis, urinary tract infection, trauma from catheterization, renal artery emboli (especially from umbilical artery catheters), renal cortical necrosis, hypercalciuria, and rarely coagulopathies. Factitious hematuria may occur as a result of blood from circumcision, perineal

irritation, uterine bleeding caused by withdrawal from maternal hormones, and uric acid crystals. **If hematuria is persistent, it should be evaluated with microscopic examination, consideration of urine culture, evaluation of urine protein and calcium excretion, assessment of GFR, and an anatomic evaluation of the kidneys.**

Pyuria. **Pyuria is common in newborns, especially females. Pyuria may indicate infection, and a urine culture should be obtained if clinically indicated.** However, pyuria also may indicate noninfectious renal injury. Interstitial nephritis is distinctly uncommon in the neonatal period.

Proteinuria. **A positive dipstick test for protein indicates the amino groups of proteins.** Although convenient, dipstick testing is subject to limitations. Because albumin and low-molecular-weight proteins give positive results, **dipstick testing cannot fully distinguish between glomerular and tubular proteinuria.** An alkaline urine (pH of ~8) may give a false-positive result, as can prolonged immersion of the strip and the presence of detergents in the urine. **The dipstick provides a qualitative assessment of proteinuria, which must be further confirmed by quantification of protein.** Because 24-hour urine collection is cumbersome in neonates, a random urine protein creatinine ratio (normal <0.5 mg/mg) may be helpful clinically.

IMAGING STUDIES

Fetal ultrasound can provide (1) estimation of amniotic fluid volume; (2) information on the appearance, size, and echogenicity of the kidneys; and (3) evidence of collecting system dilation. **Prenatal ultrasonography can define anatomy but does not accurately predict function.** Mild dilation does not necessarily denote obstruction, whereas more severe dilation and reduced amniotic fluid volume are more likely to signify obstruction and compromised renal function. The more severe the dilation (>7 mm after 32 weeks of gestation), the more likely the infant has urinary tract pathology. **The later in pregnancy that dilation is found, the more likely hydronephrosis will be confirmed postnatally. Although fetal ultrasound is helpful to detect renal anomalies, a confirmatory postnatal ultrasound is imperative.**

Nuclear renal scans (Tc99m-MAG3 [mercaptoacetyltriglycine] or Tc99m-DTPA [diethylene triamine pentaacetic acid]) are most useful to examine differential renal flow and function but are of limited value when GFR is low, due to limited filtration of tracer. **A *voiding cystourethrogram* (VCUG) can exclude vesicoureteral reflux and detect posterior urethral valves, bladder diverticula, and urinary tract fistulae. *Computed tomography (CT)* or *magnetic resonance imaging (MRI)* may be indicated in select cases when further anatomic definition is needed,** but this is rare in the neonate outside of tumor evaluation.

ACUTE KIDNEY INJURY

Introduction

***Acute kidney injury* (AKI) is a common and significant problem in the neonate.** A recent multicenter observational study demonstrated that AKI occurred in 30% of neonatal intensive care unit (NICU) admissions and was an independent risk factor for mortality among NICU patients.[95] **AKI is characterized by an abrupt decline in renal function, which manifests as a decrease in GFR, increase in serum creatinine, accumulation of nitrogenous waste products, and deranged fluid and electrolyte homeostasis. Timely detection of and intervention in AKI is important; evidence increasingly supports a relationship between AKI in the neonatal period and renal impairment in later childhood and adulthood.**[45]

Etiology and Pathophysiology

There are many causes of AKI in the newborn (Box 25.1). It is helpful to classify these etiologies as prerenal, intrinsic renal, and postrenal (obstructive).

Prerenal injury accounts for most AKI in the newborn. In prerenal AKI, renal function is diminished due to decreased renal perfusion, and the kidney is intrinsically normal. **Renal hypoperfusion can result from a true decrease in intravascular volume (e.g., hemorrhage, dehydration) or from decreased effective circulating volume (e.g., congestive heart failure, cardiac tamponade, third space losses).** Timely correction of the underlying disturbance and restoration of normal

BOX 25.1 ETIOLOGY OF ACUTE KIDNEY INJURY IN NEWBORNS

Prerenal Failure

Decreased Intravascular Volume

- Dehydration/intravascular volume depletion
- Gastrointestinal losses
- Hemorrhage
- Salt-wasting renal or adrenal disease
- Diabetes insipidus

Decreased Effective Circulating Volume

- Congestive heart failure
- Pericarditis
- Cardiac tamponade
- Third-space losses (sepsis, traumatized tissue, liver failure, nephrotic syndrome)

Intrinsic Renal Disease/Acute Tubular Necrosis

- Ischemic/hypoxic insult
- Drug induced
  - Aminoglycosides
  - Intravascular contrast
  - Nonsteroidal anti-inflammatory drugs
  - Amphotericin
- Pigment nephropathy
- Rhabdomyolysis/myoglobinuria
- Hemoglobinuria
- Vascular lesions
  - Renal artery thrombosis
  - Renal venous thrombosis
- Infectious causes
  - Pyelonephritis in a solitary kidney

Postrenal (Obstructive) Renal Failure

- Obstruction in a solitary kidney
- Bilateral ureteral obstruction
- Urethral obstruction

Adapted from Andreoli SP. Acute renal failure in the newborn. *Sem Perinatol.* 2004;28(2):112.

perfusion will return renal function to normal. Alternatively, **profound and prolonged hypoperfusion can lead to acute tubular necrosis (ATN) and even cortical necrosis.**[49] However, the evolution of prerenal failure to intrinsic renal failure is not sudden, and a number of compensatory mechanisms work together to maintain renal perfusion when it is otherwise compromised.[10]

Intrinsic renal injury is often considered synonymous with *acute tubular necrosis* and includes both tubular and vascular lesions. Glomerulonephritis and interstitial nephritis are exceedingly uncommon in the neonate. A number of intrinsic renal parenchymal diseases cause renal failure in the newborn period; these are more appropriately considered chronic in nature and are thus considered later in this chapter. **Perinatal asphyxia is associated with intrinsic renal failure in approximately 40% of affected term neonates and can manifest as either oliguric or nonoliguric renal failure.**[162] **The presence of AKI in these infants is associated with longer hospitalization and increased risk of abnormal brain MRI findings.**[157,162] **Sepsis is also a significant risk factor for AKI in term and preterm neonates.** Although distributive shock and hypovolemia do lead to prerenal AKI in the septic newborn, **sepsis also has direct microvascular effects that can lead to intrinsic renal failure, even when blood pressure and renal blood flow are maintained.**[29] Patients with congenital heart disease appear to be especially vulnerable to tubular necrosis after cardiac catheterization and cardiac surgery.[6,30]

Nephrotoxic drugs (including aminoglycoside antibiotics, diuretics, NSAIDs, intravascular contrast media, acyclovir, and amphotericin B) are commonly used in neonates and increase the risk of intrinsic renal injury. The nephrotoxicity induced by **aminoglycosides such as gentamicin typically manifests as nonoliguric renal failure, with a slow rise in serum creatinine and a hypo-osmolar urine developing after several days of treatment.** Progressive injury leads to tubular wasting of potassium, magnesium, calcium, bicarbonate, and glucose.[84]

Premature infants with symptomatic patent ductus arteriosus (PDA) may receive treatment with indomethacin or **ibuprofen**, two NSAIDs that lead to the closure of the ductus arteriosus via cyclooxygenase (COX) inhibition and a decrease in circulating prostaglandin. AKI reliably occurs in approximately 25% of neonates receiving indomethacin/ibuprofen for PDA closure.[4] **Although the vasoconstrictive effect of these medications inherently contributes to prerenal AKI, podocytes (terminally differentiated glomerular cells that do not regenerate) are found in the urine of preterm neonates receiving indomethacin, suggesting a component of tubular injury**

as well.[101] The administration of NSAIDs to preterm infants should be performed with care and frequent monitoring of renal function, even though these changes often are reversible. When a change or decline in GFR is noted (e.g., oliguria or plasma creatinine increase), the administration of NSAIDs should be halted. Patients at higher risk for significant AKI include those with persistent patent ductus arteriosus, preexisting intravascular volume depletion, and simultaneous administration of other nephrotoxic drugs. **Coadministration of furosemide and indomethacin does not improve outcome.[61]** Of note, NSAID use during the fetal period is contraindicated because it may induce renal dysplasia/dysgenesis, leading to oligohydramnios as well as in utero closure of the ductus arteriosus.[11] **Diuretics can contribute to acute tubular necrosis when given in the setting of intravascular volume depletion, and chronic use of loop diuretics can lead to nephrocalcinosis.[161]**

Vascular lesions leading to intrinsic AKI include renal artery and renal vein thrombosis. Risk factors include umbilical arterial catheters, birth asphyxia, maternal diabetes, significant **intravascular volume depletion, and coagulation abnormalities. Symptoms may include flank mass, microscopic or gross hematuria, oliguria, hypertension, and thrombocytopenia.[127]** AKI is most likely to develop when thrombosis is bilateral, or unilateral in a solitary kidney. Pigment nephropathy due to hemoglobinuria or myoglobinuria is rare in the newborn but can occur, particularly in association with hemolysis due to extracorporeal membrane oxygenation.

A variety of obstructive lesions can be associated with *postrenal AKI* in the newborn. Renal insufficiency is observed when there is functional or anatomic obstruction of both kidneys (e.g., bilateral ureteropelvic or ureterovesical junction obstruction, bladder outlet obstruction) or obstruction of a solitary kidney.

Diagnosis

Diagnosing AKI in the neonate is difficult because of the physiologic differences in neonatal renal function that complicate the interpretation of serum creatinine and urine output. Serum creatinine reflects maternal creatinine for the first 48 to 72 hours of life (longer in preterm infants), and thereafter its concentration is dependent on lean body mass, which is low in the neonate. Elevation in serum creatinine may not be noted until over 50% of GFR is lost.[130] Oliguria is likewise an unreliable and insensitive finding. Neonates enter a state of physiologic diuresis in the first 2 to 5 days of life, as fetal lung fluid is mobilized and total body water decreases.

Several definitions for AKI exist in the literature. **The modified neonatal Kidney Disease Improving Global Outcomes (KDIGO) criteria (Table 25.3) provide the current most accepted definition for AKI in neonates.[45]** This definition takes into account both absolute and relative

TABLE 25.3 NEONATAL ACUTE KIDNEY INJURY BASED ON KDIGO CLASSIFICATION

STAGE	SERUM CREATININE	URINE OUTPUT
0	No change in sCr *or* rise <0.3 mg/dL (<26.5 μmol/L)	≥0.5 mL/kg/hr
1	sCr rise ≥0.3 mg/dL (≥26.5 μmol/L) within 48 hr *or* sCr rise ≥1.5-1.9 times the reference SCr[a] within 7 days	<0.5 mL/kg/hr for 6-12 hours
2	sCr rise ≥2-2.9 times the reference sCr[a]	<0.5 mL/kg/hr for ≥12 hours
3	sCr rise ≥3 times the reference SCr[a] *or* sCr ≥2.5 mg/dL (≥221 μmol/L)[b] or receipt of dialysis	<0.3 mL/kg/hr for ≥24 hours or anuria for ≥12 hours

Differences between the proposed neonatal acute kidney injury (AKI) definition and KDIGO include:
[a]Reference sCr is defined as the lowest previous sCr value.
[b]An sCr value of 2.5 mg/dL (221 μmol/L) represents less than 10 mL/min/1.73 m^2.
KDIGO, Kidney Disease: Improving Global Outcomes; sCr, serum creatinine.
From Charlton JR, Guillet R. Neonatal acute kidney injury: diagnosis, exposures, and long-term outcomes. *NeoReviews.* 2018;19(6).

increase in serum creatinine and decrease in urine output. Despite the consensus acceptance of this definition, it has limitations for the reasons outlined previously. **Serum creatinine values that fail to decline at least 50% from birth, creatinine consistently above the 99th percentile, prolonged oliguria, or failure to achieve a diuresis all may be clinically relevant indicators of AKI.**

Urine osmolality (UOsm), urine sodium concentration (UNa), and fractional excretion of sodium (FENa) have been proposed as tools to help differentiate prerenal injury from ATN. This differentiation is based on the premise that the tubules are working appropriately in prerenal injury and therefore can conserve salt and water, whereas in ATN, the injured tubules cannot conserve sodium appropriately. However, and of importance, because the renal tubules in newborns and premature infants are relatively immature, the distinction between prerenal injury and intrinsic renal injury/ATN is not as clear as in older children. **In the newborn, values suggestive of prerenal failure include UOsm greater than 350 mOsm/L, UNa less than 20 to 30 mEq/L, and FENa less than 3%. Values suggestive of ATN are UOsm less than 350 mOsm/L, UNa greater than 30 to 40 mEq/L, and FENa greater than 4%.**[48,99] Note that these values vary according to gestational age and maturity, and there is increased overlap of values with increasing prematurity. Therefore, it is important to recognize the limitations of these indices in the assessment of renal failure in the newborn period.

A renal ultrasound examination should be considered in all neonates with AKI to assess for possible urinary tract obstruction, renal vascular thrombosis, and congenital renal abnormalities causing chronic renal disease.

Prevention

The prevention of AKI in the preterm and term infant is complicated. Nonetheless, the following are some general recommendations:

- **Avoidance and early recognition of perinatal asphyxia**
- **Avoidance of maternal and infant angiotensin-converting enzyme (ACE) inhibitor use**
- **Aggressive management of hypoxemia, hypovolemia, hypotension, acidosis, and hypothermia**
- **Early detection and treatment of infection**
- **Judicious use of agents with vasoactive or nephrotoxic properties that can exacerbate renal injury (e.g., diuretics, aminoglycosides, NSAIDs)**

Principles of Management

Once the diagnosis of AKI has been established, management of metabolic derangements needs to be initiated promptly, including consideration of fluid balance, electrolyte status, acid-base balance, and nutrition, as well as initiation of renal replacement therapy when appropriate.

The timeline for and degree of recovery of renal function in AKI depends on the nature and duration of exposure to the underlying events that precipitated the injury. Return of renal function may be accompanied by a polyuric phase characterized by excessive urine output. During this phase, close attention to fluid and electrolyte balance is important. Adequate fluid support promotes recovery and prevents additional prerenal damage or ATN from intravascular volume depletion.

Maintenance of Intravascular Volume

The mainstay of therapy for prerenal injury is improving perfusion of the kidney by restoring intravascular volume, optimizing cardiac output, and normalizing blood pressure. **In the setting of appropriate cardiac function, fluid challenge of 10 mL/kg of body weight of crystalloid for small preterm infants and up to 20 mL/kg of body weight for term infants should be attempted.** In selected cases, **colloid may be preferred, and inotropic support may be necessary. Accurate measurement of central venous pressure (CVP) may help target euvolemia.**

If restoration of intravascular volume to the euvolemic state does not improve urine output, diuretic therapy may be helpful, but the risks and benefits must be considered. The conversion of oliguric to nonoliguric AKI has not been shown to alter the course of the AKI, nor reduce mortality.[32] However, **increasing urine output can allow for increased fluid intake of vital medications and nutrition and can also facilitate mechanical ventilation in neonates by reducing pulmonary edema.**[89] **Excessive diuresis can induce**

intravascular volume depletion and exacerbate ATN. Loop diuretics are the primary agents used. Most need to be filtered before reaching their therapeutic target in the tubular lumen. Therefore, in the setting of diminished GFR, higher doses of loop diuretics (e.g., furosemide 3 to 5 mg/kg intravenously) may be required to achieve appropriate tubular fluid concentrations. Chronic loop diuretic use in neonates leads to compensatory hypertrophy of distal tubular cells, causing loop diuretic "tolerance" as sodium resorption increases at the distal tubule. This can generally be overcome with a small dose of thiazide diuretic administered 30 to 60 minutes prior to the loop diuretic.[27] Mannitol should be avoided in neonates, especially premature infants, because of its hyperosmolarity and increased risk for intraventricular hemorrhage.

Low-dose dopamine increases urine output in oliguric, normotensive neonates by improving renal perfusion.[50] However, there is no evidence that low-dose (2 to 5 μg/kg/min) dopamine prevents AKI, decreases the need for dialysis, or improves survival in neonates.[71] Fenoldopam, a selective D1-receptor agonist that also increases renal blood flow and urine output in adults, does not increase urine output or improve renal outcomes in neonates.[155,191]

MANAGEMENT OF ELECTROLYTE AND ACID-BASE DISTURBANCES

Mild hyponatremia is common in AKI and is usually the result of fluid overload leading to dilutional hyponatremia. Mild hypervolemic hyponatremia responds well to fluid restriction or free water removal by dialytic therapy. In severe cases (serum sodium <120 mEq/L), there is a greater risk for seizures. Prompt but steady correction to a sodium level of approximately 125 mEq/L with hypertonic saline should be considered.

Hyperkalemia is a common and potentially life-threatening complication of acute kidney injury. The risk for cardiac rhythm disturbances increases with the presence of acidosis and hypocalcemia.

Heel-stick capillary blood sampling is commonly performed in neonates to minimize phlebotomy losses, but hemolysis of the sample is common and can artificially inflate serum potassium measurements. Once an elevated potassium value (>6.0 mEq/L) is confirmed by venipuncture or arterial sampling, potassium-containing intravenous (IV) fluids should be stopped. Severe hyperkalemia requires prompt therapy with sodium bicarbonate, nebulized albuterol, IV glucose and insulin, and IV calcium gluconate.[139] It is important to remember, however, that maneuvers to decrease total body potassium content, such as loop diuretics, are ultimately essential because other available measures simply provide cardiac protection (calcium) or shift potassium intracellularly (albuterol, insulin, bicarbonate) without removing potassium from the body. Cation exchange resins (Kayexalate) are a mainstay of hyperkalemia treatment in older children and adults but have been associated with hypernatremia, necrotizing enterocolitis, and intestinal obstruction in neonates.[156,190] Refractory hyperkalemia is an indication for dialysis.

Hypocalcemia and metabolic acidosis are common in AKI. Severe metabolic acidosis can be treated with IV or oral sodium bicarbonate, oral sodium citrate solutions, and/or dialysis therapy. When treating acidosis, it is important to consider the serum ionized calcium level. Overly rapid correction of acidosis will decrease the ionized calcium concentration and may precipitate tetany and/or seizures. Finally, hyperphosphatemia is a common electrolyte abnormality noted during AKI. Hyperphosphatemia should be treated with dietary phosphorus restriction and with oral phosphorus binders such as calcium carbonate[130] or sevelamer. Pretreatment of certain formulas or breast milk with sevelamer has been shown to reduce dietary phosphorus content.[149,174] The goal serum phosphorus concentration is less than 6.5 to 7 mg/dL. Hyperphosphatemia alone is rarely an indication for dialysis.

In many instances, AKI is associated with marked catabolism, as evidenced by elevated blood urea nitrogen. Malnutrition can develop rapidly, leading to delayed recovery from AKI. Proper nutrition and accurate measurement of daily weight are essential in the management of the newborn with AKI.

Outcome and Prognosis

Recovery from acute kidney injury in the newborn and long-term renal prognosis are

highly dependent on the underlying etiology of the AKI. A single episode of prerenal AKI in the neonatal period, if it is managed appropriately and resolves, is unlikely to be associated with significant long-term renal injury. **However, survivors of a lengthy NICU stay may be exposed to multiple episodes of AKI. AKI from any cause is associated with increased mortality and hospital length of stay in neonates.**[95] **Other factors associated with increased mortality among infants with AKI include multi-organ failure, hypotension, need for vasopressors, hemodynamic instability, and need for mechanical ventilation and dialysis.**[10]

In general, **newborns who require more than 1 month of renal replacement therapy for AKI are considered to have end-stage renal disease (ESRD).** Newborns who recover from AKI but have suffered substantial loss of nephrons, as may occur in cortical necrosis, hypoxic-ischemic injury, and nephrotoxic injury, are at significant risk for late development of progressive chronic kidney disease long after the initial insult.[14,116] Those who required dialysis for renal failure, particularly if a prolonged course, are of particular concern.

Preterm infants are also a particular risk group for chronic kidney disease. Approximately 60% of nephrogenesis occurs in the third trimester, with an exponential increase in both renal mass and number of nephrons. Minimal nephrogenesis occurs after birth. **Preterm neonates have consistently lower nephron number and renal mass at term-corrected age.**[41,46] A smaller starting complement of nephrons, exposed to a barrage of stressors in the NICU as previously described, is hypothesized to place premature infants at even greater risk for nephron damage and chronic renal failure.[41,116]

Low birth weight and prematurity are associated with significantly increased odds of chronic kidney disease (CKD).[113] Therefore, **newborns with AKI and preterm or low-birth-weight infants should have lifelong monitoring of their renal function, blood pressure, growth, and urinalysis. Growth faltering is an early and ominous sign of CKD in infants.**[76] **Typically, the late development of chronic kidney disease will first become apparent with the development of hypertension or proteinuria and eventually an elevated blood urea nitrogen (BUN) and creatinine.** The lack of renal reserve in NICU survivors may not be apparent until puberty or later.[113]

RENAL REPLACEMENT THERAPY

Renal replacement therapy (dialysis) is indicated for fluid overload, metabolic acidosis, hyperkalemia, and hypocalcemia that are refractory to medical management; symptomatic uremia, which is unusual in the neonate; hyperammonemia refractory to medical management; and drug or toxin overdose. **Options for dialysis therapy in neonates include hemodialysis (HD), continuous renal replacement therapy (CRRT), or peritoneal dialysis (PD).** All dialytic therapies rely on the principles of diffusion (movement of solute from higher to lower concentration) and convection/ultrafiltration (bulk movement of solute in association with fluid removal). The optimal modality for any given neonate will be determined by the goals of therapy, hemodynamic stability, comorbid conditions, anticoagulation risk, and institutional preferences, as outlined next.

Hemodialysis. In hemodialysis, blood is removed from the neonate via a central hemodialysis catheter and flows across an appropriately sized artificial filter (dialyzer) while dialysate of the preferred composition travels countercurrent (in the opposite direction to blood) across the filter. In this manner, **solutes diffuse from higher to lower concentration, such that urea, creatinine, potassium, ammonia, dialyzable drugs, and toxins, amongst other substances, are removed from the patient while bicarbonate diffuses into the patient's blood.** The countercurrent flow of dialysate optimizes the diffusion gradient for solute removal. A transmembrane pressure is applied to the filter to induce fluid removal at the targeted rate. The fluid that is removed contains solutes. The blood is then returned to the neonate. **A typical hemodialysis session lasts 2 to 4 hours** but may be more prolonged if needed (e.g., for toxin or ammonia removal). An anticoagulant, most commonly heparin, is administered to prevent circuit clotting, particularly given the low rates of blood flow used for neonates, with care taken to avoid excessive anticoagulation. **The advantage of hemodialysis is that solute and fluid abnormalities can be rapidly corrected. Disadvantages include the need for vascular access** (usually a 7-Fr double-lumen venous hemodialysis catheter); **continuous skilled nursing support during the procedure; systemic anticoagulation,** which

increases the risk of bleeding complications, including intraventricular hemorrhage in premature infants; **and limited equipment targeted to the body size of neonates**. With respect to the latter, most neonates will also require a blood prime of the circuit because of the relatively large extracorporeal circuit volume.

Continuous Renal Replacement Therapy (CRRT). **CRRT has become increasingly popular in the treatment of AKI** (Fig. 25.3). The therapy consists of several variations of diffusion and convection, all of which result in net solute clearance and fluid removal from the blood. The procedure itself is similar to hemodialysis, but the therapy is provided on a continuous basis (e.g., 24 hours/day) and often for several days at a time. **Thus, CRRT allows for an overall slower rate of solute and fluid removal, which may be better tolerated in hemodynamically unstable patients**. Ongoing dialytic support may also be valuable in toxin/drug overdose in which prolonged clearance is needed or the toxin/drug is associated with a rebound of plasma levels, as the support can be aggressive initially and then decreased but maintained over time. **Disadvantages of CRRT include the need for continuous vascular access and anticoagulation and limited equipment targeted to the body size of neonates.** Anticoagulation can be systemic (e.g., heparin) or regional (e.g., citrate, which anticoagulates the blood as it leaves the patient and enters the circuit, with calcium provided as blood reenters the patient to reverse the anticoagulation). In recent years, improvements in the technologies of CRRT have made it more suitable for use in neonates, and **most centers in North America can provide CRRT routinely for acute neonatal dialysis.** However, filter sets (dialyzer and tubing) specific to the size of the neonate are not yet available for most CRRT systems in the United States, leading to the current need for a blood

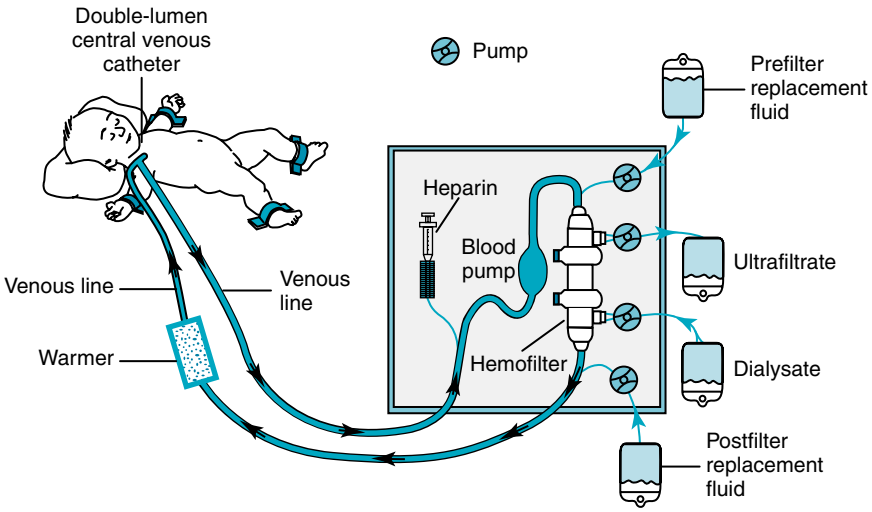


FIGURE 25.3 Continuous renal replacement therapy (CRRT) in the newborn. A typical setup is shown in the figure. Blood is pumped from the patient through a central line across a hemofilter (artificial kidney) at a rate of 5 to 10 mL/kg/min (minimum 30 mL/min). A constant anticoagulant infusion (shown here as heparin) is maintained to prevent circuit clotting. Dialysate can be administered countercurrent (in the direction opposite to blood flow) across the hemofilter (continuous venovenous hemodialysis [CVVHD]), replacement fluid can be administered pre- or post-hemofilter (continuous venovenous hemofiltration [CVVH]), or both dialysate and replacement fluid can be used (continuous venovenous hemodiafiltration [CVVHDF]). The amount of ultrafiltrate (fluid removed) is regulated according to individualized need and tolerance. The discarded ultrafiltrate contains fluid and solutes/toxins; thus, these are removed from the patient's circulation. Before the blood is returned to the patient, it is passed through a blood warmer to prevent hypothermia. With most commercially available CRRT systems, the total volume of the circuit exceeds 10% of the neonate's blood volume, so a blood prime of the circuit is required. Individual therapy goals and institutional preference affect the choice of vascular access, modality (CVVHD vs. CVVH vs. CVVHDF), anticoagulant, and flow rates.

prime of each new circuit. Some centers have experience performing CRRT via an Aquadex machine, which allows for smaller blood volumes; however, this is not yet the standard of care.[13]

Peritoneal Dialysis. Acute *peritoneal dialysis* (PD) **is a major modality of dialysis therapy for acute and chronic kidney failure in the neonate, particularly when vascular access is difficult to maintain.** PD works by the processes of diffusion and ultrafiltration using the peritoneal membrane as a filter. For this therapy, **an acute or chronic peritoneal dialysis catheter is placed into the peritoneum.** The best results are usually obtained with a well-secured "permanent" peritoneal dialysis catheter that is surgically placed by an experienced pediatric surgeon. The preferred catheter is a curled silastic Tenckhoff catheter with one or two cuffs that adhere locally to immobilize the interior portion of the catheter. **Dialysis fluid (dialysate) is infused into the peritoneal space, either via a machine or manually, and allowed to "dwell" for a designated time. During the dwell phase, particles move from high concentration to low concentration (diffusion).** The composition of the dialysate, which contains electrolytes and dextrose, is altered via this exchange of solutes between the dialysate and the peritoneal capillaries that perfuse the peritoneal lining. For example, high concentrations of urea and creatinine are filtered from the blood into the dialysate, which contains no urea or creatinine. Alternatively, the high concentration of bicarbonate diffuses from the dialysate into the blood, thus helping to counter metabolic acidosis. The concentration of dextrose in the dialysate, which is markedly higher than the serum glucose concentration, creates an osmotic gradient that stimulates the movement of fluid from the blood into the dialysate (ultrafiltration). The dialysate is then drained and discarded, and the cycle repeats. **Advantages of PD include that it is relatively easy to perform, does not require anticoagulation, and is well tolerated in hemodynamically unstable neonates.** However, a peritoneal dialysis catheter cannot be placed in children with major intraabdominal disease (postsurgical, gastroschisis, necrotizing enterocolitis, etc.). Because of the nature of the procedure, the correction of solute and fluid abnormalities occurs at a slower rate than by HD or CRRT, and fluid removal cannot be precisely controlled due to variation in individual peritoneal membrane transport characteristics. **The initial fill volume is generally 10 to 20 mL/kg progressing to 40 mL/kg for chronic dialysis; occasionally, even this small initial volume is poorly tolerated in the setting of severe respiratory failure. There is also the potential for peritonitis.**

INTRINSIC RENAL PARENCHYMAL ABNORMALITIES

Several congenital renal abnormalities can be classified by the amount of tissue, differentiation of tissue, and position of the kidneys.

Renal Agenesis

***Congenital absence or agenesis* of renal tissue can occur unilaterally or bilaterally.** Unilateral renal agenesis is seen more frequently (~1:3000 live births)[141] and may manifest as a solitary kidney with eventual enlargement caused by compensatory hypertrophy. The condition appears to be more common in males and infants of African American or diabetic mothers.[141] **Unilateral agenesis has also been associated with Turner, Poland, and VATER syndromes.** In unilateral agenesis, patients are often asymptomatic and are diagnosed inadvertently on imaging or based on the significant association with malformations of the lower genitourinary tract. **In newborns with a known solitary kidney, a VCUG should be considered to exclude vesicoureteral reflux.**[185] Renal dysplasia may rarely occur in the remaining kidney; thus, compensatory hypertrophy of the remaining kidney is an encouraging sign. Restriction from participation in contact sports based on the solitary kidney does not appear to be warranted.[77,78]

Bilateral renal agenesis, also known as *Potter disease,*[144] is seen rarely, with an incidence of 1 per 4000 births. **In bilateral renal agenesis, the majority of affected infants are male and small for gestational age with a history of maternal oligo-/anhydramnios.** The characteristic facial features accompanying Potter syndrome include wide-set eyes; infraorbital creases; a flattened nose; a receding chin; and large, low-set ears with little cartilage.

Other associated malformations can include pulmonary hypoplasia, hydrocephalus, meningocele, multiple skeletal anomalies, and imperforate anus. In the absence of fetal intervention, the fetus is typically stillborn or dies within hours of birth due to pulmonary hypoplasia. Although not the standard of care, some centers have attempted to improve pulmonary outcomes by providing serial amnioinfusion during pregnancy. Renal outcomes remain unchanged by this therapy.

Renal Hypoplasia

***Renal hypoplasia* is a deficiency in the amount of renal tissue and is expressed as an abnormally small kidney.** Histologically, the kidney structure is otherwise normal. However, the decreased nephron mass is often insufficient to maintain normal GFR throughout the child's life. The condition is apparent by ultrasound with variably echogenic kidneys, which are small for body size and do not grow at the expected rate with serial ultrasound.

Renal Dysplasia

Abnormalities in renal tissue differentiation are most commonly expressed as dysplastic kidneys. Renal dysplasia is a failure of the metanephric tissue to mature appropriately. Monogenic causes include mutations in individual genes, such as HNF1β, PAX2, and uroplakins, but there are also recent reports of children with compound heterozygote mutations in several renal/urinary tract developmental genes.[154,186] The result is a persistence of immature structures and a decrease in normal functioning renal tissue. Renal dysplasia may be seen in one or both kidneys and can involve the entire kidney, segments of the kidney, or microscopic foci of a kidney. Dysplasia is often expressed as cyst formation. **The extent of dysplasia will determine the risk of CKD and need for eventual renal replacement therapy.**

MULTICYSTIC DYSPLASTIC KIDNEY

Multicystic dysplastic kidneys (MCDKs) are nonfunctional, and therefore bilateral disease is associated with anhydramnios late in pregnancy. **Unilateral MCDK is both the most common cystic lesion of the neonatal kidney and one of the most frequently palpated abdominal masses in the newborn.** MCDK is usually sporadic, but some familial and syndromic cases have been reported. MCDK is slightly more common in males and on the left side.[9,160] Usually the ureter is absent, atretic, or stenotic. No orifice is found in the bladder. Such kidneys are enlarged and diffusely cystic. with histopathology showing nests of cartilage and mesenchymal mantles surrounding primitive tubules. A nuclear renal scan shows no flow or function of the MCDK. **Renal function and structure may be normal in the remaining kidney of infants with unilateral MCDK; however, approximately one third of patients can be shown to have abnormalities of the contralateral kidney, most commonly vesicoureteral reflux, ureteropelvic junction (UPJ) obstruction, or dysplasia.**[160] Therefore, a VCUG should be performed on every patient, with consideration of a nuclear renal scan to exclude obstruction in the setting of hydronephrosis with a normal VCUG. There is an increased risk of chronic hypertension, proteinuria, and CKD in patients with contralateral abnormalities.[121] Multicystic dysplastic kidneys generally involute with time, so a conservative approach is recommended.[57] The risk of malignancy in the MCDK has been shown to be negligible.[57] Rarely, the MCDK impacts nutrition because of its large size in the small preterm infant.

POLYCYSTIC KIDNEY DISEASE

***Polycystic kidney disease* (PKD) may present as one of two types in the infant: (1) autosomal-recessive polycystic kidney disease (ARPKD) or (2) autosomal-dominant polycystic kidney disease (ADPKD).**

Autosomal-Recessive Polycystic Kidney Disease. ARPKD manifests with varied severity, but it is always bilateral. The kidneys are enlarged, with a proliferation of renal tubules and dilated collecting tubules. These are not true "cysts" but ectatic dilations of the collecting tubules, and the kidney has a reniform shape. **Various combinations of cystic renal disease and hepatic disease occur in ARPKD,** with liver disease including congenital hepatic fibrosis due to ductal plate malformation with eventual hepatosplenomegaly and complications of portal hypertension, or nonobstructive dilation of intrahepatic bile ducts *(Caroli disease)* with a high risk of recurrent cholangitis. **Prenatal ultrasound frequently shows bilaterally enlarged echogenic**

kidneys, often associated with oligohydramnios. Significant hypertension, nephromegaly, pulmonary hypoplasia, hyponatremia, and renal insufficiency may be evident in the affected neonate.[79] However, a subset of patients manifest primarily with liver disease and may not be diagnosed until adulthood.[81] Nonetheless, ARPKD will eventually progress to ESRD at a rate of 14% by 5 years of age, 29% by 10 years of age, and 58% by 20 years of age.[52] The condition is transmitted in an autosomal-recessive manner, so there may be a history in siblings of ARPKD or a family history of miscarriage or early infant death. **Evaluation includes assessment of renal function and blood pressure.** The postnatal abdominal ultrasound typically shows enlarged bilateral kidneys with decreased corticomedullary differentiation. Liver abnormalities may be evident in the neonatal period but more commonly become apparent over time. Current treatment consists of supportive management, including control of hypertension and complications of chronic kidney disease. ACE inhibitors are frequently the preferred antihypertensive agent, although there is no evidence to support the superiority of this class of medications, and their use should be limited when GFR is less than 30 mL/min/1.73 m^2 and in preterm infants before completion of nephrogenesis. Renal replacement therapy, including kidney transplantation with or without liver transplantation, is typically required in later life. **The vast majority of children presenting with significant clinical manifestations in the neonatal period will reach ESRD in early to mid-childhood.**

Autosomal-Dominant Polycystic Kidney Disease. ADPKD involves cyst formation in any portion of the nephron and Bowman space. The condition is associated with the progressive development of renal macrocysts leading to compression of normal renal parenchyma and progression to ESRD at an average age of 60 years. Cysts also develop in other visceral organs, including the liver, pancreas, and spleen, with increasing age. There is an association between ADPKD and cerebral artery aneurysms, but the latter do not generally cause difficulty until adulthood.[25,26] ADPKD may be evident on prenatal ultrasound with enlarged echogenic and/or cystic kidneys, only rarely accompanied by oligohydramnios. In contrast to ARPKD, increased corticomedullary differentiation has been observed. However, it can be difficult to distinguish ADPKD from ARPKD by prenatal or early infancy ultrasound. The family history and sonographic evaluation of both parents can be helpful in this regard, although the **spontaneous mutation rate for ADPKD approaches 15%.** Many children who are diagnosed by prenatal ultrasound demonstrate improvement in sonographic findings over the first 1 to 2 years of life and likely would not have otherwise been diagnosed on clinical grounds for several years. However, a small subset of children with "very early onset" of ADPKD present within 18 months of birth with hypertension, gross hematuria, abnormal renal function, or other symptoms.[64,165] This group appears to show early progression of renal insufficiency. Management includes routine monitoring of blood pressure, with consideration of ACE inhibitor treatment when blood pressure exceeds the 75th percentile for age, sex, and height. ACE inhibitors in this setting may help to prevent the decline in renal function and the increase in left ventricular mass index associated with ADPKD. Recently pravastatin has been shown to slow progression of structural kidney disease in affected children and young adults ages 8 to 22 years;[37] however, this has not been studied in younger children.

RENAL VEIN THROMBOSIS

Renal vein thrombosis (RVT) can be an acute, life-threatening condition or insidious in onset.[33,58,110] **RVT is associated with conditions that cause intravascular volume depletion and decreased oxygenation within the kidney.** Perinatal associations with neonatal RVT include maternal diabetes, toxemia, maternal thiazide therapy, polycythemia, placental insufficiency, birth asphyxia, prematurity, respiratory distress syndrome (RDS), and sepsis. Angiography has also been associated with RVT. **Thrombosis most often occurs in the smaller renal veins rather than in the main renal vein. The involved kidney may enlarge secondary to obstruction to blood flow and form a palpable flank mass.** Other clinical signs and symptoms may include gross or microscopic hematuria, decreased urine output, anemia, and thrombocytopenia (<75,000). Family history

of thrombophilia should be reviewed, and evaluation pursued in appropriate settings. **Management includes treatment of the underlying illness, maintenance of appropriate intravascular volume, and consideration of anticoagulation. Administration of anticoagulants remains controversial for RVT.** Research on the effects of heparin-based anticoagulation and thrombolytic therapy on the long-term renal function of affected patients has yielded conflicting results.[33] Surgical excision of the thrombus is not usually necessary. Renal tubular dysfunction is often observed after recovery from RVT. Long-term follow-up may be needed to assess renal growth and function.

HYDRONEPHROSIS

Etiology and Associated Findings

The collecting system of the kidney is composed of the ureter, pelvis, and calyces, all of which function as a system for removing urine from the kidney. **Hydronephrosis, one of the most common causes of abdominal mass in the newborn, involves dilation of the pelvis and calyces, most often as a result of congenital obstruction.**[23,124] The impaired drainage of urine from severe or chronic obstruction during renal development may induce dysplastic and cystic changes that further impair kidney development and function.

The most common ureteral site of obstruction is at the ureteropelvic junction (UPJ). The ultrasound demonstrates ballooning of the renal pelvis with a normal appearance of the ureter and bladder. Obstruction at the ureterovesical junction (UVJ), also known as *primary megaureter,* occurs more often in the male infant. UVJ obstruction more frequently affects the left ureter. The ultrasound demonstrates hydroureteronephrosis with a normal-appearing bladder. **Affected patients with UPJ or UVJ obstruction are usually asymptomatic unless the obstruction is bilateral.** Rarely, recurrent vomiting, particularly after fluid intake, or abdominal discomfort may be evident. **A nuclear renal scan is helpful to diagnosis both UPJ and UVJ obstruction.** Definitive surgical repair can be undertaken in both conditions. In the case of UVJ obstruction, the stenotic segment can be removed and the ureter reimplanted into the bladder.

Posterior urethral valves (PUVs) are the major cause of urethral obstruction in males.[131] **Affected males show renal insufficiency and diminished urine output due to bladder outlet obstruction.** Complications include poor growth and urinary tract infection. In some cases, the enlarged bladder or hydronephrotic kidney(s) can be palpated. The ultrasound typically shows an enlarged thick-walled bladder with varying degrees of hydroureteronephrosis and renal dysplasia. **A VCUG is the definitive diagnostic study**, highlighting the trabeculated bladder and a dilated posterior urethra. In some cases, the valve leaflets are evident as lucencies; if leaflets are not apparent, prominence of the posterior urethra distally over the bulbar urethra may be noted. The anterior urethra is typically underfilled, and voiding is incomplete. **Associated vesicoureteral reflux is also often evident by VCUG. Bladder decompression is indicated until surgical repair of PUV is undertaken, and any secondary features of chronic kidney disease should be addressed.** Post-obstructive diuresis may occur with decompression, so careful attention to volume status is required. Tubular dysfunction with renal tubular acidosis or pseudohypoaldosteronism is frequent. Definitive surgical repair includes transurethral fulguration of the valves. **In preterm infants who are too small for a transurethral approach, an indwelling urethral catheter or suprapubic tube may be left in place, or a vesicostomy created, awaiting somatic growth.** Many affected males have chronic bladder dysfunction, and recent studies suggest a guarded long-term prognosis for renal function in later life, even in those who appear to do well clinically in childhood.[38,87]

Prune-belly syndrome, also known as *Eagle-Barrett syndrome,* is a less common cause of functional obstruction and dilation of the pelvis and calyces, with an incidence approaching 1:50,000. There is a strong male predominance. This triad of anomalies includes (1) absence or hypoplasia of the abdominal wall muscles, (2) bilateral cryptorchidism, and (3) urinary tract abnormality. **The loose, shriveled abdomen is responsible for the "prune-belly" appearance, which diminishes with age and rarely requires surgical correction. Renal dysplasia is usually seen in prune-belly syndrome and may range from mild to severe involvement.** The enlarged bladder may be seen in conjunction with a patent urachus draining urine. A VCUG demonstrates a hypoplastic prostatic

urethra, no evidence of PUV, and variable degrees of vesicoureteral reflux. Management includes ensuring appropriate drainage of urine, addressing any complications of chronic kidney disease, and eventual orchiopexy.

Vesicoureteral reflux is further discussed in the section on urinary tract infection.

Treatment

Mild to moderate unilateral obstruction does not require immediate treatment, assuming the other kidney is normal. Close follow-up is indicated for monitoring of kidney growth, and significant obstruction should be addressed with surgical intervention when feasible. Fetal intervention can be offered for significant bilateral disease with decreased amniotic fluid, depending on the gestational age of the fetus and severity of hydronephrosis. However, surgical intervention in utero is controversial and center-dependent, and the morbidity of this therapy is high. Although there is selection bias, in many fetal intervention cases, ESRD is reached in early childhood.

HYPERTENSION

Systemic hypertension is an important clinical problem in neonates. Although the reported incidence in all neonates is low, ranging from 0.2% to 3%,[67,168,182] **hypertension is more commonly observed in premature and other newborns cared for in the NICU, particularly those with chronic lung disease and/or a history of umbilical artery catheterization.**[21,68,164] **Hypertension in the neonate is often asymptomatic,** although rarely, marked hypertension is present and can be associated with severe sequelae such as congestive heart failure or intracranial hemorrhage.

Diagnosis

The gold standard for assessment of blood pressure (BP) in neonates is direct measurement by intra-arterial analysis of the pulse pressure waveform.[53] There is a good correlation between umbilical artery and peripheral artery catheter BPs in neonates.[35] Indirect measurement of BP by palpation or auscultation is not recommended for routine assessment in the NICU setting, and sonographic Doppler assessment has largely been replaced by oscillometric measurement.[114,134] It is important to note, however, that the latter procedure is based on detection of pressure oscillations within the artery; therefore, this method determines the mean arterial pressure and then uses an algorithm specific to each manufacturer to establish systolic and diastolic BP values. **There is generally a good correlation between oscillometric and umbilical or radial artery BP in neonates and young children.**[142] However, there are important limitations to this methodology. Few studies have compared specific oscillometric BP monitors to direct arterial measurements in neonates, and these have shown variable accuracy depending on the size of the infant,[51] with increased frequency of oscillometric methods to overread BP compared with direct measurement.[137]

It is also critical to consider the state of the infant at the time of BP assessment. Significant BP variations are observed with the neonate's level of activity, position, and particularly during feeding.[82] **A standardized protocol for conditions of BP assessment in neonates has been proposed,**[136] **including measurement of the right upper arm BP by an oscillometric device with the infant in a prone or supine position, 1.5 hours after feeding or medical intervention, using an appropriate size cuff with width to arm circumference ratio in the range of 0.45 to 0.55.** The BP is to be obtained on three successive readings at 2-minute intervals after a 15-minute period of rest after cuff placement with the infant in an asleep or quiet-awake state. This protocol has yet to be widely adopted.

Normal values for BP have been developed by body weight and postnatal age[60] **(Fig. 25.4). Studies in term and preterm infants show that BP increases with both gestational and postconceptional age as well as birth weight.**[102,103,193] **Systolic and diastolic BP have been shown to increase about 2 mm Hg/day over the first 5 days of life.** The rate of increase then slows to 0.25 mm Hg/day for systolic and 0.15 mm Hg/day for diastolic BP over the next 3 months.[193] **Preterm infants born at 28 to 31 weeks' gestation have been shown to have a more rapid rise in BP over the first 2 to 3 weeks compared with infants born at later gestational age.**[103] BP reaches a steady value for the first year of life by 2 to 3 months of age. Age-specific percentiles for normal

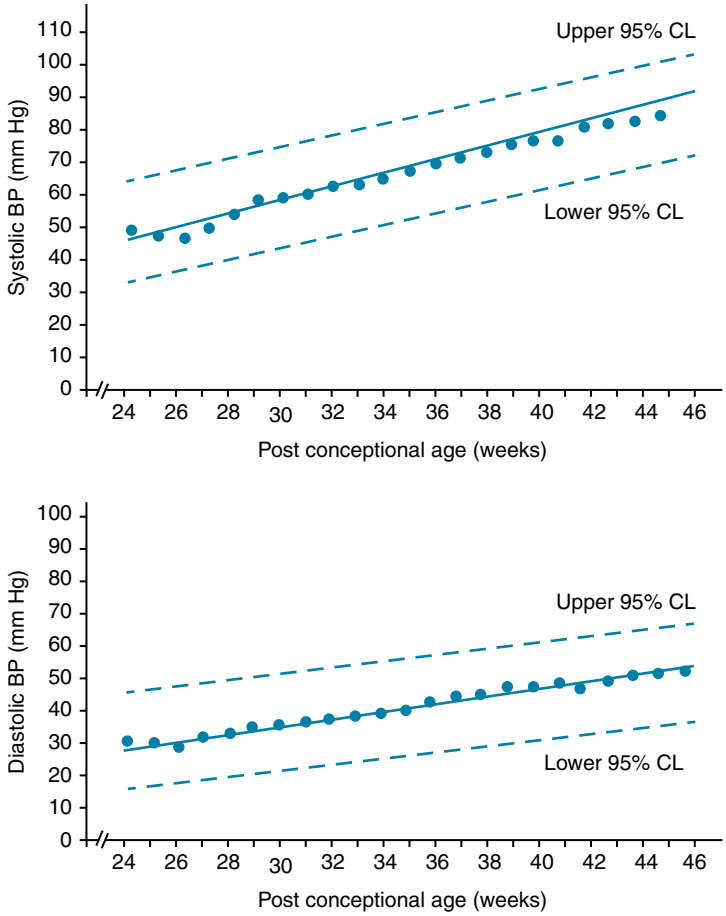


FIGURE 25.4 Linear regression of mean systolic **(upper panel)** and diastolic **(lower panel)** blood pressure (BP) by postconceptional age in weeks, with 95% confidence limits (CL, upper and lower dashed lines). (From Zubrow AB, Hulman S, Kushner H, Falkner B, and the Philadelphia Neonatal Blood Pressure Study Group. Determinants of blood pressure in infants admitted to neonatal intensive care units: a prospective multicenter study. *J Perinatol.* 1995;15(6):470.)

BP for boys and girls from birth to 12 months have been published.[133] **Normal values for BPs in neonates after 2 weeks of age are shown in** Table 25.4 **and during infancy are shown in** Fig. 25.5.

Etiology

The causes of hypertension are listed in Box 25.2. All infants with hypertension require appropriate evaluation looking for a specific etiology. **The most common etiologies of systemic hypertension in neonates include renovascular and renal parenchymal diseases.** Up to 9% of neonates with umbilical artery catheters (UAC) develop hypertension. UAC-associated thromboembolism affecting the aorta and/or the renal arteries was initially described in the 1970s[135] and can occur even in the absence of demonstrable thrombi. Not surprisingly, **longer duration of UAC placement is associated with a higher risk of thrombus formation.**[32] Although high UAC placement is associated with fewer ischemic events such as necrotizing enterocolitis, the frequency of hypertension does not differ between high and low placement.[16] Thus, it has been proposed that **UAC-related hypertension is related to thrombus formation associated with endothelial disruption at the time of catheter placement.** Renal vein thrombosis is discussed

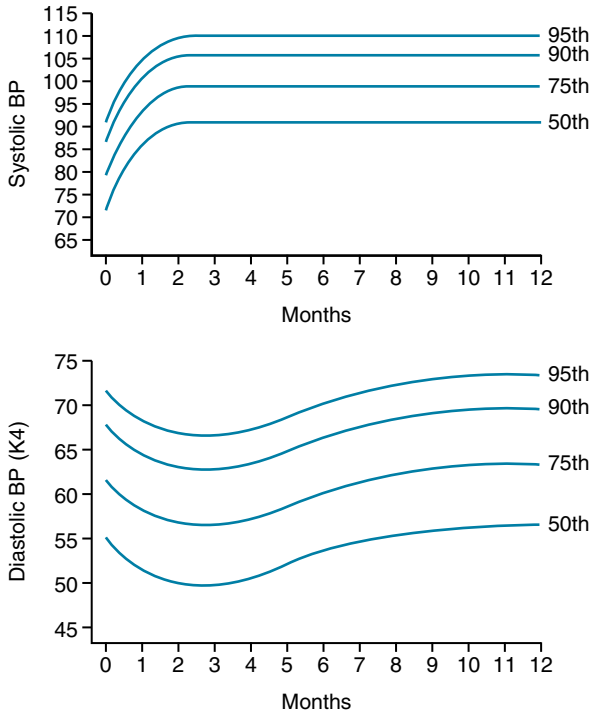
TABLE 25.4 ESTIMATED BLOOD PRESSURE VALUES AFTER 2 WEEKS OF AGE IN INFANTS FROM 26 TO 44 WEEKS' POSTCONCEPTIONAL AGE

POSTCONCEPTIONAL AGE (WEEKS)	50TH PERCENTILE	95TH PERCENTILE	99TH PERCENTILE
44			
SBP	88	105	110
DBP	50	68	73
MAP	63	80	85
42			
SBP	85	98	102
DBP	50	65	70
MAP	62	76	81
40			
SBP	80	95	100
DBP	50	65	70
MAP	60	75	80
38			
SBP	77	92	97
DBP	50	65	70
MAP	59	74	79
36			
SBP	72	87	92
DBP	50	65	70
MAP	57	72	77
34			
SBP	70	85	90
DBP	40	55	60
MAP	50	65	70
32			
SBP	68	83	88
DBP	40	55	60
MAP	49	64	69
30			
SBP	65	80	85
DBP	40	55	60
MAP	48	63	68

TABLE 25.4 ESTIMATED BLOOD PRESSURE VALUES AFTER 2 WEEKS OF AGE IN INFANTS FROM 26 TO 44 WEEKS' POSTCONCEPTIONAL AGE—CONT'D

POSTCONCEPTIONAL AGE (WEEKS)	50TH PERCENTILE	95TH PERCENTILE	99TH PERCENTILE
28			
SBP	60	75	80
DBP	38	50	54
MAP	45	58	63
26			
SBP	55	72	77
DBP	30	50	56
MAP	38	57	63

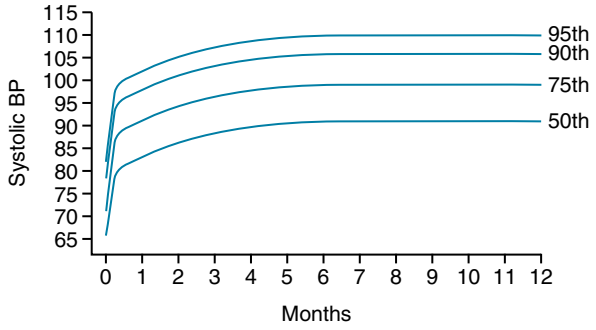
DBP, Diastolic blood pressure; *MAP,* mean arterial pressure; *SBP,* systolic blood pressure.
From Dionne JM, Abitbol CL, Flynn JT. Hypertension in infancy: diagnosis, management and outcome. *Pediatr Nephrol.* 27(1): 22, 2012.

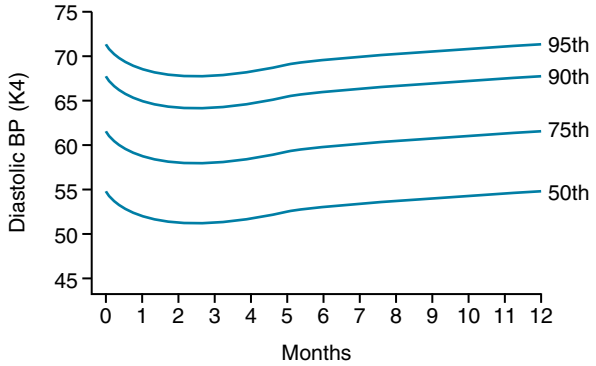


A

90th Percentile														
Systolic BP	87	101	106	106	106	106	106	105	105	105	105	105	105
Diastolic BP	68	66	63	63	63	66	66	67	68	68	69	69	69
Height (cm)	51	59	63	66	66	70	72	73	74	76	77	78	80
Weight (kg)	4	4	5	5	6	7	8	9	9	10	10	11	11

FIGURE 25.5 Age-specific percentiles for blood pressure in the first year of life in boys **(A)** and girls **(B).** *BP,* Blood pressure. (From Report of the Second Task Force on Blood Pressure Control in Children—1987. Task Force on Blood Pressure Control in Children. National Heart, Lung, and Blood Institute, Bethesda, Maryland. *Pediatrics.* 1987;79(1):1.)





B

90th Percentile													
Systolic BP	76	88	101	104	105	106	106	106	106	106	106	106	105
Diastolic BP	68	65	64	64	65	65	66	66	66	67	67	67	67
Height (cm)	54	55	56	58	61	63	66	68	70	72	74	75	77
Weight (kg)	4	4	4	5	5	6	7	8	9	9	10	10	11

FIGURE 25.5, cont'd

earlier in this chapter and can be associated with severe and prolonged hypertension. Fibromuscular dysplasia can be seen in infancy and is typically associated with branch vessel disease rather than main renal artery disease.[178] Mechanical compression of one or both renal arteries by tumor, abdominal mass, or a hydronephrotic kidney can induce renovascular hypertension.

Polycystic kidney disease, both autosomal recessive and less commonly autosomal dominant, can be associated with neonatal hypertension. Urinary tract obstruction can also be associated with hypertension in the absence of renal artery compression. **Hypertension is commonly seen in acute tubular or cortical necrosis** due to fluid overload or hyperreninemia. Hypertension may be more prominent in the recovery phase of ATN.

Abman et al. first **described hypertension associated with bronchopulmonary dysplasia (BPD)** in the mid-1980s[3] with **an incidence of hypertension upon discharge of 43% in infants with BPD compared with 4.5% without BPD. Importantly, more than half of the infants with BPD who developed hypertension did not demonstrate elevated BP until after hospital discharge, emphasizing the importance of routine BP assessment in the follow-up of NICU graduates.** The mechanism underlying BPD-associated hypertension is not known, although chronic hypoxemia and hypercarbia are known to induce diminished nitric oxide production and increased endothelial inflammation and vascular dysfunction in older children with obstructive sleep apnea.[134] **BPD-associated hypertension is correlated with a greater need for diuretic and bronchodilator**

BOX 25.2 ETIOLOGY OF HYPERTENSION IN THE NEONATE

Vascular
- Thromboembolism
- Renal artery stenosis
- Coarctation of the aorta
- Hypoplastic abdominal aorta (midaortic coarctation)
- Renal vein thrombosis
- Renal artery compression
- Congenital rubella infection
- Idiopathic arterial calcification

Renal Parenchymal Disease
- Congenital
  - Polycystic kidney disease (autosomal dominant or recessive)
  - Multicystic dysplastic kidney (rare)
  - Renal hypo-/dysplasia (rare)
  - Tuberous sclerosis
  - Urinary tract obstruction
- Acquired
  - Acute tubular necrosis
  - Renal cortical necrosis
  - Hemolytic-uremic syndrome (rare)
  - Urinary tract obstruction
  - Reflux nephropathy

Neoplasia
- Wilms tumor
- Neuroblastoma

Respiratory
- Bronchopulmonary dysplasia

Endocrine
- Adrenogenital syndrome
- Cushing disease
- Hyperaldosteronism
- Thyrotoxicosis
- Pseudohypoaldosteronism type II (Gordon syndrome)

Other
- Closure of abdominal wall defects (compartment syndrome)
- Fluid overload
- Hypercalcemia
- Increased intracranial pressure
- Medications
  - Phenylephrine
  - Corticosteroids
  - Theophylline/caffeine
  - Deoxycorticosterone
  - Vitamin D intoxication (hypercalcemia)
  - ACTH
  - Maternal cocaine or heroin use
- Adrenal hemorrhage
- Extracorporeal membrane oxygenation

From Dionne JM, Abitbol CL, Flynn JT. Hypertension in infancy: diagnosis, management and outcome. *ACTH,* Adrenocorticotropic hormone. *Pediatr Nephrol.* 2012;27(1):17.

use,[2] consistent with the concept that the risk is higher with more severe chronic lung disease. Aortic coarctation can be associated with hypertension both before and after repair, even in the absence of recurrent stenosis. Monogenic hypertension is rare in the neonate. Numerous medications can induce systemic hypertension in the neonate. **Maternal cocaine or heroin use may affect the developing kidney, resulting in an increased risk of hypertension.**[55,93] Tumors are rarely seen in the neonatal period but can cause direct compression of one or both renal arteries, urinary tract obstruction, or production of hormones that elevate blood pressure. Hypertension is commonly seen in neonates requiring extracorporeal membrane oxygenation. The underlying mechanisms are not clear.[31]

Data Collection

HISTORY

A detailed history of prematurity and associated comorbidities, including chronic lung disease or intracranial hemorrhage, is indicated. A history of UAC placement is important. It is important to review the medication history for specific contributors. The family history should be reviewed for early-onset hypertension, although monogenic hypertension is rare and often not evident within the first days of life.

SIGNS AND SYMPTOMS

Most neonates with systemic hypertension are asymptomatic. Congestive heart failure, renal

dysfunction, or hypertensive retinopathy can occasionally be seen with severe hypertension. **Nonspecific symptoms may be evident, including feeding difficulty, lethargy, irritability, failure to thrive, or seizures.** The general appearance of the infant, including any dysmorphic features, should be assessed. A careful abdominal examination may demonstrate a mass suggestive of either a hydronephrotic or polycystic kidney or tumor. Abnormal genitalia suggests congenital adrenal hyperplasia. **Femoral pulses should be assessed and BP measurements taken in all extremities to exclude coarctation of the aorta.**

LABORATORY DATA

Laboratory evaluation should include a review of electrolytes (e.g., hypokalemic metabolic alkalosis in monogenic hypertension/mineralocorticoid excess), renal function, serum calcium, and urinalysis. If proteinuria is present, it can be quantified. Assessment of serum cortisol, thyroid function tests, or serum aldosterone may rarely be appropriate in select cases. Plasma renin activity is not recommended as a routine test in the evaluation of neonatal hypertension but may be helpful in the setting of specific electrolyte abnormalities.[68] Levels are typically elevated in infancy, particularly in premature infants,[12] and peripheral plasma renin does not necessarily correlate with intrarenal pathology. Plasma renin can also be affected by medications such as caffeine and other methylxanthines as well as diuretics and ACE inhibitors.

All neonates with hypertension should have a Doppler renal ultrasound. Such imaging is valuable to evaluate renal anatomy, exclude renal vein or artery thrombosis, and look for aortic and renal artery thrombi. Color-flow Doppler can be used to exclude renal artery stenosis, although sensitivity and specificity are limited in this age group and vary with the experience of the ultrasonographer. **Magnetic resonance angiography (MRA) or CT with contrast add information about the anatomy of larger vessels,** but neither is typically sufficient to diagnose intrarenal branch stenosis. In such cases, classic contrast angiography may be helpful. However, the neonate's size and the potential for intervention should be considered before ordering these examinations. Even when intrarenal pathology is evident, definitive intervention may need to be delayed awaiting somatic growth. **Echocardiogram or VCUG** may be appropriate in select cases.

Treatment

Initial steps in management should include correction of any iatrogenic causes, treatment of hypoxemia in chronic lung disease, and hormone replacement as appropriate in endocrine disorders. **Any underlying disorders should be appropriately treated (e.g., urinary tract obstruction should be relieved). Surgical intervention may be appropriate in selected cases, such as ureteropelvic junction obstruction, tumor, and aortic coarctation.** There is general agreement that **neonatal hypertension should be treated with medications if BP exceeds the 99th percentile.**[53,68,69]

There are few controlled trials of antihypertensive medications in neonates. Therefore, treatment relies on case-series data, older clinical trials, expert opinion, and personal experience. **Drugs and dosages commonly used in the neonate are shown in** Table 25.5. In infants with **acute severe hypertension, especially with systemic symptoms, continuous IV infusion of antihypertensive medication is indicated to provide sustained control without rapid fluctuations in BP, which can contribute to cerebral ischemia or hemorrhage, particularly in premature infants.** Continuous infusions of several antihypertensive medications have been successfully used in neonates, including nicardipine, esmolol, sodium nitroprusside, and labetalol.[53,122,125] **In such situations, continuous monitoring via an indwelling arterial catheter is most appropriate.** Intermittent IV therapy with hydralazine or labetalol may be useful in neonates who cannot take oral antihypertensives. Of note, IV enalapril is not recommended in neonates because of the wide published range for appropriate dosing and risk of prolonged severe hypotension and AKI.[53] Oral antihypertensive medications commonly used in neonates include longer-acting dihydropyridine calcium channel blockers, vasodilators such as hydralazine, or beta blockers. Short-acting nifedipine has fallen out of favor for the management of hypertension because of the potential for rapid change in BP. Beta blockers should be avoided in chronic lung disease. **Diuretics may have a role in the control of BP, particularly in children with underlying chronic lung disease, who may have pulmonary benefit from the control of fluid balance.** The ACE inhibitor captopril is one of the few medications that has been studied in neonatal hypertension. However, caution is indicated

TABLE 25.5 RECOMMENDED DOSES FOR SELECTED ANTIHYPERTENSIVE AGENTS FOR TREATMENT OF HYPERTENSIVE NEONATES

CLASS	DRUG	ROUTE	DOSE	INTERVAL	COMMENTS
ACE inhibitors	Captopril	Oral	0.01-0.05 mg/kg/dose, max 2 mg/kg/day	TID	First dose can cause rapid drop in BP, especially if receiving diuretics
	Enalapril	Oral	0.08-0.6 mg/kg/day	QD-BID	
	Lisinopril	Oral	0.07-0.6 mg/kg/day	QD	
α- and β-Antagonists	Labetalol	Oral	0.5-1 mg/kg/dose; max 10 mg/kg/day	BID-TID	BPD relative contraindication
		IV	0.2-1 mg/kg/dose; 0.25-3 mg/kg/hr	Q4-6 hr; infusion	
	Carvedilol	Oral	0.1-0.5 mg/kg/dose	BID	
β-Antagonists	Esmolol	IV	100-500 mcg/kg/min	Infusion	Ultra short acting; monitor heart rate; avoid in BPD
	Propranolol	Oral	0.5-1 mg/kg/dose; max 8-10 mg/kg/day	TID	Monitor heart rate; avoid in BPD
Calcium channel blockers	Amlodipine	Oral	0.05-0.3 mg/kg/dose; max 0.6 mg/kg/day	QD	All may cause reflex tachycardia
	Isradipine	Oral	0.05-0.15 mg/kg/dose; max 0.8 mg/kg/day	QID	
	Nicardipine	IV	1-4 mcg/kg/min	Infusion	
Central α-agonist	Clonidine	Oral	5-10 mcg/kg/day; max 25 mcg/kg/day	TID	May cause mild sedation
Diuretics	Chlorothiazide	Oral	5-15 mg/kg/dose	BID	All: monitor electrolytes
	Hydrochlorothiazide	Oral	1-3 mg/kg/dose	QD	
	Spironolactone	Oral	0.5-1.5 mg/kg/dose	QD-BID	
Vasodilators	Hydralazine	Oral	0.25-1 mg/kg/dose; max 7.5 mg/kg/day	TID-QID	Tachycardia, fluid retention
		IV	0.15-0.6 mg/kg/dose	Q4h	
	Minoxidil	Oral	0.1-0.2 mg/kg/dose	BID-TID	Tachycardia, fluid retention, hypertrichosis, pericardial effusion
	Nitroprusside	IV	0.5-10 mcg/kg/min	Infusion	Risk for thiocyanate toxicity with prolonged use (>72 hr) or kidney failure

ACE, Angiotensin-converting enzyme; *BID,* twice a day; *BPD,* bronchopulmonary dysplasia; *IV,* intravenous; *kg,* kilogram; *mcg,* microgram; *mg,* milligram; *PO,* per os, orally; *Q,* every; *QD,* once daily; *QID,* four times a day; *TID,* three times a day. For ACE inhibitors, only captopril and lisinopril are approved in infancy by the U.S. Food and Drug Administration.
From Dionne JM, Abitbol CL, Flynn JT. Hypertension in infancy: diagnosis, management and outcome. *Pediatr Nephrol.* 2012;27(1):22.

because it can induce an exaggerated drop in BP in premature infants. Moreover, the renin-angiotensin system is critical for normal nephron development. **ACE inhibitors or angiotensin receptor blockers should not be given until nephrogenesis is complete, with some recommending avoidance through 44 weeks' postconceptional age.**

ABDOMINAL MASSES

Abdominal masses in neonates reflect a wide spectrum of pathologies, ranging from small lesions found incidentally to large ones occupying the entire peritoneal cavity; from unilocular cysts to complex solid cysts; from lesions that can cause

significant morbidity and mortality to entities that may be safely observed.[45,62,74,106] This spectrum is further broadened by the variety of organs that can give rise to such masses.

In the era of almost universal prenatal ultrasound, many such masses are identified, and some are even treated, before delivery. Others are discovered during the course of a thorough routine examination of the neonate. **Although most of these babies are otherwise healthy, such a finding is disturbing to new parents. It is incumbent on the infant's physician to determine the nature of the mass in a timely, safe, and cost-effective manner.**

Just over 50% of abdominal masses present during the newborn period are of renal origin.[43,62,74] The literature offers no consistent data on the frequency of abdominal masses in infants, but there is general agreement about the urgent need to comprehensively evaluate these infants to establish an accurate diagnosis and to plan appropriate intervention.

ETIOLOGY

The differential diagnosis in the infant with an abdominal mass is shown in Table 25.6. **The workup of most abdominal masses requires only a thorough physical examination and specific goal-oriented studies. Usually, the location of the mass is a helpful clue to the possible organ involved and the most likely diagnosis:**

1. **Flank: The most common cause of flank mass is renal in origin,** including hydronephrosis, multicystic dysplastic kidney, polycystic kidney disease, or renal artery or vein thrombosis. Other flank masses of importance include solid tumors of the kidney, such as the *benign congenital mesoblastic nephroma,* and *Wilms tumor.*[107] Wilms tumor occurs at a rate of 8 to 9 per 100,000 per year in the United States, with two thirds of patients presenting in the first 3 to 6 months of life. The tumor is described as firm, smooth, and confluent with the kidney. Both kidneys are involved in 10% of cases. Juxtarenal lesions include neuroblastoma, adrenal hemorrhage, bronchogenic cyst, and infradiaphragmatic (extralobar) pulmonary sequestration.
2. **Right upper quadrant (RUQ): Most RUQ masses arise from the liver and biliary tract.** In fact, the classic presentation of the most frequent benign hepatic tumor, *infantile hepatic hemangioma (hemangioendothelioma),* is a palpable RUQ mass. Other masses in this region include the benign mesenchymal hamartomas, hepatoblastoma (the only significant primary hepatic malignancy in neonates), and choledochal cysts.

TABLE 25.6 NEONATAL ABDOMINAL MASSES

TYPE OF MASS	PERCENTAGE OF TOTAL
Renal Masses	
Hydronephrosis	55
Multicystic dysplastic kidney	
Polycystic kidney disease	
Mesoblastic nephroma	
Renal ectopia	
Renal vein thrombosis	
Nephroblastomatosis	
Wilms tumor	
Genital Masses	
Hydrometrocolpos	15
Ovarian cyst	
Gastrointestinal Masses	
Duplication	15
Volvulus	
Complicated meconium ileus	
Mesenteric-omental cyst	
"Pseudocyst" proximal to atresia	
Nonrenal Retroperitoneal Masses	
Adrenal hemorrhage	10
Neuroblastoma	
Teratoma	
Hepatosplenobiliary Masses	
Hemangioendothelioma	5
Hepatoblastoma	
Hepatic cyst	
Splenic hematoma or cyst	
Choledochal cyst	
Hydrops of gallbladder	

Adapted from Kirks DR, Merten DF, Grossman H, et al. Diagnostic imaging of pediatric abdominal masses: an overview. *Radiol Clin North Am.* 1981;19(3):527.

3. **Left upper quadrant (LUQ):** Splenic cysts or hematomas are rarely observed in infancy.
4. **Midabdominal: Midabdominal masses usually involve the intestine. Duplications of the gastrointestinal (GI) tract can occur anywhere from the esophagus to the anus** and are usually cystic or less commonly tubular. **They are typically present as an asymptomatic palpable mass but may also cause pain, intestinal obstruction, GI bleeding, or even volvulus.** Other midabdominal masses include intestinal lymphatic malformations, meconium pseudocyst, and omphalomesenteric remnants. Failure of the vitelline duct to fully resorb can result in a variety of related entities, including *Meckel diverticulum* and omphalomesenteric sinus, cyst, or fistula.
5. **Pelvic: A residual pelvic mass after voiding in a female infant may represent an enlarged vagina (hydrocolpos) or uterus (hydrometrocolpos).** Such findings indicate a need for further examination of the perineum and vaginal introitus. Other pelvic masses include ovarian masses, urachal cysts, and teratomas. Cystic ovarian tumors are more common than solid ones, and the majority of them are benign; however, cystic ovarian masses require further investigation as malignancies have been reported. Urinary bladder masses, although rare in the neonate, typically present with lower tract symptoms and are initially seen on ultrasonography but require tissue sampling in order to verify the diagnosis. The most commonly found malignancy of the bladder in neonates is rhabdomyosarcoma, whereas the most commonly diagnosed benign bladder lesion is papillary urothelial neoplasm of low malignant potential (PUNLMP).[166]

Physical Examination

The infant should be in the supine position for abdominal examination. **Visual inspection of the abdomen before manual exploration enables the examiner to see a mass that may be missed with a tense abdomen.** The shape of the abdomen should be noted, along with the position of the umbilicus and the presence of any hernias. **Bimanual palpation using the flat surface of the fingers while supporting the infant's flank with the other hand facilitates exploration of the abdomen during deep palpation. Characteristics of the mass, including location, size, shape, texture, mobility, and tenderness, should be documented.** The differentiation between solid and cystic masses can be difficult on physical examination. Percussion may outline the suspected area, and transillumination is sometimes helpful.

If gastric distention or intestinal obstruction is suspected, a nasogastric tube is inserted and air and fluid are evacuated. If there is a question of urinary retention, the infant should be reexamined after placement of a urinary catheter or after inducing voiding with a Credé maneuver. Rectal examination, applied judiciously, may provide useful information, particularly for pelvic masses. Clues to the nature of the lesion may be external or distant to the mass.

Signs and Symptoms

Many abdominal masses are asymptomatic in neonates but can be detected by thorough physical examination. Renal masses may be associated with hypertension, abnormal renal function, or hematuria. If not detected by prenatal ultrasound, autosomal-recessive polycystic kidney disease commonly presents with bilateral nephromegaly perceived to be abdominal masses. Liver masses are occasionally associated with evidence of hepatobiliary obstruction or liver dysfunction. **A large mass may affect the infant's ability to feed successfully, particularly the preterm infant, and may also cause diaphragmatic embarrassment.**

Laboratory Data

Assessment of hepatobiliary and renal function may be helpful. However, radiographic imaging is usually the next step. **Plain films** can provide a surprising amount of information, such as organomegaly, calcifications in a number of tumors, or displacement of the intestines as a subtle clue to the presence and sometimes the nature of a mass. **Ultrasound is perhaps the most important tool in the assessment of abdominal mass in the neonate.** Ultrasound is noninvasive, accessible for bedside studies, radiation-free, and painless and can provide detailed information on the location, nature, and vascularity of the mass and adjacent structures. **Doppler sonography is particularly helpful to assess flow in the setting of renal artery or vein thrombosis.** When ultrasound is not definitive, it

may provide clues that help to determine the next appropriate studies. **Renal scintigraphy can be helpful to differentiate a nonfunctioning multicystic dysplastic kidney from a hydronephrotic or cystic dysplastic kidney** but is not frequently needed for this purpose. **A voiding cystourethrogram is the method of choice to diagnose vesicoureteral reflux,** which can be associated with significant hydroureteronephrosis and/or bladder outlet obstruction. **CT or MRI is occasionally indicated,** especially in the evaluation of the origin and extent of tumors.

Treatment and Prognosis

Treatment and prognosis are dependent on the nature of the underlying lesion. Specific renal lesions have been reviewed previously in this chapter. **Wilms tumor generally has an excellent prognosis with treatment, which often includes surgical removal of the tumor, irradiation, and chemotherapy.**[107] Survivors with reduced renal mass warrant follow-up with a nephrologist to screen for the development of chronic kidney disease. The prognosis in malignant neuroblastoma is related to the site of the primary tumor, histologic appearance of the tumor, staging of the disease, and age of the patient. Significant hydronephrosis may be associated with chronic issues with glomerular or tubular dysfunction.

Renal Tubular Disorders

Although most of the renal tubular disorders are congenital, many do not manifest clinically during the newborn period.[42] However, in sick infants admitted to the intensive care unit, **these tubular abnormalities can lead to severe and life-threatening electrolyte disorders and fluid depletion.**

Etiology

The term *renal tubulopathy* encompasses a wide variety of conditions. Proximal tubular defects can include proximal (type II) renal tubular acidosis (RTA), which can be an isolated phenomenon or can occur in the setting of generalized proximal tubular dysfunction *(Fanconi syndrome).* **Isolated proximal RTA rarely causes major difficulties in the neonatal period, although normal anion gap hyperchloremic metabolic acidosis and failure to thrive may be evident in later infancy;** the condition often spontaneously resolves in early childhood. **In contrast, Fanconi syndrome, which is characterized by proximal renal tubular acidosis (RTA), aminoaciduria, phosphaturia, hyperuricosuria, and glycosuria, can be associated with several underlying genetic and metabolic diseases, including cystinosis, Lowe (oculocerebrorenal) syndrome, tyrosinemia, galactosemia, hereditary fructose intolerance, and a variety of mitochondrial cytopathies.**

Bartter syndrome **is a tubulopathy of the loop of Henle,** which in its classic form is characterized by maternal polyhydramnios, premature birth, perinatal salt wasting, chronic polyuria and polydipsia, hypokalemic metabolic alkalosis, and nephrocalcinosis.[128] The metabolic findings are akin to treatment with a loop diuretic. Specific mutations in the distal tubule contribute to *Liddle syndrome* (hypertension with hyporeninemic hypokalemic metabolic alkalosis), pseudohypoaldosteronism type 1 (recurrent episodes of life-threatening hyperkalemia associated with aldosterone resistance), or pseudohypoaldosteronism type 2 (*Gordon syndrome;* hypertension with hyperkalemic metabolic acidosis).

Distal (type 1) RTA can be attributed to a variety of defects in the distal tubule that impair acidification of the urine, resulting in normal anion gap hyperchloremic acidosis with high urine pH, with clinical features including failure to thrive and nephrocalcinosis.[129] Autosomal-recessive distal RTA can be associated with progressive sensorineural deafness. Obstruction of the urinary tract, which is frequently diagnosed prenatally, is commonly associated with RTA, particularly the hyperkalemic type (type IV) from the impaired effect of aldosterone on the epithelial sodium (ENaC) channels. Similarly, defects of the vasopressin V_2 receptor or aquaporin-2 water channels in the collecting duct result in *nephrogenic diabetes insipidus* (NDI), with clinical features including polyhydramnios, impaired urinary concentrating ability, polyuria and polydipsia, neonatal failure to thrive, and a high risk for recurrent dehydration with hypernatremia/hyperosmolality. V_2 receptor mutations are inherited in an X-linked manner, whereas aquaporin-2 mutations are less common and usually autosomal recessive or dominant in nature.

Given the inherited nature of many tubulopathies, a review of the family history can be helpful, particularly with respect to the health of siblings.

Treatment and Complications

Although many tubular disorders are not clinically evident at birth, the clinician should keep a high index of suspicion in those infants with a prenatal diagnosis of urologic abnormalities or serious abnormalities in water and electrolyte metabolism. **Treatment depends on the underlying condition but often requires replacement of the electrolytes or minerals that are lost in the urine.** Therapies to mitigate tubular losses specific to several tubulopathies do exist but are beyond the scope of this chapter to review in detail. It is important to note, however, that **early evaluation and treatment of renal tubular disorders may prevent catastrophic complications such as life-threatening episodes of dehydration and delayed growth and development.**

URINARY TRACT INFECTION

Urinary tract infections (UTIs) affect approximately 1% of full-term infants and 3% of premature infants. Male infants are affected 5 times more frequently than females.[18,24,88] *Vesicoureteral reflux* (VUR) is a common radiographic finding in infants. Primary reflux is seen in abnormalities of the ureterovesical junction, ureteral duplication, and ureterocele. Secondary VUR is associated with PUV, neurogenic bladder, and other causes of bladder outlet obstruction. In addition to causing significant acute illness, UTIs can also lead to long-term renal sequelae, such as scarring with resultant hypertension, decreased functioning renal mass, glomerular hyperfiltration, and/or chronic kidney disease.

Etiology

Abnormalities of the urinary tract are responsible for a large number of UTIs in the neonate.[182] Whether the infection is more commonly spread in an ascending or hematogenous matter is not clear, but certainly the identification of VUR should prompt evaluation for potential secondary etiologies. Reflux is graded on a four- or five-point scale depending on the rating system utilized, with grade IV to V denoting VUR into the kidney with massive hydroureteronephrosis with tortuosity of the ureter.

Maternal urinary infections also have been associated with neonatal UTI.[104] **Symptomatic manifestations include abnormal weight loss during the first days of life, decreased feeding, dehydration, irritability, lethargy, cyanosis, jaundice, and septicemia.** In some cases, the affected kidneys are palpable. **Infected infants also may be asymptomatic.**

Data Collection

Evaluation of a neonate with suspected UTI includes immediate urine and blood cultures and a complete blood count (CBC). The optimum method of obtaining urine for culture is suprapubic aspiration of the bladder or catheterization. Catheterization may not be recommended in the neonate if there is concern for urethral stricture, which is more commonly observed in males. **Urine obtained in a urine bag should not be used for cultures because it is easily contaminated. With a diagnosis of UTI, radiographic evaluation should be undertaken to rule out anatomic abnormality. Evaluation should include renal and bladder ultrasound and may also include VCUG,** as significant reflux may be present without anatomic abnormality. Current recommendations vary depending on the weight given to the sensitivity of diagnosis, radiation exposure, and cost.[98,109] One study in infants suggests that the timing of VCUG does not affect the presence or severity of observed VUR after UTI;[54] however, given the potential risks, the urine should be sterile before obtaining the VCUG. Some have advocated obtaining the VCUG as soon as sterile urine is documented due to the risk of loss to follow-up. Renal scintigraphy can be useful to document the presence and/or extent of renal scarring; however, this is rarely needed in the newborn period.

Treatment

Pyuria (10 to 15 white blood cells [WBCs] per hpf) can be observed in the neonate normally. Treatment for UTI is indicated when an organism is cultured from the urine following sterile collection. However, a low threshold for antibiotic treatment awaiting culture results may be needed, particularly when other concerning symptoms are present. **Any growth in a urine specimen obtained by suprapubic aspiration**

should be considered to represent an infection if the procedure was cleanly performed. Any aspiration of bowel contents must affect the interpretation of culture results. Traditional antibiotic coverage consists of both ampicillin and an aminoglycoside pending culture results. The advent of third-generation cephalosporins has allowed for excellent gram-negative coverage without the nephrotoxicity of the aminoglycosides. ***Escherichia coli*** is the organism most often implicated in neonatal UTIs, followed by ***Klebsiella***.[12] Sulfonamides are contraindicated in the neonate because of their potential to complicate hyperbilirubinemia.

Antibiotic therapy should continue for 10 to 14 days, with a follow-up urine culture 3 days after therapy is discontinued. Many practitioners recommend antibiotic prophylaxis until significant reflux or anatomic abnormality is ruled out. The value of prophylactic antibiotics for the prevention of reflux nephropathy in the setting of documented VUR remains controversial.[189] The potential benefits need to be weighed against risks, knowing that neonates and young infants with acute UTI may present with more vague or nonspecific symptoms compared with older children.

NEUROGENIC BLADDER

Neurogenic bladder is an anatomic interruption of the micturition reflex normally triggered by a full bladder.[19,72] The bladder may be flaccid and unable to empty urine or spastic, hyperreflexive, and unable to store urine. Infants with lumbosacral spinal malformations commonly have neurogenic bladder. Lower motor neuron deficit causes bladder atony, and upper motor neuron deficit can cause spasticity.

Signs and Symptoms

Often there is a mixed presentation of symptoms. The flaccid bladder requires aggressive intervention in the neonate. Diagnosis begins immediately at the bedside when the newborn has no apparent voiding stream or the urine flow rate falls below expectations without other explanations. Further clarification of the diagnosis can be made by VCUG and cystometric studies. If there is concern for bladder dysfunction, renal function should be assessed because obstruction can lead to obstructive nephropathy.

Treatment

Surgical intervention may be indicated in the neonate with neurogenic bladder with associated obstruction, especially in the setting of severe VUR or recurrent UTI. The urologist creates a vesicostomy to allow the free flow of urine into diapers.[171]

Complications

Early diagnosis and intervention for infants with neurogenic bladder can decrease the risks of future complications. Long-term complications of neurogenic bladder include recurrent UTI and vesicoureteral reflux, obstructive uropathy, and associated electrolyte imbalances. Obstructive nephropathy is a leading cause of chronic kidney disease in children and can result in ESRD with resultant dialysis or transplant dependence.

NEPHROCALCINOSIS AND NEPHROLITHIASIS

Nephrocalcinosis and nephrolithiasis are common in infants, particularly those who are preterm or who have had a prolonged NICU course.[44,105,132] Studies suggest that nephrocalcinosis/lithiasis may affect 30% to 60% of preterm infants, with increasing risk at lower birth weight and earlier gestational age. Loop diuretics such as furosemide, which increase urinary calcium excretion, appear to be major contributors to these findings. Additional risk factors include relative hypercalcemia in late gestation, low urinary citrate excretion, and renal ischemia or use of nephrotoxic drugs, which can enhance intrarenal deposition of calcium phosphate or oxalate crystals in the setting of tubular injury. Specific conditions associated with nephrocalcinosis include William syndrome, which can be associated with chronic hypercalcemia;[112] neonatal primary hyperparathyroidism; distal renal tubular acidosis; primary hyperoxaluria; and neonatal Bartter syndrome. Thiazide diuretics can be used for the treatment of renal calcium deposition due to their hypocalciuric effect. Potassium citrate may also be helpful in the

setting of documented hypocitraturia but has not been shown to prevent the development of nephrocalcinosis when given on a prophylactic basis to preterm infants.[159] Adequate hydration is generally important in the approach to stone disease; however, this goal should not supersede appropriate nutrition. Whether nephrocalcinosis confers long-term risk for poor renal function and growth in this population remains controversial[105,143] because the prematurity-associated decrease in nephron mass is a confounding factor.

END-STAGE RENAL DISEASE

With advances in fetal therapeutic intervention and neonatal care, **the number of infants requiring chronic dialysis is rising. Such therapy is accompanied by unique ethical dilemmas. Many providers continue to view neonatal dialysis as optional rather than obligatory therapy due to the associated high medical, financial, and psychosocial burdens placed on the family and society, as well as uncertainties about long-term outcomes.**[108,152,192] These ethical concerns are certain to increase in complexity with advances in fetal urologic surgery and the ability of serial amnioport infusions to prevent death from pulmonary hypoplasia in oligo-/anhydramnios, even with complete absence of the kidneys.[28] It is therefore **important to educate parents as comprehensively as possible regarding the anticipated course and potential complications for neonates in whom chronic dialysis is indicated.** Management of these complex neonates requires a multidisciplinary team of pediatric specialists, including the neonatologist, nephrologist, urologist, transplant surgeon, dialysis nurse, renal dietitian, and social worker.

Renal Replacement Therapy in Neonatal ESRD

The goal of dialysis is to permit appropriate growth and health maintenance in infants until they are suitable candidates for kidney transplantation. Hemodialysis (HD) or peritoneal dialysis (PD) can be offered on a chronic basis to support infants with ESRD, with PD preferred at most institutions. Although neonates and infants can tolerate HD routinely, functioning vascular access and intradialytic anticoagulation are required. Moreover, because of the large-volume component of nutrition as well as the metabolic rate in infancy, **most infants will require chronic HD 5 to 7 days/week,** in contrast to older children and adults who require HD three times per week. Families who do not reside within convenient distance of a pediatric hemodialysis center must relocate for such therapy. These factors obviously have major psychosocial and financial implications for the family.

PD is often technically easier to accomplish in the small child and can be performed by the family within the home setting; the home caregiver(s) are trained to provide continuous cycling peritoneal dialysis for a 10- to 12-hour treatment on a nightly basis under the supervision of a pediatric nephrology program. Thus, **PD is the most common choice for renal replacement therapy in small children.**[7,183] Contraindications to chronic PD include documented loss of peritoneal function; extensive intraabdominal adhesions that limit dialysate flow, the latter seen most commonly in children who have required major or recurrent intraabdominal surgery; uncorrectable mechanical defects that prevent effective PD or increase the risk of infection (e.g., omphalocele, gastroschisis, diaphragmatic hernia, bladder exstrophy); and absence of a social support system to perform PD within the home. Although technically challenging, more long-term PD has been performed in very-low-birth-weight infants with birth weights as low as 930 g.[59,150] Despite continued improvement in the availability of infant catheters and dialysis tubing, chronic PD remains extremely time-consuming, challenging, and demanding for the infant, the family, and medical personnel.

Dialysis in the small child is routinely considered to be a bridge to kidney transplantation. Kidney transplantation is rarely performed with recipient body weight less than 7 to 8 kg, and many programs prefer a minimum body weight of 10 kg to minimize technical and other complications because the majority of donor kidneys are obtained from adults. En bloc or single kidney transplants from infant donors have historically been associated with increased risk of major complications and are thus currently avoided by most pediatric transplant programs. **The average 2- to 3-year patient survival rate is approximately 80% for children initiating dialysis before 1 month of age, with infection and cardiopulmonary disease being the**

leading causes of death.[40,180] However, worsened survival is observed in children who begin dialysis before 3 months of age (hazard ratio fourfold higher) compared with those between 1 and 2 years of age.[7,172] These cohorts of ESRD children have similar median age at transplant, likely due to the current standards for recipient body weight as described earlier; thus, the time awaiting transplant is more prolonged with decreasing age at dialysis initiation. **The median survival of a kidney allograft in the current era is 10 to 12 years.**[179] Therefore, neonates with ESRD can anticipate multiple kidney transplants with interval periods of dialysis during their lifetime. Because of antigen sensitization, it is unusual in the current era to receive more than three allografts for any individual patient. Although little is known regarding the life expectancy of neonates with ESRD, all-cause mortality rates in children receiving maintenance dialysis are at least 30 times higher than those of the general pediatric population, with even higher relative risks in very young children.[123] **Thus, the decision to embark on chronic renal replacement therapy in the neonate requires careful consideration and discussion with the family.** With these considerations, we now turn to particular concerns in the management of ESRD in neonates and young infants.

Management of ESRD in Neonates and Infants

Neonates and infants who require chronic dialysis experience the same complications of chronic renal failure that are observed in older children and adults, including anemia of chronic disease, secondary hyperparathyroidism, chronic acidosis, hypertension, and iron and vitamin D deficiency. However, **certain aspects of ESRD are unique to childhood and of particular concern with onset of ESRD during infancy, including altered nutrition, impaired somatic growth, and impaired neurocognitive development.**

NUTRITION AND GROWTH

Appropriate nutrition is a critical aspect of ESRD management during infancy. Multiple factors contribute to growth failure in infants with chronic kidney disease, including anorexia; nausea and vomiting; gastroesophageal reflux, which can be exacerbated by abdominal distention from indwelling dialysate during peritoneal dialysis; altered gastrointestinal motility, including delayed gastric emptying, which can be associated with the use of calorically dense formulas; the need for fluid and electrolyte restriction; salt-wasting nephropathy, renal osteodystrophy; chronic anemia; and developmental abnormalities that affect the mechanics of oral intake. Except for during the gestational period, linear growth is highest in the first year of life and depends primarily on the provision of optimal nutrition.[126] **Although oral feeding is desired and supported, enteral feedings will be necessary in the vast majority of cases to meet protein and caloric requirements sufficient to promote somatic growth and neurocognitive development in the setting of renal failure.**[181,194] ***Gastrostomy tubes* are usually preferred to nasogastric tubes given the anticipated lengthy duration of support.** The timing of gastrostomy placement is important because there is a risk of infection, including fungal peritonitis, as well as the loss of peritoneal membrane function with gastrostomy placement in children already receiving PD. Fundoplication may be required and can be performed concurrently; in our experience, symptoms of gastroesophageal reflux often increase once PD is started because of the pressure associated with increasing volumes of intraabdominal dialysate. **Placement of feeding tubes also supports successful administration of the numerous medications that these infants routinely require.** Tube feedings that are administered as supplements to oral intake can be provided either as daytime bolus feeds given in intervals that mimic usual infant feeding patterns or as continuous nightly infusions at rates that are regulated by a feeding pump.

Energy Intake. There is no evidence to suggest that children with chronic renal failure require increased energy compared with healthy children of the same age. The recommended goal for energy intake is 100% of the estimated energy requirement for chronologic age and sex, adjusted for physical activity level and body size, with a balance of carbohydrate, saturated and unsaturated fat, and protein similar to infant formula (36% to 56% carbohydrate, 40% to 54% fat, 7% to 12% protein).[100] **Low-birth-weight infants and children with established growth delay will require supplemental calories to support catch-up growth.** Glucose absorption from peritoneal dialysate can be significant, providing an

additional 10 to 20 kcal/kg/day,[117] and should be estimated in children with greater-than-expected weight gains.

Protein Intake. Protein goals, calculated in grams/kg ideal body weight, vary by stage of CKD. **Protein goals for children on peritoneal dialysis are set at dietary reference intake (DRI) plus 0.15 to 0.3 g/kg/d to compensate for dialysate-related protein and amino acid losses.** When replacing or augmenting breast milk with commercially available formulas, it is important to consider the type of protein as well; whey protein is more bioavailable than casein, and evidence suggests that whey protein may promote more rapid gastric emptying.[70] Compared with casein-predominant formulas, breast milk and whey-predominant formulas are preferred for their lower aluminum content.[86] Previous reports have documented that excess aluminum intake can lead to toxicity and cause bone disease and encephalopathy.[86,100]

Milk Intake. Additional caloric or protein supplements may be added as appropriate. The patient's renal limitations and gastrointestinal tolerance will guide which infant formula to use. **Breast milk is low in potassium and phosphorus and thus is often well tolerated by neonates with ESRD. Alternatively, specialized formulas for chronic kidney insufficiency that are low in potassium and phosphorus content are available for infants**, older children, and adults (Table 25.7). Similac PM 60/40 (Ross Abbott) and Goodstart Gentle (Gerber) are both appropriate first choices for infants with kidney failure. **Concentration of formula is often necessary to achieve an adequate intake of energy, protein, and other nutrients within accepted volumes.**

FLUID AND ELECTROLYTE REQUIREMENTS

Fluid and electrolyte requirements for neonates with kidney failure vary widely depending on the underlying kidney disease, degree of kidney failure, and mode of renal replacement therapy. ***Anuric or oliguric* children require fluid and sodium restriction. In contrast, children with *polyuric renal failure,* as is often seen with congenital obstructive uropathy, may require sodium and fluid supplementation.** Parekh et al. demonstrated improved growth of children with polyuric, salt-wasting renal insufficiency when they received 180 to 240 mL/kg/d of dilute (0.3 to 0.5 kcal/mL) formula that contained sodium supplementation on the order of 2 to 4 mEq/100 mL formula.[140] **Neonates undergoing peritoneal dialysis may demonstrate significant sodium loss through the dialysate, necessitating sodium supplementation.**[152,176] Restriction of dietary potassium intake may be indicated in some neonates. **When adequate nutrition is limited by potassium intake, breast milk and formula can be treated with sodium polystyrene to decrease the potassium content before feeding.**[34,176] Diluted adult renal formulas can also be provided,[90] but the effect of adult formulas on infants is not known, and thus it may be prudent to use infant formulas in those under 1 year of age.[70]

CALCIUM AND PHOSPHORUS

Normal serum calcium and phosphorus levels are higher in infants compared with older children, and age-specific norms should be targeted to optimize bone health. **Calcium intake from nutritive sources and phosphorus binders should be 100% to 200% of DRI for age and gender,** and phosphorus intake should be decreased if secondary hyperparathyroidism is present, with or without hyperphosphatemia.[100] If an older infant still receiving breast milk presents with hyperphosphatemia, a phosphate binder can be administered to the infant or the breast milk can be treated with a phosphorus binder to effect phosphate reduction.[63,149]

Vitamins. It is recommended that children with CKD meet 100% of DRI for B vitamins; folic acid; vitamins C, A, E, K; and copper and zinc. If this cannot be achieved through dietary intake alone or if there is clinical evidence of a deficiency, supplementation of these nutrients up to DRI is indicated. However, excess vitamin A intake from supplemental feeds or multivitamins may result in hypervitaminosis A, which is associated with hypercalcemia in dialysis patients.[120] **Additionally, it is suggested that children on dialysis receive supplemental water-soluble vitamins to replace dialysate-related losses.**[100] Several commercial renal multivitamin formulations are available, including a liquid that can be easily dosed and added to breast milk or formulas.

TABLE 25.7 INFANT FORMULAS AND MODULAR SUPPLEMENTS IN RENAL FAILURE

	FORMULA (per 100 mL)							
	BREAST MILK	SIMILAC PM 60/40	GOODSTART GENTLE	SIMILAC ADVANCE	SUPLENA	NEPRO	RENALCAL	RENASTART (STANDARD DILUTION)
Energy (kcal)	67-77	68	68	68	180	180	200	100
Macronutrient Distribution (% Total Calories)								
CHO	36	41	46	43	42	34	58	51
Protein	4	9	9	8	10	18	7	6
Fat	41	50	46	49	48	48	35	43
CHO (g)	6.9-7.5	6.9	7.8	7.3	19.6	16	29	12.6
Protein (g)	0.85-1.25	1.6	1.5	1.4	4.5	8.1	3.4	1.52
Fat (g)	3.5-4.3	3.8	3.4	3.65	9.6	9.6	8.2	4.81
Sodium (mmol)	0.69-0.96	0.7	0.8	0.7	3.5	4.6	0.3	2.13
Potassium (mmol)	1.26-1.44	1.5	1.9	1.8	2.9	2.7	0.2	0.61
Calcium (mg)	25.4-30.6	38	45	53	105	105	6	22.8
Phosphorus (mg)	11.8-16.2	19	26	28	72	72	10	18.6
Iron (mg)	0.02-0.04	0.15	1	1.2	1.9	1.9	—	1.0

	MODULARS			
	BENEPROTEIN	MICROLIPID	MCT OIL	DUOCAL
Formulation	Powder	Liquid	Liquid	Powder
Per unit measure	7 g/21 mL	15 mL	15 mL	100 g
Energy (kcal)	25	68	115	492
Macronutrient Distribution (% Total Calories)				
Protein	100	0	0	0
Fat	0	100	100	41
CHO (g)	0	0	0	73
Protein (g)	6	0	0	0
Fat (g)	0	7.5	14	22.3
Sodium (mmol)	0.43			<0.87
Potassium (mmol)	0.9			<0.13
Calcium (mg)	30			<5
Phosphorus (mg)	15			<5
Iron (mg)				

CHO, Carbohydrate; *MCT,* medium-chain triglyceride.

Similac PM 60/40, Similac Advance, Suplena, and Nepro are produced by Ross Abbott Nutrition. Goodstart Gentle is produced by Gerber. Renalcal and Renastart are produced by Nestle Health Science.

Polycose is produced by Ross Abbott Nutrition. Beneprotein, Microlipid, and MCT oil are produced by Nestle Health Science. Duocal is produced by Nutricia.

Adapted from Foster BJ, McCauley L, Mak RH. Nutrition in infants and very young children with chronic kidney disease. *Pediatr Nephrol.* 2012;27(9):1432.

Infant Growth. **Half of adult height is realized by 2 years of age, and during this phase, a child may experience a loss in growth potential that cannot be recovered. ESRD is associated with linear growth failure due to relative resistance to growth hormone (GH).** Such resistance is multifactorial in nature but includes reduced density of GH receptors in target organs and reduced levels of free insulin-like growth factor (IGF)-1 due to increased inhibitory IGF-binding proteins.[118] **Growth hormone therapy is essential in pediatric ESRD to attain a normal adult height**[65,66] and is often started in the toddler or early school age years. Although recombinant human growth hormone has not been fully investigated in infants, recent studies suggest that growth hormone treatment in infancy is generally well tolerated and may be useful as an adjunct for children who continue to grow poorly despite optimization of dialysis therapy and nutrition.

The nutritional management of infants with kidney disease is complex. It is recommended that the growth parameters of infants with moderate CKD be monitored twice as frequently as those of healthy infants and that those of children with severe CKD be monitored with even greater frequency.[100] **Frequent assessment is necessary to ensure that timely and effective nutrition intervention and support can be offered to pave the way for the best possible outcomes. For this reason, it is imperative that a skilled pediatric renal dietitian guide the multidisciplinary team in the nutrition plan for this population.**

Neurocognitive Development

Emerging evidence suggests that neurocognitive deficits are common in children with ESRD. A cross-sectional study of children with moderate to severe chronic renal insufficiency demonstrated that approximately one third of participants scored at least 1 standard deviation below the mean on measures of intelligence quotient, academic achievement, attention regulation, or executive functioning.[92] A more recent but small study in children initiating dialysis before 16 months of age showed significant deficits in intellectual and metacognitive functioning compared with sibling controls.[96] **Fewer months on dialysis and younger age at transplant were associated with better outcomes.** Although limited data are available at this time, these results have important implications for long-term educational and occupational outcomes and support the need for early intervention services for affected infants.

NURSING CARE OF THE NEONATE WITH RENAL FAILURE

Clinical and Metabolic Assessment

Nurses play a critical role in assessing and managing the neonate with renal failure.[75,80,169,173] **Changes in the neonate, including decreased urine output, weight gain, and electrolyte imbalance, can signal concern for acute renal failure. Symptoms of fluid overload include generalized edema in the face, extremities, and abdomen; increased work of breathing; and increases in BP and weight.**

Because electrolyte abnormalities are common in renal failure, nurses should note these values and report them, as well as anticipate clinical signs and symptoms that will follow. *Hyponatremia* often indicates excess intravascular volume due to fluid retention in the setting of renal failure; however, some neonates have salt-losing nephropathy, which leads to hyponatremia and dehydration. Treatment for low sodium concentration may therefore include fluid restriction or replacement of sodium depending on the underlying mechanism. *Hyperkalemia* can result in a medical emergency if not appropriately monitored and treated. Treatment includes restriction of potassium intake in formula and parenteral fluids and discontinuation or alteration of medications known to contribute to high serum potassium concentrations. Measures to shift potassium intracellularly, such as IV sodium bicarbonate or insulin and glucose, will temporarily decrease the plasma potassium concentration, but more definitive removal of potassium from the body through the urinary (potassium-wasting diuretics) or GI (cation exchange resins) tracts is warranted. The ***electrocardiogram* should be monitored closely because hyperkalemia can lead to ventricular arrhythmias.** IV calcium can stabilize the myocardium to help minimize the effect of hyperkalemia on cardiac rhythm. Low serum bicarbonate concentrations are

often observed in renal failure because the kidney is instrumental in maintaining acid-base balance in the blood.

Assessment and Management of Peritoneal Dialysis

PD is often the dialysis treatment of choice for the neonatal patient. The process of PD is described in detail earlier in this chapter. Regulation of electrolyte and fluid balance must be closely monitored by following serum electrolytes and by close documentation of intake and output and daily weight. These measures provide critical data for clinical management because fluid removal by PD is inexact, being affected by multiple factors, including the dextrose concentration of the dialysate and individual peritoneal membrane transport characteristics. **PD relies on an intact abdomen for success.** Therefore, hemodialysis or CRRT is occasionally indicated in infants or small children who have abdominal defects or surgery that prevents the use of the abdomen for PD.

Nurses have an essential role when dialysis is initiated. The nephrologist determines the type of dialysate, including any additives that may be required, such as heparin or electrolytes. **The fill volumes are based on the weight of the infant and usually start at 10 to 20 mL/kg with an eventual goal of 40 mL/kg.** These small initial volumes are necessary to prevent leakage of the newly placed catheter and to "stretch" the peritoneal cavity gradually for comfort. Neonates typically start with continuous manual PD, which is a closed system connected to warmed dialysis solution bags that fill the peritoneum by gravity from a premeasured volume control administration set. **The fluid dwells in the abdomen for the designated time prescribed by the nephrologist and then is drained from the abdomen by gravity into a drainage system by turning a stopcock.** Accurate measurement of the drained fluid is crucial, performed by subtracting the fluid that was infused and recording the difference as the net output. The bedside nurse will perform the manual dialysis, which can be a tedious but life-sustaining job. The nurse must also monitor the abdomen, with particular attention to the dressing of the PD catheter to ensure that no leakage of dialysate is occurring along the catheter tract or at any post-laparoscopy sites. The risk for leaks can be decreased by delaying the use of the catheter after placement; however, this is not always clinically possible. When the infant is bigger and can tolerate a fill volume of at least 100 mL, the dialysis can be delivered by an automated PD machine. The machine can be programmed to deliver the prescribed amount of dialysate, allow the fluid to dwell, and automatically drain the abdomen for the designated time. Trained dialysis nurses typically are involved at this point to manage the setup of the machine.

Complications that can occur with PD include the following:

1. *Infection:* Infection of the exit site and/or peritonitis (infection of the peritoneal lining) can occur if strict attention to aseptic technique is not followed. At least weekly dressing changes over the exit site using sterile technique are recommended until the catheter site is healed, which can take 2 to 6 weeks. More frequent dressing changes should be performed if drainage is excessive or the dressing becomes soiled or wet. The risk of infection is significantly higher in the presence of a leak. Application of a topical antibiotic cream or ointment at the time of the dressing change is recommended. Immobilization of the catheter below the dressing to restrict movement is helpful to prevent trauma to the insertion site. Daily tubing changes for manual dialysis setup should be performed with sterile technique for connection of bags and tubing. Once the infant is on an automated dialysis machine, trained dialysis staff perform daily bag and tubing changes. Assessment of the quality of the PD effluent during drain cycles is necessary to detect any signs of peritonitis, such as effluent that is cloudy or has increased fibrin. Fever and abdominal pain are also indicators of possible peritonitis. If concern for peritonitis exists, the PD fluid should be sent for cell count and differential, Gram stain, and culture. Antibiotics may need to be administered pending culture results. The nephrologist may prescribe intraperitoneal antibiotics to be directly added to the bags of dialysate; these antibiotics are systemically absorbed and are dosed to reach blood concentrations similar to those obtained with IV administration.
2. *Inflow/outflow problems:* Inflow and outflow problems may occur while performing PD either manually or via the automated dialysis machine. Accurate measurement of the dialysate

is done with each manual exchange. If problems occur with inflow, check lines for closed clamps or kinks. Attempt to reposition the patient to encourage better flow. Manual dialysis relies on gravity, so ensure the patient is positioned higher than the drainage system. Good inflow but poor outflow can signal migration of the PD catheter tip, blockage of the catheter tip by omentum, or constipation. Notify the nephrology team of the problem. An abdominal x-ray can be helpful to detect the presence of stool and determine the location of the catheter tip. Correction of the problem may be as simple as evacuating stool and as complicated as returning to the operating room for catheter revision. In any event, if the problem is not corrected, dialysis cannot continue. The success of the dialysis treatment depends on a functioning catheter.

3. ***Potential fluid overload or dehydration:*** Accurate measurement of the inflow and outflow of each exchange is essential when determining fluid balance. Check weights before and after the dialysis treatments, and review intake and output measurements to ensure fluid balance. Frequent monitoring of vital signs to detect any changes in heart rate or blood pressure will help to determine signs of dehydration or fluid overload. Symptoms of dehydration, including poor skin turgor, sunken eyes and fontanel, delayed capillary refill, hypotension, tachycardia, and weight loss, signal excessive fluid removal with the current dialysis plan. Signs of fluid overload include generalized or increasing edema, rapid weight gain, increasing blood pressure, and potentially respiratory distress. The physician should be notified of any of these discrepancies so that adjustments can be made to the dialysis plan.
4. ***Hernias:*** Hernias are a complication of PD. Umbilical and inguinal hernias are the most common and can occur due to the increased intraabdominal pressure from the dialysate load. Decreasing the fill volume until hernia repair can be performed, as well as immediately postoperatively, is recommended to diminish stress in this area.

Renal failure and its treatment in the neonate with PD require competent nursing assessment and accurate documentation of vital signs, weight, and intake/output. **The chronic nature of dialysis at this young age can be stressful on the family.** Spousal tension, sibling neglect, and financial stress are common. **The family's success in managing the infant's dialysis and nutritional needs requires the support of all members of the multidisciplinary care team.** Successful growth and development over the coming years need to be the goal of all team members to ensure eventual renal transplant and hopes for a long, healthy life.

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26 NEUROLOGIC DISORDERS

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The developing nervous system provides ongoing challenges for researchers and clinicians. Investigations continue in a wide variety of areas, yet basic mechanisms for a pathophysiologic understanding of common events such as neonatal seizures and intraventricular hemorrhages (IVHs) remains unclear.

Improved neonatal care in recent years has not significantly reduced neurologic sequelae. Whether this is a reflection of survival of sicker and more immature infants is difficult to assess. Primary neurologic disease and secondary neurologic complications from such common conditions as cardiopulmonary disease, metabolic derangements, shock, infection, and coagulopathies still represent major problems encountered in every intensive care nursery. Serious congenital nervous system anomalies still appear with regularity, although in small numbers.

This chapter deals with selected topics in neonatal neurology, including congenital malformations, trauma, seizures, hypoxic-ischemic encephalopathy (HIE), hypotonia, stroke, and IVH.

CONGENITAL MALFORMATIONS

Physiology, Etiologic Factors, and Clinical Features

Congenital malformations of the nervous system occur when the usual sequence of maturation and development is interrupted[13] (Table 26.1). These malformations are present at birth, and the etiology is multifactorial and sometimes unclear. Although strictly destructive lesions (e.g., hydranencephaly resulting from bilateral carotid artery occlusion) are separate from primary failures of morphogenesis, both may be included in the broad category of congenital malformations. The distinction between the two types lies in an understanding of the causes.

Understanding congenital malformations requires an appreciation of the normal embryologic sequence. The clinical and pathologic identification of normal and abnormal structures makes it possible to determine the timing of the insult or development failure. Once timing is established, an appropriate search for the cause can be made.

Neural Tube Defects

The incidence of neural tube defects (NTDs) worldwide is approximately 0.5 to 2 in 1000 births[13,20] (Box 26.1). Although the prevalence of NTDs has decreased, they are **one of the most common congenital anomalies contributing to morbidity and mortality in neonates.**[20] Changes in vertebral, vascular, meningeal, and dermal structures are typically found along with the defects. The more common types of NTDs are anencephaly and myelomeningocele.[25] **Genetic and environmental factors play a role in the development of NTDs.** Familial incidence also plays a role; when one family member is affected, the risk increases to 3% in subsequent offspring and to 12% if two or more family members are affected.[29] **While the etiology of NTDs appears to be multifactorial, the interaction of genetic and environmental factors, including nutrition and teratogens, may determine risk.**[13,92] In 60% to 70% of cases genetic factors play a role.[20,30] Environmental factors associated with NTDs include maternal obesity, diabetes,

BLUE type highlights content that is particularly applicable to clinical settings.

TABLE 26.1 CENTRAL NERVOUS SYSTEM DEVELOPMENT AND RELATED DEFECTS

MATURATIONAL PROCESS	TIME	ASSOCIATED DEFECTS
Neural tube defects (dorsal induction, neurulation)	3-4 weeks	Craniorachischisis Anencephaly Myeloschisis Encephalocele Myelomeningocele Chiari malformation
Prosencephalic development	2-3 months	Cyclopia Holoprosencephaly Arrhinencephaly Septo-optic dysplasia Agenesis of corpus callosum Agenesis of septum pellucidum
Proliferation	2-4 months	Microcephaly Megalencephaly Neurocutaneous syndromes (?)
Migration	3-5 months	Schizencephaly Lissencephaly Pachygyria (macrogyria) Microgyria (polymicrogyria) Neuronal heterotopias
Neuronal organization and functional organization	6 months	Down syndrome (?) Mental retardation (?) Genetic epilepsy (?)
Myelination	2nd trimester	Anoxic/ischemic damage

BOX 26.1 CRITICAL FINDINGS
Neural Tube Defects

- As many as 50% or more of neural tube defects (NTDs) are preventable.
- Two-thirds of American women fail to ingest an adequate amount of folic acid, and enriched grain products supply only one-fourth of daily need.
- All women of childbearing age should consume **400 mcg** of folic acid daily even when not planning to become pregnant.
- **At increased risk:** women with a previous NTD pregnancy. For these women, the recommended dose of folic acid is **increased to 4 mg daily**. It should be taken at least 1 month before conception.
- **Sources:** Dietary supplements, enriched grain products, and consumption of foods with folic acid content (citrus fruit, beans, leafy greens).
- The Centers for Disease Control and Prevention, American Academy of Pediatrics, and March of Dimes have all recommended an increase in the amount of folic acid used to fortify grain products from 140 to 350 mcg per 100 g of grain.
- Inadequate education of women continues to be a problem.

hyperthermia, and lower socioeconomic status.[13,20] Drugs that have been linked to NTDs include valproic acid, carbamazepine, thalidomide, and a fungal product fumonisin.[13,30,92]

The major environmental factor linked to NTDs is a dietary level of folic acid.[13] Folic acid supplements before and during pregnancy have been cited as substantially lowering the incidence of these NTDs. The U.S. Public Health Service issued a **recommendation that women of childbearing years consume 400 to 800 mcg of folic acid each day to prevent NTDs.[91]** The American Academy of Pediatrics (AAP) also supports this recommendation.[7] Such an intake can be achieved by dietary supplementation of folate, adding folic acid to U.S. enriched grain products (e.g., bread, flour), and consuming foods containing folic acid (e.g., citrus, beans, leafy greens). The Food and Drug Administration (FDA) required all enriched grain products to be fortified with[7] folic acid by 1998. In 2016 the voluntary addition of folic acid to corn masa flour was approved by the FDA.[72,90] Corn masa flour is a food staple in the Hispanic population.[7] Studies have demonstrated higher rates of NTDs in the Hispanic population, which prompted the recommendation by the FDA.[33,72] Folic acid fortification has increased folic acid levels in the United States, although a recent study suggested that about 25% of women of reproductive age still had red blood cell (RBC) folate levels that were less than optimal. Half of the women in the study (48%) revealed that the sole source of folate acid was enriched cereal grain products and only 29% took a supplement that included folate.[21]

A 2015 *Cochrane* review confirmed that folic acid prevents NTDs, including second occurrence NTDs.[24] Current recommendations for

folic acid supplementation is 400 to 800 mcg of folic acid daily for all women planning to or capable of becoming pregnant. Supplementation should begin at least 1 month before pregnancy and continue until 12 weeks of gestation. Women at high risk for a pregnancy with an NTD should take 4 mg (4000 mcg) of folic acid daily. Supplementation should begin 3 months before pregnancy and extend through 12 weeks of gestation. Women in the high risk category include women who have had an NTD themselves or previously had a pregnancy affected by an NTD, whose partner has been affected by an NTD, or who have had a previous child with an NTD.[19,91] Improved consumption of folic acid will not completely prevent NTDs because of multifactorial etiologic factors such as the environment and genetics.

There are four phases that occur in the formation of the spinal cord. The four phases are gastrulation, primary neurulation, secondary neurulation, and dorsal midline closure of the mesodermal-cutaneous ectodermal layers. The presence of the primitive streak is the first evidence of gastrulation. A second streak, the notochordal process, develops alongside the primitive streak. The notochord is responsible for the induction of both the neural plate and the neurenteric canal. Cells proliferate along the lateral margin of the neural plate to form the neural folds around the central neural groove.[30,70]

Cells at the apex of the neural folds make up the neural crest. Schwann cells, pia-arachnoid cells, sensory ganglia, melanocytes, and various secretory cells arise from the neural crest. The neural folds meet and fuse with the rostral neuropore (anterior) and caudal neuropore (posterior) ends, closing by approximately the end of the fourth embryonic week.[30,70]

Failure of development at this stage results in the defects of neurulation (or dorsal induction). The most severe of these defects is craniorachischisis, in which there is significant malformation of the brain (as in anencephaly), absence of the posterior skull, and an open spine along the full length of the spinal cord. Only a few affected embryos survive to early fetal stages.[30]

Anencephaly is similar to craniorachischisis without the spinal defect. **There is essentially no normal brain tissue above the brainstem and thalami,** and parts of those structures are malformed. Onset is thought to occur before 24 days of gestation. Although traditionally anencephaly is thought to be an NTD, there are some who theorize that the defect occurs as a result of a skeletal (mesodermal) defect. About one-fourth of the fetuses survive into the neonatal period, but three-fourths are stillborn.[30] **The majority of anencephalic infants die within the neonatal period.**[30]

Myeloschisis involves the failure of the posterior neural tube to close. There is no well-defined sac protruding from the defect, and there is a continuous leak of cerebrospinal fluid (CSF) fluid.[13]

Encephaloceles are now believed to be caused by disorders of cranial mesoderm that occur during development. They most commonly are found in the occipital region and less commonly in the frontal, temporal, and parietal regions. Meninges, brain tissue, and/or CSF may be found in the lesion, and it is usually connected to the rest of the brain by a narrow stalk of tissue. Many of the lesions may be covered by skin.[30]

Myelomeningoceles (or the more limited meningoceles) are a limited form of myeloschisis with failure of closure at the caudal (tail) end of the neural tube. With meningocele, the meninges protrude through the vertebrae and are contained within a sack. The spinal cord and nerve roots are generally in normal position, which improves the outcomes for these children. Unfortunately, myelomeningoceles, the more common defect, results in protrusion of both meninges and spinal cord through the opening in the spinal column. **Neurologic deficits occur below the level of the protrusion.**[25,30,95] Chiari malformations are typically included in this category. Chiari II malformations are often seen in conjunction with myelomeningocele, and involve the brainstem and cerebellum. A small posterior fossa is the central feature of Chiari II malformations. The hindbrain and midbrain, including the cerebellum, and the cervical spinal cord are involved in the defect. Hydrocephalus occurs as a result of abnormalities in the flow of CSF secondary to aqueductal stenosis, obstruction of the fourth ventricle, and subarachnoid space compression. Dilation of ventricles often occurs without increased head circumference or clinical symptoms of increased intracranial pressure in this group of infants; therefore, serial ultrasound scans should be performed with a fast sequence T2-weighted magnetic resonance imaging (MRI) when surgical intervention is being considered. **Symptoms of brainstem involvement such as central apnea or vocal cord paralysis may be present.** Any defect in which the spinal or cranial

contents are "open" to the outside, such as myelomeningocele or encephalocele, are associated with an elevation of alpha-fetoprotein (AFP) in the amniotic fluid. This is important in prenatal diagnosis.[30]

Segmentation Defects

After formation and closure of the neural tube, the development of different regions of the brain begins to occur. Division of the brain into hemispheres, formation of the ventricular system, and formation of the major gyral patterns all occur between 2 and 3 months of gestation.[28,70] Major areas of the brain, including the cerebellum, basal ganglia, brainstem nuclei, thalamus, and hypothalamus, form at this time.[28] Defects of segmentation and cleavage occur during this phase of neural development. For unknown reasons, defects of segmentation and cleavage are far less common than defects of neurulation. Because these malformations involve abnormalities of ventral induction rather than dorsal induction (e.g., neurulation), the face, eyes, nose, mouth, and hair are also involved. When any of these brain malformations are suspected or when features suggestive of them are seen, careful examination of the hair, eyes, ears, mouth, and nose may reveal other related anomalies.

Holoprosencephaly is characterized by a single midline lateral ventricle, incomplete or absent interhemispheric fissure, absent olfactory system, midfacial clefts, and hypotelorism (abnormally decreased space between the eyes). Various subtypes of holoprosencephaly, including alobar, semilobar, lobar, and middle interhemispheric have been described. The most severe form of holoprosencephaly is cyclopia (a single fused midline eye) and supraorbital nasal structure. At times, the nasal structure and eye are absent. An intermediate form is cebocephaly, which includes ocular hypotelorism and a flat nose with a single nostril.[28]

Migration and Cortical Organizational Defects

The remaining development of the brain takes more than twice as long as previously described development and includes cellular proliferation, migration, organization, and myelination. Cells that later form the cerebral cortex begin in the germinal matrix (near the caudate nucleus around the lateral ventricles). These cells then migrate in a radial fashion to their final positions near the surface of the brain. Abnormalities of cellular migration result in collections of gray matter in unusual places (heterotopias), abnormal gyri and sulci, abnormal spaces in the brain, and clinical signs of gray matter dysfunction. Frequently, these clinical problems are not apparent in the newborn period.

Microcephaly **means "small brain" and is manifested as a head circumference measuring greater than two standard deviations below average for infants at that gestational age.**[13] Microcephaly may be (1) genetic (dominant, recessive, sex-linked) or chromosomal (translocation [see Chapter 27]), (2) caused by teratogens (cocaine, alcohol), (3) caused by infection (rubella, cytomegalovirus, zika), or (4) of unknown cause. Occasionally, there is a paucity of germinal matrix cells or they fail to adequately migrate, resulting in a brain cortex with a decreased number of neuronal cells.[13]

In *lissencephaly,* the brain is smooth in appearance, having few or no gyri (convolutions). An important fact is that the normal fetal brain is smooth early in gestation, with convolutions forming throughout gestation, creating the sulci and gyri seen in term infants. Lissencephaly is a cortical migrational abnormality, resulting in agyria, pachygyria, and other issues in term infants.[80]

Although not generally present at birth, poor head growth resulting in microcephaly usually occurs within the first year in type I lissencephaly. Neonatal seizures may also occur, but seizures are more commonly present at 6 to 12 months of age. A general phenotype is marked by hollowing at both temples, a small jaw, and generalized hypotonia. Several generic disorders involving chromosome defects of the 17p13.3 gene and Xq22.3 gene have been associated with type I lissencephaly. *Miller-Dieker syndrome,* a major form of type I lissencephaly associated with 17p13.3 gene have characteristics including narrow forehead, long philtrum, upturned nose, retrognathia, retinal hypervascularization, and digit abnormalities. In type II lissencephaly, macrocephaly is generally present at birth or develops soon afterward. Retinal, cerebellar, and muscular abnormalities always are present. Fukuyama congenital muscular dystrophy, Walker-Warburg syndrome, and muscle-eye-brain disease are disorders that are consistently associated with type II lissencephaly. Other clinical features of lissencephaly include hypotonia, feeding problems, and decreased movement sometimes presenting with

arthrogryposis in the newborn. Abnormalities on the electroencephalogram (EEG) are noted. Later, significant intellectual disability and severe spasticity may be noted and death may occur.[80]

Additional Defects

Cerebellar malformations are quite varied. Most often, at least a portion of the cerebellum is preserved, but total absence is possible. Hemispheric hypoplasia-dysplasia or vermis hypoplasia-dysplasia or agenesis is seen, and familial forms have been reported. *Dandy-Walker cyst* is another complex malformation involving the cerebellum in which the fourth ventricle is dilated into a cystic structure, hypoplasia-agenesis of the cerebellar vermis, and posterior fossa enlargement. The foramina of Magendie is atretic, and hydrocephalus results. The cerebellum is small and displaced upward. Associated anomalies include heterotopias, agenesis of the corpus callosum, aqueductal stenosis, and syringomyelia. The differential diagnosis includes an arachnoid cyst of the posterior fossa. In the case of an arachnoid cyst, the fourth ventricle is not part of the malformation and is normal, although it may be displaced.[27] Clinical features of Dandy-Walker cyst include progressive hydrocephalus, enlargement of the occipital shelf and posterior part of the skull, and clinical symptoms of increased intracranial pressure. Symptoms may be absent in the newborn period. Malformations in other organ systems such as the renal and cardiac systems are frequently associated.[27]

***Craniosynostosis* is the abnormally early closure (fusion) of the bones of the skull.** The cause in most of these malformation is unknown. Familiar or complex syndromes make up about 10% of craniosynostosis cases. In these cases a mutation in the processing of fibroblast growth factor is thought to be the etiology. **The premature closure of sutures may involve one or multiple sutures, with resulting deformity of the skull.** Various skull shapes such as brachycephaly, scaphocephaly, and acrocephaly may result depending on which sutures are prematurely fused.[101]

Craniosynostosis should be suspected in the presence of microcephaly or misshapen head. **Appropriate evaluation requires a clinical assessment with palpation of the sutures to determine whether they are overriding or fused** and x-ray films of the skull and/or a computed tomography (CT) scan to define which of the sutures are stenosed and whether there might be an associated brain malformation or hydrocephalus.[78] **Craniosynostosis should be differentiated from positional deformities occurring from an infant lying in one position for a prolonged period of time.** A classic example is dolichocephaly (narrow and elongated shape) seen in premature infants and plagiocephaly in term infants.

Hydrocephalus may occur as a result of various etiologies. **Hydrocephalus results when the normal flow of CSF is obstructed.** This may be the result of an atretic portion of the ventricular system, blockage from the outside, inflammation within the ventricular system causing a permanent blockage, or, rarely, overproduction of CSF. An inherited X-linked form of hydrocephalus exists. Intrauterine infection is another cause. Hydrocephalus may be associated with many of the malformations described previously.[103]

Data Collection

The diagnosis of malformations of the central nervous system (CNS) may be quite obvious (as in anencephaly) or very subtle. **Careful examination of all newborns results in the identification of most malformations.** At times, the diagnosis is suspected not based on examination findings but with the presence of accompanying signs such as seizures.[25] Prenatal diagnosis of congenital malformations of the nervous system can be made using imaging studies. Ultrasonographic examination (an abdominal ultrasound scan of the mother) or fetal MRI, which is now available at many large centers, provides an opportunity to identify certain malformations by viewing the fetus during development. Hydrocephalus, encephaloceles, myelomeningoceles, cerebellar malformations, hemorrhage and stroke, and anencephaly may be identified prenatally.

Determination of AFP levels in the amniotic fluid and maternal serum allows the identification of anencephaly and open myelomeningoceles. A nonenclosed nervous system is associated with a significant rise in AFP in the amniotic fluid. Amniocentesis provides the amniotic fluid necessary for this determination. Testing of maternal serum for AFP is also an option and may be used along with ultrasonography or fetal MRI for diagnosis, allowing amniocentesis to be omitted.[13,30] Elevated AFP levels can be found in other fetal conditions,

including fetal wall defects.[29] Clinical signs and symptoms have been described for each individual nervous system malformation presented earlier in this chapter.

Treatment

Limited treatment is available for congenital malformations of the nervous system. A variety of strategies are available for reducing secondary complications or providing earlier management to handle these complications more efficiently.

The greatest efforts and accomplishments have been made for infants with congenital malformations who might be expected to have productive lives. When secondary complications are managed appropriately, the majority of children with myelomeningoceles are ambulatory (total or partial) and continent of urine.[30]

Myelomeningocele generally is surgically repaired as soon as possible (within 24 to 72 hours).[25,30,40,95] Prevention of infection is paramount. In addition to sterile technique, prophylactic antibiotics have been shown to be beneficial.[30] **Trauma to the area should be avoided by keeping the infant in the prone position and maintaining sterile gauze moistened with warm, sterile normal saline. Preventing fecal contamination is vital.** Several authors recommend the use of a sterile, plastic drape fastened above the anus but below the lesion to keep fecal material isolated from the site.[25,95] **Latex precautions also should be initiated because these infants have an increased propensity for developing sensitivity to latex.**[19]

Spina bifida has been repaired in utero at early gestational age. Such repairs have risks for both mother and fetus but have resulted in a significantly lower risk of infants requiring a ventriculoperitoneal (VP) shunt for hydrocephalus. The National Institutes of Health (NIH) sponsored Management of Myelomeningocele Study (MOMS) trial was a multicenter, prospective, randomized controlled trial comparing prenatal surgery with standard neonatal treatment. The trial was stopped early because of the efficacy of the prenatal surgery. **The study demonstrated that surgery before 26 weeks of gestation decreased the need for VP shunts, decreased hindbrain herniation, and preserved neurologic function.** Improved ambulation without the need for orthotics or devices was noted in the prenatal surgery group compared to postnatal surgery group. However, there were complications of premature delivery and some maternal complications as well. The MOMS II study will continue to follow the cohort of 183 babies to monitor neurologic and cognitive function as well as bowel and bladder function to determine whether benefit is sustained.[5,41]

Some of the malformations are lethal soon after birth (anencephaly), limiting management options to **comfort measures and family support** (see Chapter 32). When appropriate, genetic counseling should be requested. **For other malformations, treatment requires management of symptoms such as seizures, signs of increased intracranial pressure, and infection.** A consult to neurosurgery and neurology is indicated. Other helpful consults may include physical therapy, urology, and orthopedics.[25,40] For hydrocephalus, shunting may become necessary (Boxes 26.2 and 26.3 and Fig. 26.1).[30]

Generally, **skull deformity is present in infants with craniosynostosis.** It is prudent to consider the presence of craniosynostosis in any infant with an abnormal cranial shape.[25,95] If present, total craniosynostosis, or premature fusion of all the sutures should be treated surgically.[95]

The management of congenital hydrocephalus consists primarily of early shunting as soon after birth as possible. Fetal surgery for placement of a ventriculoamniotic shunt has been done in a few studies, but an improvement in outcomes compared with surgery after birth is uncertain. In addition, hydrocephalus in a fetus is often associated with serious developmental abnormalities that may increase morbidity and mortality.[29]

Shunting soon after birth often produces a far better outcome than would be assumed with minimal motor deficit and only a mild to moderate deficit in intellect.[30] Monitoring of pregnancies with fetal ultrasound allows the detection of congenital hydrocephalus. In the past it had been recommended to give antenatal steroids and deliver a fetus prematurely if there was evidence of rapid ventricular dilation and to proceed with postdelivery shunt placement. That is no longer recommended because of evidence that late preterm delivery may be associated with adverse neurodevelopmental outcomes.[30]

BOX 26.2 POSTOPERATIVE VENTRICULOPERITONEAL SHUNT CARE

- Positioning:
  - Place infant on unaffected side (may position on shunt side with "doughnut" over operative site once incision has healed). Keep head of bed flat (15 to 30 degrees) to prevent too-rapid fluid loss.
  - Support head carefully when moving infant.
  - Turn every 2 hr from unaffected side of head to back.
- Shunt site:
  - Use strict aseptic technique when changing dressing.
  - Pump shunt if and only as directed by neurosurgeon.
  - Observe for fluid leakage around pump.
- Observe and document all intake and output. Watch for symptoms of excessive drainage of cerebrospinal fluid:
  - Sunken fontanel
  - Increased urine output
  - Increased sodium loss
- Observe, document, and report any seizure activity or paresis.
- Observe for signs of ileus:
  - Abdominal distention (serially measure abdominal girth)
  - Absence of bowel sounds
  - Loss of gastric content by emesis or through orogastric tube
- Perform range-of-motion exercises on all extremities.
- Observe and assess for symptoms of increased intracranial pressure (shunt failure):
  - Increasing head circumference (measure head daily)
  - Full or tense fontanel
  - Sutures palpably more separated
  - High-pitched, shrill cry
  - Irritability and/or sleeplessness
  - Vomiting
  - Poor feeding
  - Nystagmus
  - Sunset sign of eyes
  - Shiny scalp with distended vessels
  - Hypotonia and/or hypertonia
- Observe and assess for signs of infection:
  - Redness or drainage at shunt site
  - Hypothermia and/or hyperthermia
  - Lethargy and/or irritability
  - Poor feeding and/or poor weight gain
  - Pallor
- Parent teaching:
  - Demonstrate and receive return demonstration of drug administration.
  - Teach parents side effects of medications.
  - Document on neonatal intensive care unit's routine discharge teaching checklist with routine care.

Complications

Many of the expected complications were dealt with previously in the sections describing the malformations and their associated problems. It is **difficult to separate true complications from problems resulting from the malformation.** For example, hydrocephalus develops in many infants with myelomeningocele and may be present at birth.[25,40] Other complications or associated problems of myelomeningocele include bowel and bladder incontinence, urinary tract infections, and paralysis.[25,30]

Malformations carry with them altered anatomy and physiology that is reflected in abnormal function. Common comorbidities may include seizures, intellectual disability, sensorimotor abnormalities, disturbances in primary sensory function such as vision and hearing, urologic, and orthopedic problems.[30]

Associated problems encountered are ordinarily explained on the basis of the malformation and the anatomy involved. Often midline defects in the brain (particularly at the base of the brain) result in clinical problems involving the hypothalamus and the hypothalamic-pituitary axis. This dysfunction may manifest itself in impaired temperature regulation, thyroid abnormalities, diabetes insipidus, and adrenal insufficiency. When absence of the septum pellucidum is diagnosed, the optic nerves should be evaluated to rule out septo-optic dysplasia, which is frequently associated with hypothalamic and electrolyte abnormalities.

Involvement of the cortex causes seizures, cognitive deficits, and sensorimotor problems. White matter damage can cause spasticity. If the brainstem is involved in the malformation (e.g., Chiari or Dandy-Walker malformations), apnea, deafness, sleep disturbance, oculomotor disturbances, and problems with sucking and swallowing

BOX 26.3

PARENT/CAREGIVER TEACHING

Wolfson Children's Hospital Parent Handout: Newborn Ventriculopertoneal Shunt (For Use With Ventriculoperitoneal Shunt Teaching Checklist)

Purpose of Ventriculoperitoneal Shunt

- Ventricles are compartment-like spaces located in the normal brain. Spinal fluid forms daily in these ventricles. This clear fluid flows out over the brain and down around the spinal cord. Spinal fluid helps cushion the brain from injury, keeps the brain moist, and carries away waste products.
- Hydrocephalus is a condition in which an abnormally large amount of spinal fluid builds up in your baby's ventricles and usually is caused by a blockage in the spinal fluid path. Because the ventricles continue to make spinal fluid daily, a buildup of fluid occurs when it cannot escape. This excess fluid can cause pressure on the brain and result in permanent damage to the brain unless it is properly treated.
- The purpose and function of your baby's VP shunt is to allow the excess spinal fluid to drain through a tube from the ventricle into the abdomen, where it is absorbed.

Pathway of the Ventriculoperitoneal Shunt (see Fig. 26.1)

- A small incision is made on the scalp, and the tube is passed through the skull and into the ventricle. Located under the skin, the tube passes behind the ear, passes down the side of the neck, and continues to the abdomen, where a second incision is made to put the end of the tube into the abdominal cavity. A third incision is sometimes needed in the neck area with some babies.
- The scalp incision will be hidden as your baby's hair grows. You will see and feel the shunt tubing (like a large vein under the skin), but it is barely noticeable after the baby gains weight.

Signs and Symptoms of Shunt Infection

- The shunt is at risk for infection because it is a foreign object located inside the body. You will have to watch for these signs of shunt infection and report them **immediately** to your doctor:
  - Temperature of 101°F or higher
  - Swelling, redness, or drainage along the pathway of the shunt tube
  - Lethargy or irritability (change in behavior)
  - Loss of appetite or poor feeding

Signs and Symptoms of Shunt Failure/Increased Intracranial Pressure

- The spinal fluid contains proteins and chemicals that may build up and block off the shunt. It is also possible for tissue within the brain or abdomen to block the shunt or for the shunt device itself to fail. This shunt failure (malfunction) means that the spinal fluid will once again build up and result in pressure on the brain and possible irreversible damage. Therefore it is very important for you to watch for the signs of increased pressure in the brain that occurs with shunt failure and report them to your doctor immediately:
  - Lethargy or sleepiness
  - Unusual irritability, fussiness, or excessive crying
  - Repeated vomiting
  - Poor feeding
  - Bulging soft spot when baby is sitting up quietly
  - Shrill, high-pitched cry
  - Eyes that look downward
  - Increase in spaces between the bones of the skull
  - Seizures/posturing

Reason and Importance of Prompt Treatment of Health Problems

- Prompt treatment of your baby's health problems (e.g., ear infections, skin infections) is important to prevent infections spreading to the shunt. It is also vital to seek medical care for signs of shunt infection or failure as noted.

Importance of Close Medical Follow-Up

- Your baby will have to be followed up by a neurosurgeon and your pediatrician after being discharged. Bring the baby to every follow-up appointment so that your baby's head can be measured and physical condition can be evaluated. Your baby will also go to the Developmental Evaluation Clinic, where a specialist in baby development can examine him or her. If development problems occur, this will ensure early diagnosis and treatment.

Care of the Shunt

- You can handle, cuddle, and play with your baby like any baby. Your baby also can sleep in any position after the initial postoperative period.

BOX 26.3

PARENT/CAREGIVER TEACHING—CONT'D

Wolfson Children's Hospital Parent Handout: Newborn Ventriculopertoneal Shunt (For Use With Ventriculoperitoneal Shunt Teaching Checklist)

BAPTIST MEDICAL CENTER
WOLFSON CHILDREN'S HOSPITAL
JACKSONVILLE, FLORIDA

Wolfson Children's Hospital at Baptist Medical Center

VENTRICULOPERITONEAL (VP) SHUNT TEACHING CHECKLIST

GOAL/SKILL	NURSING (Date and Initials)	CARE GIVER #1	CARE GIVER #2	CARE GIVER #3
1. Verbalizes understanding of reason for VP shunt.	H - "An Introduction to Hydrocephalus" ☐			
2. Identifies the pathway of the VP shunt and the shunt's function.	H - "Ventriculoperitoneal Shunt" (Newborn) ☐ H - "Hydrocephalus and Shunts" (For infants with Cordis Shunts) ☐ H - "Your Valve System for Hydrocephalus" (For Cordis Valve System Shunts) ☐ H - "Just Like Any Other Little Beagle" ☐ V - "Just Like Any Other Little Beagle" ☐			
3. Lists signs and symptoms of shunt infection and emergent need to notify MD.				
4. Lists signs and symptoms of shunt failure and emergent need to notify MD.				
5. Discuss the reason and importance of prompt treatment of health problems.				
6. Verbalizes understanding of importance of close medical follow-up.				

SIGNATURE/INITIAL		TEACHING CODES	PARENT SIGNATURE(S)
		L - Lecture/Discussion	
		D - Demonstration (or return demo)	
		U - Verbalizes Understanding	
		R - Reinforced Teaching	PATIENT LABEL
		V - Video	
		H - Handout	
		E - Equipment	

20-207 Rev 5/96

Courtesy Baptist Medical Center, Wolfson Children's Hospital, Jacksonville, Fla.

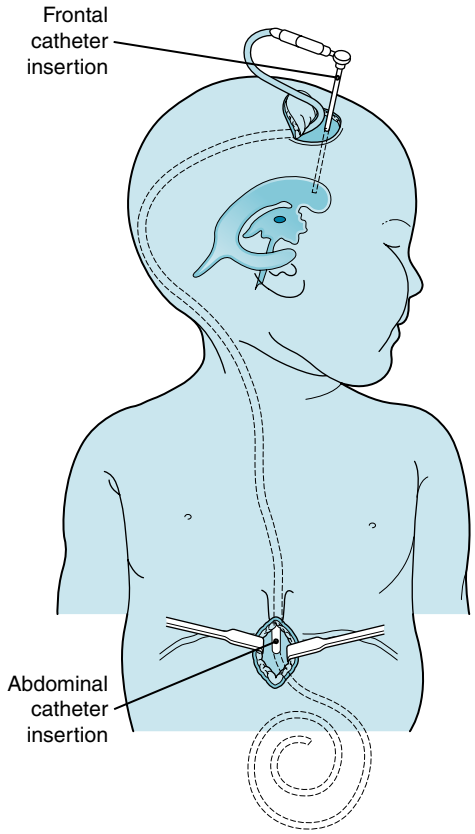

FIGURE 26.1 Ventricular peritoneal shunt. (From Rengachary SS, Ellenbogen RG. *Principles of Neurosurgery*. 2nd ed. Edinburgh, UK: Mosby; 2005.)

may be seen. Spinal cord lesions cause quadriplegia or paraplegia. Genitourinary problems and, to a lesser extent, gastrointestinal problems also are seen.

Most of the complications occur after the newborn period. In many circumstances, the problem is already present but functional expression such as impaired ambulation, intellectual disability, or deafness, is lacking. In the infant's follow-up examinations, careful attention must be given to problems likely to develop or intensify with age. When a specific malformation is diagnosed, it is necessary to become familiar with potential sequelae, not only to anticipate problems as they appear but also to lessen any secondary damage that might occur if the diagnoses go unrecognized.

Parent Teaching

Parents of an infant born with congenital malformations are faced with a stressful event that may develop into a major life transition. Parents, especially mothers, report feelings of guilt and self-blame, although they may not initially share these feelings with hospital staff. **After the birth of a malformed child, they go through stages of grief (see Chapters 29 and 30): shock or denial, anger, bargaining, depression, and acceptance.** Chronic grief over their loss of a healthy child can be seen in parents who have a child with a disability. Symptoms of acute posttraumatic stress disorder also can be seen.[52]

Social support received from hospital personnel, family, and friends can help parents in dealing with the stress of having an ill infant. **The ability of the staff to accurately anticipate and assess parental feelings and concerns can be invaluable when assisting families through this difficult time.** Parents often need to be supported to verbalize their feelings and fears. Reassurances, when appropriate, are provided (e.g., parents were not responsible for the congenital malformation; it is normal for the mother to experience [or at least report] more fears than her husband). **The ultimate goal of intervention is to reduce stress, assist families to confront fears, improve coping, and facilitate the parent-infant bonding process.**[52]

Infants with congenital malformations present such a complex variety of problems that parent teaching and emotional support need to begin as early as possible. With improved surveillance such as ultrasound and fetal MRI, parents often know from the time of birth or earlier that a major problem exists. In other circumstances, the anomaly is detected only after appropriate studies are performed.

When the infant is not viable, care should be directed at meeting the emotional needs of the family. **Every effort should be made to give family members positive experiences and memories by encouraging early parental holding of the infant and, whenever possible, participation with care** (see Chapter 30). Anticipatory counseling from social services, the palliative care team, and chaplain staff can help the family during grieving and with funeral arrangements. If there are also questions about etiologic factors and genetics, these questions should be dealt with according to the family's wishes (see Chapter 27).

If serious handicaps are anticipated and the infant is expected to survive, the parents should be encouraged to participate in the care of the infant from the beginning. Both adjustment and

specific aspects of care within the circumstance will be enhanced, and learning will be more effective if parents are supported. **A multidisciplinary team approach to parent education and support allows individualized hospital resources for specific needs of the patient and family.** In addition to medical, nursing, social service, palliative care, and chaplain involvement, team members can be drawn from psychology, developmental specialists, physical therapy/occupational therapy, and other services based on specific needs and circumstances. **Parent teaching and support must be individualized according to the anomaly.** When available, support groups, integrative discharge planning, and specialized clinics can help with postdischarge care and parent education.

Parent teaching for mothers and fathers of infants with congenital anomalies should (1) be started early, (2) involve the parents in the care of the infant, (3) use the resources of the hospital and community for specialized help, and (4) continue after the infant has gone home from the hospital or dies.[65]

BIRTH INJURIES

Physiology and Etiology

Birth injuries (birth traumas) are the direct result of difficulties encountered during the delivery process. These may be minor injuries without expected sequelae or the direct cause of death in the neonatal period. Classification of birth injuries usually is etiologic (predisposing factors or mechanisms of injury) or anatomic. An anatomic classification is used in this discussion to illustrate commonly encountered problems (Table 26.2).

The timing of birth injuries can be used to identify and describe causes. Etiologic classification of birth injuries includes uterine injury (antenatal), fetal monitoring procedures, abnormal or difficult presentations or methods of delivery, and multifactorial injuries. It should be recognized that an injury might have multiple causations. Thus, a cephalhematoma could be the result of forceps delivery, vacuum extraction, or routine vaginal delivery. A variety of specific predisposing factors increase the risk for birth injury, as follows:

- Macrosomia
- Cephalopelvic disproportion
- Uterine abnormalities
- Dystocia
- Prematurity
- Prolonged or precipitous labor
- Breech presentation/abnormal lie
- Instrumented delivery: forceps/vacuum
- Rotation of fetus
- Version and extraction
- Handling after delivery

Multiple factors often are present. When multiple predisposing factors are present, a single underlying maternal disease often links them. A common example is that of a premature, macrosomic fetus with a diabetic mother in whom labor is not progressing properly.

The common factors that are present in deliveries complicated by birth injuries are as follows:

TABLE 26.2 ANATOMIC CLASSIFICATION OF BIRTH INJURIES

SITE OF INJURY	TYPE OF INJURY
Scalp	Caput succedaneum Cephalhematoma Subgaleal hemorrhage
Skull	Linear fracture Depressed fracture Occipital osteodiastasis
Intracranial	Epidural hematoma Subdural hematoma (laceration of falx, tentorium, or superficial veins) Subarachnoid hemorrhage Cerebral contusion Cerebellar contusion Intracerebellar hematoma
Spinal cord (cervical)	Vertebral artery injury Intraspinal hemorrhage Spinal cord transection or injury
Plexus injuries	Erb palsy Klumpke paralysis Total (mixed) brachial plexus injury Horner syndrome Diaphragmatic paralysis Lumbosacral plexus injury
Cranial and peripheral nerve injuries	Radial nerve palsy/nerve injuries Medial nerve palsy Sciatic nerve palsy Laryngeal nerve palsy Diaphragmatic paralysis Facial nerve palsy

- **Unusual progress of labor**
- **Unusual size or shape of the fetus (large for gestational age or hydrocephalus)**
- **Problems encountered during delivery (dystocia or forceps application)**
- **Unusual or unexpected presentations (breech or unexpected twin)**

The maternal history always must be explored for an underlying disease process or condition that might increase the risk of a birth injury.

Prevention

Careful attention to risk factors and the appropriate planning of delivery should reduce the incidence of birth injuries to a minimum. Transabdominal and transvaginal ultrasonography facilitate awareness of macrosomia, hydrocephalus, and unusual presentations before delivery. Particular pregnancies then may be delivered by controlled elective cesarean section to avoid significant birth injury. Care must be taken to avoid substituting a procedure of greater risk. **A small percentage of significant birth injuries cannot be anticipated until the specific circumstances are encountered during delivery.** Emergency cesarean delivery may provide last-minute salvage, but in these circumstances, the injury may be truly unavoidable.

SPECIFIC BIRTH INJURIES

Injuries to the Scalp

The three common forms of extracranial scalp injuries are caput succedaneum, cephalhematoma, and subgaleal hemorrhage and are distinguished not only in clinical manifestations but also in pathophysiology (Box 26.4).[98] These three extracranial scalp injuries are included with neurologic birth injuries, not because they have associated neurologic problems, but because the family or health care providers often raise the question of possible neurologic involvement.

PHYSIOLOGY AND ETIOLOGY

***Caput succedaneum* is caused by trauma to the scalp,** usually during a routine vertex vaginal delivery. **The caput is the result of hemorrhagic edema superficial to the periosteum of the scalp.** Therefore, spread of the edema is not restricted to suture lines and is soft and pitting because of its superficial location.[25,95,98]

***Cephalhematoma* is a subperiosteal collection of blood that is confined by the skull sutures.**

BOX 26.4 CRITICAL FINDINGS
Extracranial Hemorrhage

There are three common forms of extracranial hemorrhage but with different etiology and clinical assessment findings, as follows.

1. Caput succedaneum
   a. *Etiology:* Trauma to scalp (usually vertex vaginal delivery) results in hemorrhagic edema superficial to the aponeurosis of the scalp.
   b. *Findings:* Soft, pitting edema that crosses suture lines.
2. Cephalhematoma
   a. *Etiology:* Mechanical trauma; most common in primiparous women, with delivery using forceps or in vacuum-assisted deliveries.
   b. *Findings:* Firm, tense collection of blood confined by the sutures. Area often increases in size after delivery. No significant blood loss. Blood collects beneath the periosteum (subperiosteal).
   c. *Warning:* Associated with linear skull fracture in up to 25% of cases.
3. Subgaleal hemorrhage
   a. *Etiology:* Forces that compress and then drag the head through the pelvic outlet.
   b. *Findings:* Firm swelling that crosses suture lines and is fluctuant to palpation. Blood collection is under the aponeurosis (connective tissue connecting the occipital and frontal muscles). Bleeding (swelling) may continue after birth and dissect along tissue planes into the neck.
   c. *Warning: Acute blood loss may occur.* Presenting symptom may be shock.

Monitor VS for signs of shock:
- Elevated HR
- Decreasing BP

Monitor baby for signs of shock:
- Pallor
- Delayed capillary refill time
- Diminished tone
- Respiratory distress

Transfusion may be necessary: type and crossmatch.
Serial Hct should be followed.
Elevated bilirubin is a common complication as a byproduct of broken-down red blood cells.

BP, Blood pressure; *Hct,* hematocrit; *HR,* heart rate; *VS,* vital signs.

The incidence is 1% to 2% of all live births. The cause is nearly always mechanical trauma, and its occurrence is more common in primiparous women and in forceps or vacuum-assisted delivery. Males are generally more likely to be affected than females. It is associated with an **underlying linear skull fracture in 10% to 30% of cases.** The firm, tense collection of blood frequently increases in size after birth, but significant blood loss does not occur.[25,95,98]

Forces that compress and drag the head through the pelvic outlet are associated with *subgaleal hemorrhage.* Significant acute blood loss can occur with shock as the presenting symptom. Bleeding may continue after birth with enlargement of the accumulated blood and dissection of the blood along tissue planes into the neck. Such a hemorrhage carries the greatest potential for complications, but fortunately it is the least common form of birth injury to the scalp.[25,95,98]

DATA COLLECTION

With caput succedaneum, physical examination reveals soft, pitting edema that is diffuse and crosses suture lines. Laboratory tests are not needed.[95,98]

Cephalhematomas may occur anywhere but are most commonly found in the parietal area on one side. Because the location of the blood is subperiosteal, the blood is confined by suture lines. Symptoms are normally absent. A skull fracture underlying the cephalhematoma is present in 10% to 30% of affected infants. X-ray examination of the skull defines the fracture. Rare complications include infection, osteomyelitis, hyperbilirubinemia, meningitis, and late-onset anemia.[95,98]

Because the subgaleal collection of blood is under the aponeurosis (connective tissue connecting the occipital and frontal muscles) and superficial to the periosteum, subgaleal hemorrhage crosses suture lines. Extravasated blood progresses down to the nape of the neck from the scalp, may result in a protruding ear, and is firm but fluctuant to palpation. **Vital signs should be carefully monitored for symptoms of shock. Serial measurements of head circumference should be documented. Pallor, delayed capillary refill time, diminished tone, respiratory distress, elevated heart rate, or decreasing blood pressure should be observed for and treated promptly.** Transfusion may be necessary. **The hematocrit should be serially followed, and bilirubin levels should be determined during recovery.**[95,98]

TREATMENT

Usually, no treatment is necessary for caput or cephalhematoma. **In subgaleal hemorrhage, treatment of blood loss and shock may be necessary. During resolution, the breakdown of the blood may cause hyperbilirubinemia requiring treatment** (see Chapter 21).[95,98]

PARENT TEACHING

Parents of an infant with a cephalhematoma should be instructed that the cephalhematoma may enlarge but that they should not be concerned unless localized changes occur, suggesting secondary infection (erythema, induration, or drainage). This lesion should not be drained and may be evident for several weeks to months. A small calcification may remain after reabsorption of hemorrhage. The calcification may take months to resolve. The hemorrhage can be significant enough to cause hyperbilirubinemia or (rarely) anemia. **Outpatient evaluation of bilirubin levels and hematocrit may be needed in some cases.**

Parents of an infant with caput succedaneum should understand that the swelling is outside of the cavity of the brain and will usually reabsorb within a few days.[95] **Careful preparation of the parents for the acute side effects of subgaleal hemorrhage is important. Parents should be warned of the possibility of swelling and discoloration of the face, head, and neck.** The purpose of serial hematocrit and bilirubin checks should be explained. **Parents can expect 2 to 3 weeks for the swelling to resolve.**[95,98]

Skull Fractures

Three forms of skull fracture should be identified and differentiated: linear fractures, depressed fractures, and occipital osteodiastasis.[95,98]

PHYSIOLOGY AND ETIOLOGY

Linear skull fracture (a nondepressed fracture) is the most common type of skull fracture. The result of compression of the skull during delivery, **a linear skull fracture most often has no associated injuries and causes no symptoms.** Bleeding may be seen extracranially (common) or intracranially (rare). Intracranial bleeding causes symptoms referable to the bleeding rather than to the fracture itself.[95,98]

The typical depressed skull fracture is of the "ping-pong" type, an indentation without loss of bony continuity. When forceps are used during delivery, the direct cause of injury may result but is often without complications or sequelae. When neurologic signs are present, direct cerebral injury, intracranial bleeding, or free bone fragments should be suspected.[95,98]

Occipital osteodiastasis, a separation of the cartilaginous joint between the squamous and lateral portion of the occipital bone, occurs during traumatic breech deliveries. This injury results in a posterior fossa subdural hemorrhage that is associated with contusion of the cerebellum.[98] Although a planned breech delivery may be considered depending on the health care provider's experience and the patient's wishes, the American College of Obstetricians and Gynecologists recommends a detailed informed consent that includes risks of neonatal mortality or short-term serious neonatal morbidity should be documented.[8]

DATA COLLECTION

A linear skull fracture usually produces no signs or symptoms unless intracranial bleeding has occurred. Skull x-ray films most frequently demonstrate a parietal fracture. **A depressed skull fracture may be noted by** presence of a visible depression or a palpable "ping-pong" fracture in the parietal or temporal area. No other signs and symptoms are present unless intracranial bleeding or focal irritation of the cortex causes them. **Evaluation with MRI or a CT scan is necessary to delineate the type of fracture and identify complications.**

TREATMENT

No treatment is necessary for a linear skull fracture. Treatment of a depressed skull fracture varies. **If free bone fragments or clots are identified, neurosurgical intervention is necessary.** More conservative approaches are indicated when no complications or neurologic symptoms are present. Noninvasive treatments such as vacuum extractors and breast pumps have been used with success to raise the depressed bone segment. Spontaneous elevation of the depressed fracture has been reported.[98]

COMPLICATIONS

With a linear skull fracture, the single complication to be aware of is a "growing" skull fracture. A dural tear may allow leptomeninges to extrude into the fracture site, setting up the possibility of a leptomeningeal cyst. As the cyst enlarges, the edges of the fracture may fail to fuse and even spread apart, giving the appearance of a "growing" fracture. Palpation and x-ray examination demonstrate the lesion. Surgical correction may be necessary to ensure healing and prevent further complications. With a spontaneous depressed skull fracture, intracranial bleeding and direct cerebral injury with seizures or residual neurologic deficit are rare. Intracranial bleeding, specifically epidural or subdural hemorrhages, is more common when the depressed skull fracture was the result of instrumentation at delivery.[98]

PARENT TEACHING

Parents should be instructed to have the fracture site monitored for several months to ensure that reunion of the bone has taken place. Patients will require no other aftercare unless neurosurgical intervention was necessary or complications developed.

Intracranial Birth Injuries

Three major forms of intracranial bleeding occur: epidural hematoma, subdural hemorrhage, and subarachnoid hemorrhage (Box 26.5). Added to these are cerebellar hemorrhages, cerebellar contusions, and cerebral contusions. Each has its own particular set of signs and symptoms, complications, and sequelae. **Shearing forces may cause trauma** and are covered separately in this chapter.

PHYSIOLOGY AND ETIOLOGY

An *epidural hematoma* is pathophysiologically difficult to form in newborns resulting from a relatively thick dura. When present, it is almost always accompanied by a linear skull fracture across the middle meningeal artery.[98]

Subdural hemorrhage **is more common in term infants than in preterm infants, and occurs from trauma tearing veins and venous sinuses.** Although some assume its presence represents birth trauma, several authors indicate that this is not necessarily the case.[42,95] Subdural hemorrhage has been linked with maternal use of aspirin and also to maternal ingestion of phenobarbital. Four major pathologic entities are defined: (1) laceration of the tentorium, (2) laceration of the fax, (3) laceration

BOX 26.5 CRITICAL FINDINGS
Intracranial Birth Injuries

1. Epidural hematoma
   a. *Occurrence:* Rare.
   b. *Location:* Bleeding occurs into the epidural space. Blood is located between the inner area of skull bone and the periosteum.
   c. *Pathophysiology:* Most (not all) with history of traumatic labor or delivery.
   d. *Clinical findings:*
      - Increased intracranial pressure (swollen fontanel).
      - Seizures may occur.
   e. *Associated problems:* Almost always accompanied by a linear skull fracture.
2. Subdural hemorrhage
   a. *Occurrence:* More common in term infants than in preterm.
   b. *Location:* Bleeding is produced from tear of cerebral vein or sinus, which is often accompanied by a tear in the dura. Exact location of the hematoma depends on the location of the bleeding source.
      - Laceration of the tentorium
      - Laceration of the falx
      - Laceration of the superficial cerebral vein
      - Occipital osteodiastasis
   c. *Pathophysiology:*
      - Debate as to whether its presence indicates birth trauma. Volpe indicates that most cases result from trauma.[98]
      - Linked to maternal use of aspirin and maternal ingestion of phenobarbital.
   d. *Clinical findings:* Neurologically abnormal at birth, if massive bleed:
      - Seizures
      - Stupor or coma
      - Skew deviation of eyes
      - Pupil changes: unequal pupils, poorly responsive pupils, fixed and dilated pupils
      - Nuchal rigidity
      - Apnea and bradycardia
      - Signs of increased intracranial pressure
   e. *Associated problems:* Risk for herniation with lumbar puncture.
3. Subarachnoid hemorrhage
   a. *Occurrence:* Most common type of neonatal intracranial hemorrhage.
   b. *Location:* Blood is within the subarachnoid space but not because of extension from other areas. Small hemorrhages are more common than large ones. Source believed to be small vascular channels.
   c. *Pathophysiology*:
      - Term: Usually caused by trauma
      - Preterm: Usually caused by hypoxia
   d. *Clinical findings:*
      - Most common: Minimal or no symptoms
      - Seizures (especially with term infants): "Well baby with seizures"
      - Apnea (especially with preterm infants)
      - For massive bleed (rare): Sudden and marked deterioration; death
   e. *Associated problems:*
      - Usually none for infants without significant trauma or hypoxia.
      - After major bleed:

      Hydrocephalus (most common sequela)
      Neurologic residual
      Death

of the superficial cerebral vein, and (4) occipital osteodiastasis. Tentorial laceration causes a posterior fossa clot with compression of the brainstem. The straight sinus, vein of Galen, lateral sinus, and infratentorial veins may be involved. Laceration of the falx is caused by rupture of the inferior sagittal sinus. The laceration usually occurs at the junction of the tentorium and the falx, and the clot appears in the longitudinal cerebral fissure over the corpus callosum. Laceration of superficial cerebral veins causes subdural bleeding over the convexity of the brain. Subarachnoid bleeding or contusion of the brain also may be present.[42,95]

A subarachnoid hemorrhage is the most common type of neonatal intracranial hemorrhage. In term infants, trauma is the most common cause, whereas in preterm infants, hypoxia is more often the cause. Small hemorrhages are more common than massive ones and usually result from venous bleeding.[42]

Cerebral contusions are uncommon as an isolated event. Focal blunt trauma is necessary to produce a contusion. Pathologically, focal areas of hemorrhage and necrosis are seen. Shearing forces may cause slit-like tears in the white matter.[98]

Cerebellar contusion is usually seen in association with occipital osteodiastasis and infratentorial

subdural hemorrhage.[98] **Intracerebellar hemorrhage was once thought to be uncommon but more recently has been increasingly found on routine neuroimaging of preterm infants. Intracerebellar hemorrhages are more frequently seen in preterm infants but also can be seen in infants born at term.**[23,61] They are usually associated with a supratentorial hemorrhage but also can be an isolated finding. Although mortality has improved, these infants, especially those with larger lesions, almost always have neurologic deficits.[61]

DATA COLLECTION

For epidural hemorrhage, the signs and symptoms may be diffuse (increased intracranial pressure with a bulging fontanel) and may include focal or lateralizing seizures, eye deviation, and hemiplegia syndromes.[98] **Laboratory tests should include x-ray examination to look for fractures and CT scan or MRI to identify bleeding.**

Infants with subdural hemorrhage are often neurologically abnormal at birth. Tentorial lacerations and laceration of the falx tend to produce brainstem signs caused by pressure. These signs include skew deviation of the eyes, unequal pupils, apnea, or coma. Nuchal rigidity and opisthotonus are signs of progressive herniation. Signs and symptoms of subdural hemorrhage from laceration of the superficial cerebral veins are variable. Small clots may produce no identifiable dysfunction. Typical signs are those of focal or lateralized cerebral dysfunction, including seizures, although increased intracranial pressure may occur. **Cranial MRI, including views of the posterior fossa, should be obtained immediately when a subdural hemorrhage is suspected. If MRI is unavailable, a CT scan is recommended. Lumbar puncture is not used as a diagnostic tool because of the risk for herniation.**[42]

With subarachnoid hemorrhage, underlying contusion may cause focal neurologic signs. Often no significant increase in intracranial pressure is found acutely. Irritability and a depressed level of consciousness may persist. **Seizures are common in term infants, whereas apnea is common in preterm infants.** Diagnosis generally is made with MRI or CT scan. If a lumbar puncture is performed, it is generally done for another reason (e.g., meningitis workup) and shows elevated RBCs and protein.[42] For infants without serious injury from trauma or hypoxia, the prognosis is good.[42] Focal signs predominate in cerebral contusions.[98]

TREATMENT

Surgical evacuation of epidural and subdural clots may be necessary as emergency procedures. Subdural taps may be useful in the symptomatic infant with subdural bleeding from laceration of superficial cerebral veins. In the presence of coagulation defects, prompt intervention may require platelets, vitamin K, or replacement therapy for deficient coagulation factors. **Many infants with intracranial bleeding may require treatment for seizures.**[42]

COMPLICATIONS

The complications of epidural hemorrhage range from none to permanent neurologic deficits with or without seizures. Sequelae of subdural hemorrhage occur in 10% to 20% of affected infants. **The most common sequelae are focal neurologic signs.** Seizures and hydrocephalus are seen less often. **Hydrocephalus, although rare, is the major potential complication of subarachnoid hemorrhage.**[42]

PARENT TEACHING

Because long-term outcome is variable and may be abnormal even in infants who appear normal at discharge from the nursery, parent teaching must be individualized. **Emphasize the need for appropriate follow-up and intervention.** Referral to available support groups is usually beneficial.

Spinal Cord Injuries

PHYSIOLOGY AND ETIOLOGY

Injuries to the spinal cord (usually the lower cervical–upper thoracic portion) are seen most often in complicated breech deliveries. Before cesarean deliveries were routinely performed for breech delivery, fatal attempts to deliver vaginally were often associated with intraspinal hemorrhage. **Breech presentation in conjunction with a hyperextended head is the most dangerous situation and is worsened by fetal depression.** Traction, rotation, and torsion cause mechanical strain on the vertebral column. Cephalic deliveries are not entirely safe because of the difference in

mechanical forces; a different clinical picture is seen with an upper to mid-cervical injury.[42]

DATA COLLECTION

Clinical manifestations depend on the severity and location of the injury. Clinical syndromes include stillbirth or rapid neonatal death, respiratory failure, and spinal shock syndrome. High cervical cord injuries are more likely to cause stillbirths or rapid death of the neonate. Lower lesions cause an acute cord syndrome. **Common signs of spinal shock include flaccid extremities (may involve just the lower extremities if the cervical cord is spared); a sensory level, diaphragmatic breathing; paralyzed abdominal movements; atonic anal sphincter; and distended bladder. Useful laboratory tests include MRI, CT scan, or ultrasound of the spine. Response to pinprick and evaluation of deep tendon reflexes are important to determine sensory level involvement.** The differential diagnosis includes dysraphism, neuromuscular disease, and cord tumors.[42]

COMPLICATIONS

After the acute phase, chronic lesions include cysts, vascular occlusions, adhesions, and necrosis of the spinal cord. **Flaccid or spastic quadriplegia is expected.** Some infants with spinal cord injuries are ventilator dependent, and bowel and bladder problems continue.[98]

PARENT TEACHING

Parents should understand fully the implications of severe injury to the spinal cord. Recovery is frequently minimal to nonexistent. Continued specialized care may be necessary, including ventilator therapy. The overwhelming implications for the family cannot be emphasized strongly enough.

An individualized multidisciplinary team approach to discharge planning is vital to parental confidence and a timely discharge. The problems of both patient and family are complex and not limited to medical concerns. **A successful discharge is unlikely unless family emotional, financial, and educational concerns are addressed early in the planning process.** The timely assessment of needs and involvement of supportive agencies allow resolution of problems well before the projected discharge date. Such assistance should include early family referral to available federal programs for financial aid (e.g., Supplemental Security Income [SSI]) and assistance with patient transportation to their multiple outpatient follow-up appointments. Early assessment of equipment needs and home nursing requirements is also of primary importance and should include a determination of the availability of these resources in the community, parent acceptance of their use, and whether the home can accommodate them (i.e., adequate electrical system and space).

Plexus Injuries

PHYSIOLOGY AND ETIOLOGY

Plexus injuries occur more commonly than cord injuries and result from lateral traction on the shoulder (vertex deliveries) or the head (breech deliveries).[98] Risk factors include large infant, fetal depression, breech delivery, and a variety of obstetric factors. **Any factor resulting in a difficult vaginal delivery of the baby can increase the risk for injury** (e.g., prolonged second stage of labor, shoulder dystocia),[95,98] although factors may not be in control of the delivery provider.[98] Estimates of the incidence of brachial plexus injuries range from 0.5 to 2.5 per 1000 live births.[98] Extremely mild cases often have undetectable findings and may remain unidentified.

Pathologic changes range from edema and hemorrhage of the nerve sheath to actual avulsion of the nerve root from the spinal cord. Of the reported cases of plexus injuries, 90% involve the cervical nerve 5 (C5) to C7 nerve roots and are classified as Erb palsy.[98] In a small minority of cases, the C4 nerve root is also affected. The site of injury in Erb palsy is Erb palsy point, where C5 and C6 nerve roots join to form the upper trunk of the brachial plexus. The shoulder and upper arm are involved, and the biceps reflex is decreased or absent. When C4 is involved, diaphragmatic dysfunction is present.

Total brachial plexus palsy occurs in less than 10% of the cases. Plexus involvement is diffuse (cervical 5 [C5] to thoracic nerve 1 [T1] and occasionally C4). **The upper and lower arm and hand are involved. Biceps and triceps reflexes are decreased.** When T1 is involved the sympathetic fibers become affected with an ipsilateral *Horner syndrome* (ptosis, anhidrosis, and miosis) and possible delay in pigmentation of the iris.

Klumpke palsy rarely occurs in the newborn period and involves only the distal upper extremity (lower arm and hand), whereas the muscles in the proximal extremity are normal. The lower part of the

plexus, C7 to T1, is involved. Triceps reflex may be decreased. When both distal and proximal weakness occur, it should be classified as total plexus palsy.[98]

DATA COLLECTION

Signs of brachial plexus palsies vary somewhat, most often because of the overlap of pure clinical syndromes. **Shoulder and arm findings are characteristic of a true Erb palsy.** Involvement of the hand and fingers is seen in total forms or Klumpke palsy. Table 26.3 lists the specific spinal cord levels involved, as well as their various functions that might be assessed.

Evaluation of diaphragmatic function by real-time ultrasound is at times necessary. Spinal cord MRI may be necessary to identify nerve root avulsion, which generally should be suspected when recovery does not occur. Serial electromyography may be helpful in the evaluation process.[98]

TABLE 26.3 BRACHIAL PLEXUS EXAMINATION: DISTINGUISHING FEATURES

PART EXAMINED	SPINAL LEVEL
Diaphragm movement (downward)	C4 (C3-5)
Deltoid muscle	C5
Spinatus muscle	C5
Biceps muscle	C5-6
Brachioradialis muscle	C5-6
Supinator of arm	C5-6
Biceps tendon reflex	C5-6
Wrist extensors	C6-7
Long extensor of the digits	C6-7
Triceps tendon reflex	C6-7
Wrist flexor	C7-8, T1
Finger flexors	C7-8, T1
Dilator of iris (sympathetic chain, *Horner* syndrome)	T1
Eyelid elevator (full elevation) (same as above condition)	T1
Moro reflex (shoulder abduction)	C5
Moro reflex (hand motion)	C8-T1
Palmar grasp	C8-T1

C, Cervical; *T*, thoracic.

TREATMENT

Treatment includes passive range-of-motion exercises followed by a gradual increase of activity to the affected limb. Initially, treatment may include immobilization for 1 to 5 days, followed by gentle passive range-of-motion exercises to prevent contractures. Wrist splints also may be necessary. For infants failing to achieve sufficient functional recovery by 3 months of age, referral to a clinic specializing in brachial plexus injury should be considered. Rarely, nerve graft surgery of the injured nerve root is necessary.[98]

COMPLICATIONS

Associated trauma may occur and should be carefully investigated. **Common associated injuries include clavicle fracture, shoulder dislocation, cord injury, facial nerve injury, and humeral fracture.**[98] Full recovery of plexus function was seen in 88% to 92% of cases in the first year of life during the National Collaborative Perinatal Study.[59]

PARENT TEACHING

Parents should be taught passive range-of-motion exercises to encourage the infant's mobility and prevent contractures. Instructions should begin before discharge from the hospital. Usually a neonatal nurse or occupational or physical therapist gives the instructions.

Parents may equate the presence of a brachial plexus injury with poor obstetric care. This is often not the case. Good communication with parents concerning the variety of risk factors associated with plexus injuries will hopefully alleviate their concerns. Discharge follow-up should include appointments with neurology, physical therapy, and rehabilitative medicine.

Cranial and Peripheral Nerve Injuries

Median nerve injuries usually are postnatal and result from brachial and radial artery punctures. Sciatic nerve injury may be a result of inferior gluteal artery spasm or thrombosis (umbilical artery line drug instillation). Recovery is variable.[98]

Median nerve palsy is manifested by decreased pincer grasp, decreased thumb strength, and the continuous fixed position of the fourth finger. *Radial nerve damage* usually is seen in conjunction with humeral compression or less frequently humeral fracture. Difficult labor may be present.

Congenital amniotic bands also may be causative. Recovery takes place over weeks to months. Radial nerve palsy is manifested by wrist drop (decreased finger and wrist extension) and normal grasp.[98]

Laryngeal nerve palsy may be seen in conjunction with facial or diaphragmatic paralysis. **If the paralysis is unilateral, a hoarse cry may be heard. Bilateral involvement causes breathing to be difficult and the vocal cords to remain closed in the midline.** In these cases, it is essential to rule out intrinsic brainstem disease. Often the presence of other brainstem-related abnormalities such as oculomotor problems, apnea, or facial palsy helps clarify this. In-utero rotation and flex positioning of the head/neck or during delivery may cause injury to the laryngeal nerve. **Laryngeal nerve palsy may also occur after trauma associated with a patent ductus arteriosus ligation, cardiac surgery, placement of neck cannulas for extracorporeal membrane oxygenation and tracheoesophageal atresia repair.**[98]

Laryngeal nerve palsy is manifested by difficulty in swallowing (superior branch), difficulty in breathing (bilateral), and difficulty in vocalizing (recurrent branch). Also, the head is held high and fixed laterally with slight rotation. Severe cases may require tracheotomy and assisted feedings by gavage or gastrostomy tube.[98]

***Diaphragmatic paralysis* is most often seen in association with plexus injuries (80% to 90% have an associated plexus injury) and has the same etiology.** Some series involving unilateral paralysis have a mortality rate of 10% to 20%. **Most patients recover fully in 6 to 12 months.** Although fewer than 10% of patients have bilateral diaphragmatic paralysis, the mortality rate for these patients is almost 50%. Treatment has consisted of using continuous positive airway pressure (CPAP), ventilators, intermittent negative-pressure ventilation, or surgical plication. Because diaphragmatic paralysis may occur in other conditions such as a myotonic dystrophy, attention to the differential diagnosis is important, particularly when an associated brachial plexus problem is not present.[98]

Diaphragmatic paralysis is demonstrated by respiratory difficulty in the first few hours of life. Real-time ultrasound or fluoroscopy shows elevation of the hemidiaphragm with paradoxic movement that may disappear on positive end-expiratory pressure (PEEP) or CPAP.[98]

Facial palsy may be part of intrinsic brainstem disease (see previous discussion of laryngeal nerve palsy), prenatal compression, trauma, malformation of the nerve itself, or other conditions such as Möbius syndrome or myotonic dystrophy. When it is traumatic in origin, facial palsy is thought to be caused by the position of the face on the sacral promontory at the exit of the nerve from the stylomastoid foramen.[98] Normally, both the upper (temporofacial) and lower (cervicofacial) branches are involved. **Facial palsy is seen on the left side in 75% of cases. Features include a widened palpebral fissure, flat nasolabial fold, and decreased facial expression. Most infants completely recover within 3 weeks, although some infants continue to have deficits months later.** Known complications (from lack of total resolution) include contractures and synkinesis.[98]

PARENT TEACHING

Infants with facial palsy may require the **use of artificial tears if unable to completely close the eye on the involved side.** Occasionally it may be necessary to tape the eye to prevent injury to the cornea. **Parents also should be taught to expect some drooling of formula from the corner of the mouth during breast or bottle feedings.**

Most infants with laryngeal nerve palsy recover in the first 6 to 12 months of life. **Symptoms initially require supplemental parent education and support. An infant's risk for aspiration necessitates careful feeding and appropriate response if choking occurs.** Additional education for gavage feedings, a tracheotomy, or an apnea monitor may be necessary for the parents of a few infants. The teaching requirements for the infant with diaphragmatic paralysis also must be tailored to meet the individual needs and circumstances of the infant and family.

HYPOTONIA

Hypotonia is a common presenting symptom in the newborn. It is important to distinguish between hypotonia and muscle weakness. **The majority of infants with hypotonia have a cause centered in the CNS.** In these cases, hypotonia is more prominent than weakness. Hypotonia might be due to a congenital encephalopathy (HIE being the most common), intracranial hemorrhage, a congenital

brain malformation, metabolic disorder, or genetic mutation.[86] Causes of motor weakness may involve cranial nerve motor nuclei (as in Möbius syndrome), anterior horn cells (as in spinal muscular atrophy), spinal cord injury (causing severe weakness), peripheral nerves, the neuromuscular junction (neonatal myasthenia gravis), or muscle itself (myotonic dystrophy, congenital myopathy, muscular dystrophy).[60,86,100]

Data Collection

A cranial MRI is performed to evaluate for a CNS cause for hypotonia. If this is normal, investigation then turns to other causes. Physical examination may reveal congenital abnormalities and, in such cases, consideration should be given to performing a chromosomal microarray.[67] Next-generation genome sequencing (NGS) also has become a powerful tool in revealing causes of hypotonia. Discussion with a medical geneticist or a genetic counselor can be helpful in directing testing.[78] Creatine kinase (CK) level that is quite elevated may determine a dystrophic process, with breakdown in muscle fibers. The CK is modestly elevated for a few days after vaginal birth. An aldolase level rarely adds additional information and is not necessary. A lumbar puncture can be performed to look for elevated CSF protein seen in demyelinating syndromes. **Genetic testing for myotonic dystrophy and spinal muscular atrophy are readily available** and should be performed if clinically indicated. When myotonic dystrophy is suspected, both parents should be examined for myotonia, which can be helpful in diagnosing their infant with the same disorder. **An electromyogram (EMG) and nerve conduction study (NCS) can be performed to help determine whether weakness is due to a nerve or muscle problem.** EMGs are difficult in newborns and require a skilled examiner. A muscle biopsy can be performed if absolutely necessary, although many times it is more helpful when the infant is older. Additionally, because many genetic causes of hypotonia demonstrate overlapping pathologic findings on biopsy, genetic testing may provide more precise diagnosis.[14,75] In general, DNA-based testing should be performed as first-line testing while NCS and EMG are reserved for cases in which genetic testing is unrevealing.[60,67,78,86]

Parent Teaching

Parent teaching will depend on the infant's diagnosis. In general, **infants who have a neuromuscular disorder have respiratory and feeding issues.** These infants may need ventilatory assistance and nasogastric or gastrostomy tube feedings. Physical and occupational therapy should be involved to help with positioning and recommending equipment for the family at home. In the case of a genetic disorder, genetic counseling should be provided to the family. Rarely, an infant with hypotonia will be found to have a diagnosis that is considered life limiting.[78] In such cases, involving a specialist in palliative care can be very helpful for families as they navigate challenging decisions with the medical team.[53,62]

NEONATAL SEIZURES

Seizures are among the most frequent clinical signs, occasionally the only sign, of CNS dysfunction in neonates. The occurrence of neonatal seizures should prompt an immediate search for the underlying etiology as well as an overall assessment of associated medical disorders. Depending on the clinical history, suspected etiology, and seizure frequency, use of antiepileptic medications may be indicated in addition to correcting any underlying metabolic disturbances.

The overall incidence of neonatal seizures is difficult to ascertain, in part because the incidence varies in relation to gestational age and birth weight. For infants weighing less than 1500 g, the seizure frequency is 57.5 per 1000, whereas it is 2.8 per 1000 for infants weighing 2500 to 3999 g. **Seizures occur more frequently during the neonatal period than at any other period of life.**[1,37,93]

Neonates with seizures are at increased risk of having or developing other neurologic deficits, developmental impairments, and an increased risk of death.[36,89] **Aggressive seizure management improves the infant's neurologic and developmental outcome.**[1] **The occurrence of neonatal seizures may also predispose the child to later cognitive and behavioral complications as well as epilepsy.**[37,89] Outcome is largely dependent on the underlying cause of neonatal seizures.

Recognition and treatment of neonatal seizures and their underlying etiology are critical

to improving the child's short- and long-term outcomes. Seizures are commonly related to significant general medical disorders, which may also require specific treatment. Untreated neonatal seizures may interfere with supportive therapies such as assisted ventilation and nutrition. **Experimental data suggest that repetitive or prolonged seizures may cause brain injury and contribute to an adverse clinical outcome.**[3]

Epileptic seizures are the result of excessive synchronous electrical discharges from neurons within the CNS. **In general, neonatal seizures should be viewed not as a specific disease entity, but as a symptom. There are a number of epileptic encephalopathies that may present in the neonatal period, but overall these are rare.**[35] **Seizures may be associated with many disorders that directly or indirectly affect the brain by altering its electrochemical stability.** Intracranial processes that may result in neonatal seizures include meningitis, intracranial hemorrhage (subdural, intraventricular, primary subarachnoid), ischemic cerebral infarction (stroke), encephalitis, and cerebral malformations.[89,93]

Seizures also occur secondary to systemic or metabolic disturbances, including hypoglycemia, hypoxia-ischemia, hypocalcemia, hypomagnesemia, hyponatremia, drug intoxications, drug withdrawal, and inborn errors of metabolism.[10,22] A link between intrapartum fever and unexplained seizure activity in term infants also has been reported in the literature. Presence of fever increased the likelihood of seizure activity by four times normal even when the presence of an infection was not confirmed.[89,95]

Clinically, seizures are characterized by a paroxysmal alteration in neurologic functions, including behavioral, motor, or autonomic functions. These clinical signs are typically accompanied by electrical abnormalities detectable by scalp EEG recordings. A large proportion of neonatal seizures may be subclinical or subtle and only identified on EEG.[16,37] **Clinical presentation of seizures in neonates differs considerably from the well-organized seizure activity seen in older children and adults.**

Etiology and Data Collection

Neonatal seizures may be caused by a variety of acute and chronic disorders of the brain. Table 26.4 lists the general groups of causes of neonatal seizures. A detailed history of perinatal problems

TABLE 26.4 COMMON CAUSES OF NEONATAL SEIZURES

CLASSIFICATION	CAUSES
Acute metabolic conditions (assess blood gases, pH, HCO_3^-, Na, K, Ca, Mg, glucose, blood urea nitrogen)	Hypocalcemia Hypoglycemia, hyperglycemia Hypomagnesemia Pyridoxine dependency or deficiency Hyponatremia, hypernatremia
Inherited metabolic conditions (acidosis is common; assess blood amino acids, blood lactate and pyruvate, blood ammonia [NH_3] galactose, and urine amino and organic acids)	Maple syrup urine disease Nonketotic hyperglycemia Hyperprolinemia Hyperglycinemia Galactosemia Urea cycle abnormalities Organic acidemias
Infections (12% of cases; assess CSF; culture blood, CSF; polymerase chain reaction assay in CSF; imaging)	Viral encephalitis, herpes or enterovirus infection Congenital infections Bacterial meningitis Sepsis Brain abscess Septic venous thrombosis
Intracranial hemorrhage (15% of cases; assess imaging; CSF examination)	Subdural hematoma Cerebral contusion Subarachnoid hemorrhage Epidural hemorrhage Intraventricular hemorrhage (premature)
Hypoxic ischemia (0-3 days) most common (60%) Cerebral infarction Congenital malformations Neonatal drug withdrawal (see Chapter 11) (e.g., opiates) Local anesthetic intoxication Kernicterus Specific nongenetic syndromes Benign familial neonatal seizures Idiopathic (in only 10%, no cause is found)	

CSF, Cerebrospinal fluid.

often narrows the differential diagnosis to one or two likely causes. **Acute, reversible, or treatable metabolic disorders that can cause seizures need to be investigated quickly.** Blood glucose should be checked immediately in the neonatal intensive care unit with a glucometer, and also in the laboratory, because hypoglycemia is a dangerous but treatable cause of seizures (Table 26.5).

Lumbar puncture should be done to diagnose or exclude bacterial meningitis, another dangerous but treatable cause of seizures. Sepsis should never be overlooked as a potential cause of seizures because the responsible infectious agent may directly invade the CNS. Systemic infections may also cause seizures through complications such as shock,

TABLE 26.5 DRUG THERAPY FOR NEONATAL SEIZURES[4]

DRUG	DOSE	COMMENTS
Glucose	10% solution 2 mL/kg bolus IV if hypoglycemic. *Maintenance:* as high as 8 mg/kg/min IV (see Chapter 15).	Treat if hypoglycemic with glucose meter testing (e.g., Accu-Chek; One Touch II).
Phenobarbital (drug of choice for neonatal seizures)	*Loading:* 20 mg/kg IV given slowly over 10-15 min; additional 5 mg/kg can be given 1 hour after dose to maximum of 40 mg/kg total for refractory seizures.	*Therapeutic level:* 15-40 mcg/mL (obtain levels any time); respiratory depressant; incompatible with other drugs in solution.
	Maintenance: 3-4 mg/kg/24 hr in 2 divided doses beginning no earlier than 12 hours after last loading dose.	Maintain adequate oxygenation and ventilation.
Fosphenytoin (Cerebyx) preferred over phenytoin* (added if seizures not controlled by phenobarbital alone)	Fosphenytoin dose is expressed in PE; fosphenytoin 1 mg PE = phenytoin 1 mg. *Loading:* 15-20 mg PE/kg IM or IV† given slowly over minimum of 10 min. Flush IV with normal saline before and after.	*Fosphenytoin advantages:* high water solubility; pH value closer to neutral; faster, safe rate of administration; safe to give IM; absence of tissue injury with IV infusion; easy to prepare in IV solution. *Therapeutic level:* measure trough serum phenytoin (not fosphenytoin) 48 hr after IV loading dose; 10-20 mcg/mL desirable level.
	Maintenance: 4-8 mg PE/kg/24 hr IM or IV slow push (see above for dilution); infuse no faster than 1.5 mg/kg/min. Flush IV before/after with NS. Maintenance should be initiated 24 hr after loading dose. Term infants older than 1 wk of age may need up to 8 mg PE/kg/dose every 8-12 hr.	Monitor blood pressure closely during infusion; can be given with lorazepam or phenobarbital at terminal injection site. Safety with newborns still not clearly established; use with caution in infants with hyperbilirubinemia.
Phenytoin used instead of Cerebyx to control seizures that are not controlled by phenobarbital alone	Loading: 15-20 mg/kg IV infusion over at least 30 min (no more rapidly than 0.5 mg/kg/min). Flush with NS before and after giving. ***Never give IM.*** ***Never give in central lines.*** *Maintenance:* 4-8 mg/kg/24 hr‡ IV slow push (no more rapidly than 0.5 mg/kg/min) or by mouth (PO). Flush with NS before and after. Absorption erratic with PO route. Term infants older than 1 week of age may need up to 8 mg/kg/dose every 8-12 hr.	Phenytoin disadvantages: incompatible with glucose and all other drugs; cannot be given IM (crystallizes in the muscle); rapid administration can result in bradycardia, dysrhythmias, hypotension. The pH of IV solution is 12, which is irritating to veins. Extravasation may result in tissue necrosis. *Therapeutic level:* measure trough level 48 hr after loading dose. Serum level 6-15 mcg/mL initially and 10-20 mcg/mL after the first few weeks.

TABLE 26.5 DRUG THERAPY FOR NEONATAL SEIZURES[4] — CONT'D

DRUG	DOSE	COMMENTS
Pyridoxine (vitamin B_6) as indicated	50-100 mg IV push or IM.	Used to diagnose and treat seizures resulting from pyridoxine (vitamin B_6 deficiency). Monitor EEG while giving. Protect from light. Diagnostic when seizures cease within minutes and the EEG normalizes within minutes or hours.
Lorazepam (Ativan) for seizures uncontrolled by phenobarbital and fosphenytoin (or phenytoin if used)	0.05-0.1 mg/kg IV slow push over several min.	Enters brain rapidly; onset of action in less than 5 min. Monitor for respiratory depression. Monitor IV site for phlebitis or extravasation. Safer to use than diazepam (Valium), which is contraindicated for use in the newborn.
Additional Therapy As Indicated		
Calcium gluconate, 5% solution Magnesium sulfate, 50% solution IV antibiotics (bacterial infection; see Chapter 22) Acyclovir (herpes; see Chapter 22)		

*Appears to be preferred, although safety has not been clearly established.
†Must be diluted in NS or D_5W to a concentration of 1.5 to 25 mg PE/mL for IV use.
‡Volpe cites 3 to 4 mg/kg/24 hr IV in divided doses every 12 hr, starting 12 hr after loading dose.[4]
EEG, Electroencephalogram; *IM,* intramuscularly; *IV,* intravenously; *mcg,* micrograms; *NS,* normal saline; *PE,* phenytoin equivalents.

coagulopathy, impaired oxygenation, and multisystem organ failure. When the CSF is examined, not only should the changes associated with infection be identified but also evidence of bleeding (RBCs) or cell destruction (protein) may be detected. **Peripheral blood glucose always should be compared to CSF glucose *at the time of lumbar puncture***. When the ratio of CSF glucose to peripheral blood glucose is less than 60% or CSF glucose is less than 40 mg/mL, consideration should be given to a diagnosis of glucose transporter 1 (GLUT1) deficiency.[93]

Neuroimaging studies are performed to detect underlying structural lesions. If the infant's clinical status allows safe transport to radiology, MRI or CT imaging can be done. **If the infant cannot be transported safely, cranial ultrasound (CUS) imaging can be done at the bedside.** CUS can detect IVH, periventricular white matter injury, hydrocephalus, and other structural lesions related to seizures.

The infant's clinical history may be the best tool available to the clinician for identifying the etiology. Physical examination may provide further clues to the diagnosis. Blood should be drawn for assessment of arterial blood gases, electrolytes, glucose, calcium, and magnesium.

Appropriate cultures must be obtained of blood, urine, pharyngeal and tracheal aspirates, and CSF. The CSF should be examined for red and white cells, protein concentration, glucose concentration, and Gram stain. In addition, viral cultures and polymerase chain reaction tests may be ordered.

In addition to its initial contribution to identifying the etiology of seizures, **CUS imaging can be used to monitor the evolution of IVH and hydrocephalus.** With ultrasound imaging the infant is not exposed to radiation, and there are no known immediate or long-term risks or complications. **CUS may be repeated as often as needed and has the advantage of being performed at the infant's bedside.**

TABLE 26.6 CRITICAL FINDINGS
Traditional Categorization of Neonatal Seizures

CLASSIFICATION/TYPES	CLINICAL MANIFESTATIONS	DEFINITION/DESCRIPTION
Clonic • Focal clonic • Multifocal clonic	• Rhythmic jerks (1-3/sec) • Rate slows during seizure • + EEG seizure activity	• Focal: well-localized to a body part • Multifocal: several body parts jerking simultaneously or in migrating order
Tonic • Focal tonic • Generalized tonic	• Characterized by posturing • Focal: + EEG seizure activity • Generalized: usually no EEG seizure activity	• Focal: continued posturing of limb or a posturing (asymmetric) of trunk or neck • Generalized: extension of lower limbs with either upper limb extension (looks like decerebrate posturing) or upper limb flexion (looks like decorticate posturing)
Myoclonic • Focal myoclonic • Generalized myoclonic	• Faster jerking than in clonic seizures • Flexor muscles (limbs) involved • Focal: usually no EEG seizure activity • Generalized: + EEG seizure activity	• Focal: flexor jerking of upper limbs • Generalized: bilateral jerking of upper extremities; sometimes lower limbs are involved; often single or irregular jerks
Subtle (more common in the premature infant)	• Abnormal behavioral, autonomic, or motor activities that do not result from the other three seizure classifications • + EEG seizure activity with only some of the seizure activities	• Ocular: nystagmus, horizontal or vertical deviation of eyes, staring episodes, eyelid flutter or blinking • Facial: repetitive sucking, mouth movements, tongue protrusion, chewing, drooling • Limb: bicycling, swimming movements, "boxing" or "hooking" motions, stepping • Apnea: only 2% result from seizures • Autonomic or vasomotor changes

EEG, Electroencephalogram.

Clinical Seizure Types

The use of continuous EEG video recordings and continuous amplitude-integrated EEG recordings allows for a more accurate diagnosis of subtle behaviors, apneic and bradycardic spells, and other jerks and movements commonly seen in preterm newborns and suspected of being epileptic seizure activity. Amplitude-integrated EEG, while convenient, may lead to under-detection of seizures. **Full-set video EEG, with review by a pediatric epileptologist, should be performed whenever feasible and continues to be the gold standard for identification of neonatal seizures.**[1,16,37]

Seizures result from abnormal, excessive electrical discharge or depolarization of cortical neurons. They are most often manifestations of an underlying disorder, rather than being an isolated disorder. As a paroxysmal alteration of neurologic function, these behavioral, motor, or autonomic clinical phenomena are associated with EEG electrical seizure activity. Table 26.6 lists the classification of clinical seizure types and usual EEG findings. **Many neonatal electrical seizures identified by EEG are not accompanied by any motor or behavioral clinical activity, a phenomenon referred to as subclinical seizure activity or electroclinical dissociation.**

Focal clonic and multifocal clonic seizures are the most likely types of seizure activity to be associated with an electrocerebral seizure pattern on EEG. Eye blinking, a type of clonic manifestation, or nystagmus may be seen as the only outward manifestation of a seizure. **Focal clonic seizures are important manifestations of cerebral infarction and stroke in the neonate. Apnea accompanied by electrical seizure activity has been seen as an ictal manifestation, most commonly in full-term infants.** Apneic episodes in the premature population, however, are most often not epileptic events and are not associated

TABLE 26.7 CRITICAL FINDINGS
Seizures Versus Jitteriness

CLINICAL OBSERVATIONS	SEIZURE	JITTERINESS
Ocular abnormalities (eye deviations or staring)	Yes	No
Gentle restraint of the involved body part halts the activity	No	Yes
Activity is easily elicited with stimulation (e.g., voice, motions)	No	Yes
Dominant movement is a slower clonic jerking having both fast and slow elements	Yes	No
Tremor in which the amplitude and rate of the alternating movements are equal	No	Yes
Autonomic changes are present (e.g., apnea, tachycardia, elevated blood pressure, pupil changes, increased salivation)	Yes	No

with epileptiform EEG patterns. **The best EEG-clinical correlation can be made by obtaining an EEG during a period of the suspected seizure activity.**[4,16,37]

A commonly used classification of neonatal seizures is presented in Table 26.6. The classification of neonatal seizures is distinct from the International Classification of Seizures applicable to seizures in older children and adults. **Seizures are more subtle and more difficult to recognize in neonates than in older infants and children.** Further compounding the difficulty of diagnosis are **conditions that mimic epileptic neonatal seizures, such as neonatal jitteriness** (Table 26.7).[3,16]

Prevention

Many neonatal seizures can be successfully prevented through careful attention to possible metabolic changes expected on the basis of the infant's condition. Hypoglycemia, hypocalcemia, hypomagnesemia, and often hypoxia can be anticipated and controlled. Those infants born with brain malformations or brain injuries or who develop neonatal infections, intracranial hemorrhages, or strokes can be observed carefully for the early occurrence of seizures and treated promptly.

Treatment

The initial treatment of neonatal seizures involves stopping seizure activity with a loading dose of an antiepileptic medication, preventing further seizures with maintenance doses of medication, minimizing side effects of seizure therapy, and correcting underlying treatable conditions.

The first goal is stopping repetitive or prolonged seizures. **Frequently recurring and prolonged or persistent seizures may result in injurious metabolic changes in the brain and also lead to cardiorespiratory difficulty.** Seizures are associated with increased energy consumption by neurons, which may interfere with cerebral perfusion and adequate oxygenation. Although the neonatal brain appears to be less sensitive to seizure-induced injury than the adult brain, **repeated seizures may nevertheless be detrimental to the developing nervous system.**[37]

Phenobarbital continues to be recommended as first-line treatment for neonatal seizures. The debate over the best choice of second-line treatment continues, with fosphenytoin and levetiracetam being mentioned frequently (see Table 26.5). **Levetiracetam,** in particular, has gained popularity because of its effectiveness at high doses and relatively benign side effect profile.[64] Other medications such as lorazepam, midazolam, and topiramate are being used with increasing frequency. **When the administration of a single drug fails to result in seizure control, a second or third antiepileptic medication is indicated. Both phenobarbital and fosphenytoin are given initially as an intravenous loading dose of 20 mg/kg,** which produces a therapeutic blood concentration in most infants. Subsequent to the loading dose, maintenance doses of phenobarbital can be continued using doses typically between 3 and 5 mg/kg/day, orally or intravenously. Because the **half-life of phenobarbital in neonates is 40 hours or more, monitoring blood levels can be helpful in guiding dosing frequency and in avoiding dose-related, systemic side effects and neurotoxicity.**

Intravenous levetiracetam in a loading dose ranging from 20 to 60 mg/kg per dose also may be used. Dosing guidelines for levetiracetam have not been well established, but a recent prospective study suggested doses of 45 to 60 mg/kg/day for persistent seizures. This is consistent with the American Epilepsy Society's recent guideline for the treatment of status epilepticus, which suggests levetiracetam be dosed at 60 mg/kg.[31,38,55,64]

The duration of prophylactic antiepileptic therapy is based on the severity and frequency of seizures as well as the presence of other neurologic impairments. **A common approach is to treat with antiepileptic medications for several weeks or months after the child is discharged,** and then reassess the need for continued therapy. Increasingly, medications are being discontinued before patients leaving the hospital, especially when hypoxic ischemic encephalopathy is considered causative.[32,71]

The identification and correction of underlying treatable conditions will assist in seizure management. Empirical administration of glucose, calcium, and pyridoxine may be considered, particularly for frequently recurring seizures or seizures refractory to antiepileptic medications. For seizures that remain refractory to usual therapy, genetic testing may be considered to determine whether the infant has an identifiable gene mutation related to neonatal or early infantile seizures, such as mutations affecting sodium channels, potassium channels, or gamma-aminobutyric acid (GABA) receptors. Knowing that such a mutation is present may assist in selecting antiepileptic drugs that will be most beneficial or in avoiding drugs that might worsen seizure activity.[78]

Complications and Outcome

It is difficult to separate potential deleterious effects of seizures from those of the underlying cause. Some of the **metabolic disorders, such as hypocalcemia, are relatively benign conditions that once corrected allow full recovery without complications.** In contrast, **seizures related to cerebral malformations, hypoxic-ischemic injury, stroke, IVH, or meningitis are likely to persist and evolve into epilepsy.**[34,79,94] Those infants who have an abnormal neurologic examination or who have severely abnormal EEG patterns, such as burst-suppression or diffuse very low voltage, are likely to have seizures that persist into later childhood and beyond.

Parent Teaching

Parents need to know what seizures are and what may be the cause of seizures in their infant. Accurate information should address the specific concerns of each parent. Appropriate first aid measures should be discussed to ensure that the parents have a clear understanding of how their child is being treated in the nursery and how parents will need to manage seizures should they occur after the infant goes home. Parents need to know the significance of tests (e.g., EEG and brain imaging tests), the limitations of these tests, and how future tests will be used to monitor the child's condition. **Parents also need information about the different types of seizures that can occur during early infancy. While the child is still in the nursery, the parents need to be educated on how to recognize and document seizure activity** (Box 26.6). **Handouts written in a clear simple style are useful when parents are learning to care for an infant with seizures. Handouts should be available in a variety of languages to meet the needs of a diverse population.**

While the infant is in the hospital, the parents should become involved in the daily care, including administering medications. In the hospital, parents can be coached and encouraged by the nursing staff. During this time, the parents also can be informed about local and national parent support groups and organizations designed to assist and support families after their infant is discharged from the hospital.

HYPOXIC-ISCHEMIC ENCEPHALOPATHY

Pathophysiology

The combination of hypoxia and ischemia is a common cause of brain injury in both term and preterm neonates. *Hypoxemia* refers to low levels of oxygen in the blood and potentially in brain tissue. *Ischemia* refers to a reduction in cerebral perfusion. *Asphyxia* is impaired exchange of oxygen and carbon dioxide across the respiratory organ (placenta before birth, lungs after birth) resulting

BOX 26.6

PARENT TEACHING

Seizure Disorder Family Teaching Checklist

BAPTIST MEDICAL CENTER
WOLFSON CHILDREN'S HOSPITAL
JACKSONVILLE, FLORIDA

SEIZURE DISORDER FAMILY TEACHING CHECKLIST

GOAL/SKILL	PRESENTATION/ NURSE DEMONSTRATION DATE AND INITIAL	CARE GIVER/ PATIENT DEMONSTRATION DATE AND INITIAL	CARE GIVER/ PATIENT DEMONSTRATION DATE AND INITIAL	COMMENTS/ HANDOUTS DATE AND INITIAL
1. Verbalizes understanding of seizure pathophysiology.				Handouts given:
2. Describes signs that indicate a seizure.				
3. Lists important observations to make during a seizure.				"Seizure Recognition"
4. Describes care of a child during a seizure.				
5. Identifies child's a. medication, dosage and schedule b. side effects of anticonvulsants c. consequences of non-compliance d. correct administration of medication				Medication _____ Dosage _____ Schedule _____ Medication handout given _____
6. Verbalizes how to seek emergency assistance from home.				
7. Identifies resources for families with a child with a seizure disorder.				
VIDEOS FOR PARENTS (Date that care giver/ patient views)	_____ "How Medications Work" _____ "Understanding Seizure Disorders"			

Courtesy Wolfson Children's Hospital, Jacksonville, Fla., 1996.

in comorbidities, low levels of circulating oxygen, and high levels of carbon dioxide. **When comparing hypoxemia and ischemia, ischemia is more devastating** because there is impaired delivery of oxygen and glucose to cerebral tissue and impaired removal of lactate and other neurotoxic byproducts of cellular metabolism.[76]

Brain injury due to hypoxemia and ischemia occurs in two phases.[37,96] **Tissue is first injured directly by the initial lack of oxygen and blood flow that leads to a decrease in high-energy phosphate compounds and acidosis. During the second phase, reperfusion injury occurs 8 to 16 hours after oxygenation and perfusion has been restored.** This second period of injury relates to a secondary decrease in high-energy phosphate compounds. During this secondary phase, metabolic derangements develop that lead to further brain injury as a result of elevation in tissue glutamate levels, release of neurotoxic cytokines, inflammation, impairment of mitochondrial function, and generation of free radicals. **The period between the primary phase of injury and the secondary phase is the *therapeutic window* for potential neuro-protective interventions.**[96]

Etiology

Impaired placental or pulmonary function (i.e., asphyxia) is a common, but rarely the only, cause of HIE. HIE occurs in approximately 1 to 2 neonates per 1000 live births with about one-third of these neonates demonstrating significant neurologic sequelae.[68] About 20% of cases are related to antepartum events, such as maternal hypertension, maternal diabetes, or intrauterine growth restriction. About 35% are related to intrapartum events, including placental abruption, cord prolapse, or traumatic delivery; and about 10% are related to postnatal cardiopulmonary failure. **In approximately 35% of cases, there are combinations of antepartum and intrapartum difficulties.**

Guidelines have been published by the AAP and the American College of Obstetrics and Gynecology regarding criteria needed to attribute neurologic injury to intrapartum HIE[7]:

1. **Metabolic acidosis is severe with pH <7.0 and base deficit ≥12 mmol/L.**
2. **The neonate (34 weeks of gestation or later) should have displayed a significant, moderate to severe encephalopathy during the neonatal period.**
3. **For cerebral palsy to be attributed, it should either be spastic quadriplegia or dyskinetic type.**

Other potential causes of neonatal encephalopathy (meningitis, encephalitis, genetic conditions, or thrombophilic disorders) should have been excluded. In addition to these major criteria, **the task force considered the following to be suggestive of timing to the intrapartum period**[6]: **(1) a sentinel hypoxic event** occurring immediately before or during labor; (2) **a sudden and sustained fetal bradycardia or absence of fetal heart rate variability in the presence of persistent, late, or variable decelerations,** usually after a hypoxic sentinel event when the pattern was previously normal; (3) **Apgar scores of 0 to 3 at 5 minutes or more after birth;** (4) **multisystem involvement with an onset within 72 hours of birth;** and (5) **the presence of evidence of acute, nonfocal cerebral abnormality shown on an early imaging study.**

Prevention

Preventing HIE requires the early anticipation, avoidance, and early treatment of those conditions (antepartum, intrapartum, or immediate postpartum) that lead to impaired oxygen delivery and blood flow to the brain. For example, the early detection and treatment of chorioamnionitis may reduce the risk of cerebral injury related to circulating cytokines. **Postpartum cardiopulmonary support is essential to reducing the risk of CNS injury. Keeping blood glucose levels normal is important** because both high and low levels may be deleterious in the setting of HIE.

Data Collection

HISTORY

The diagnosis of HIE depends in part on a detailed history of the antepartum, intrapartum, and postpartum events, as well as a thorough physical examination. Infants may have a history of intrauterine distress evidenced by abnormal fetal heart rate patterns or sudden cessation of movements. The infant may be depressed at birth or have low Apgar scores that persist beyond 5 or 10 minutes. Multiorgan damage may be evident, and there are signs of a significant encephalopathy.

TABLE 26.8 CRITICAL FINDINGS
Stages of Hypoxic-Ischemic Encephalopathy and Neurologic Assessment[7,61,89]

STAGE	NEUROLOGIC ASSESSMENT
Stage I: Mild encephalopathy	Hyperalert, with normal tone and activity, exaggerated response to stimulation, reactive pupils, no seizure activity
Stage II: Moderate encephalopathy	Hypotonic, weak suck, constricted but reactive pupils; periodic breathing or apnea Development of seizure activity or lethargy indicates deteriorated status
Stage III: Severe encephalopathy	Stupor or coma, absent reflexes, pupils nonreactive, no spontaneous activity, requires mechanical ventilation

SIGNS AND SYMPTOMS

The diagnosis of HIE also may be supported by physical findings indicative of encephalopathy[6,47] (Table 26.8). **HIE is also suspected when seizures occur within the first 12 hours after birth.**

LABORATORY DATA

Laboratory information often reflects multisystem dysfunction, including altered electrolyte concentrations, elevated hepatocellular enzymes, altered liver function tests, abnormal renal function tests, and abnormal coagulation studies. **Blood gases may provide evidence of hypoxemia, hypercarbia, and either metabolic or respiratory acidosis, or both. The ECG may be indicative of hypoxic-ischemic cardiac injury.** CSF studies may provide evidence of infection or subarachnoid hemorrhage. Chest x-ray studies may show evidence of pulmonary dysfunction and immaturity. **An EEG will assist in the diagnosis of seizures and the assessment of the neonatal encephalopathy.**[47] Burst-suppression patterns, isoelectric patterns, and very low EEG amplitude all indicate severe CNS dysfunction and are associated with poor prognosis. MRI provides valuable information regarding the nature, distribution, and extent of CNS injury and regarding specific patterns of injury that correlate highly with hypoxic-ischemic injury.[99] MRI scan can also provide valuable sequential monitoring of specific injuries and their evolution.[47]

Treatment

Treatment is focused largely on general supportive care, including the following: support of ventilation; maintenance of normal blood pressure; temperature regulation; maintenance of normal glucose, calcium, and electrolyte levels; and control of seizures.

In addition to general supportive measures, **the use of moderate hypothermia has become standard treatment during the past few years. *Head cooling* or *whole-body cooling* techniques have been used** (Box 26.7). **Inducing modest hypothermia provides neuroprotection of injured CNS cells and also provides a method to control cerebral edema. The use of hypothermia has been shown to improve outcome of neonates with HIE, including lowering the rate of neurodevelopmental disability.** Complications of cooling procedures include disorders of cardiac rate and rhythm, hypotension, thrombocytopenia, coagulopathy, renal dysfunction, and subcutaneous fat necrosis. Procedural details of these cooling methods are beyond the scope of this chapter. Other neuroprotective strategies being investigated include the use of free radical scavengers, anti-inflammatory agents, neurotrophic factors, antagonists of excitotoxic amino acids, and implantation of stem cells.[49,76]

Complications

Neonates who suffer HIE have an increased mortality rate, with up to 20% to 50% dying in the neonatal period. Long-term neurologic complications include epilepsy, hyperactivity, spasticity, movement disorders, dystonia, ataxia, hearing loss, visual loss, and intellectual and cognitive impairments.[18,76,83]

INTRAVENTRICULAR HEMORRHAGE

IVH is a major problem **in preterm infants, with a large percentage of these infants developing neurodevelopmental complications.** With recent medical advances and the increased survival of premature infants, IVH continues to be a significant

BOX 26.7 CRITERIA FOR NEONATAL COOLING FOR HYPOXIC-ISCHEMIC ENCEPHALOPATHY

Screening Inclusion Criteria

- Postmenstrual age ≥36 weeks
- Admitted ≤6 hours of age with a diagnosis of encephalopathy
- pH ≤7 or base deficit >16 mmol/L on cord blood or blood gas within first hour of life (for head cooling)
- pH 7.01-7.15 and base deficit 10-15.9 mmol/L in the first hour of life (for whole body cooling)
- If no blood gas available in the first hour, there also must be:
  - Evidence of an acute perinatal event, *or*
  - 10-minute Apgar score <5 *or*
  - Assisted ventilation (PPV or CPAP) initiated at birth and continued for a minimum of 10 minutes

Inclusion Criteria

- Seizure activity present
- Diagnosis of moderate or severe encephalopathy, which includes any one of the following:
  - Lethargy
  - Decreased tone (may have normal peripheral tone but have central hypotonia), abnormal tendon reflexes, myoclonus, weak suck, abnormal Moro reflex
  - Any evidence of seizures
  - Abnormal breathing
  - Moderate to severe EEG amplitude reduction (lower margin <5 microvolts and/or upper margin <10 microvolts) on a 20-minute aEEG or evidence of seizures

Exclusion Criteria

- >6 hours of age
- Severe intrauterine growth restriction (<1.8 kg)
- Major congenital anomaly
- Head trauma resulting in severe intracranial hemorrhage (head cooling)
- Prophylactic high-dose anticonvulsants (head cooling)
- Parents do not grant consent
- Inability to initiate cooling by 6 hours of age

Data from Gluckman PD, Wyatt JS, Azzopardi D, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicenter randomized trial. *Lancet.* 2005;365(9460):663; Higgins RD, Tonse NKR, Perlman J, et al. Hypothermia and perinatal asphyxia: executive summary of the National Institute of Child Health and Human Development workshop. *J Pediatr.* 2006;148(2):2, 170; and Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med.* 2005;353(15):1574.

aEEG, Amplitude-integrated electroencephalogram; *CPAP,* continuous positive airway pressure; *EEG,* electroencephalogram; *HIE,* hypoxic-ischemic encephalopathy; *PPV,* positive-pressure ventilation.

issue for neonates.[12,87] **IVH is found in 20% to 25% of preterm infants with incidence higher in those with very low birth weight.[12] IVH mainly occurs in infants less than 32 weeks of gestation, with the incidence increasing with decreasing gestational age.[63]** The incidence of IVH in term infants is approximately 3.5%, making IVH both an uncommon and unanticipated diagnosis in this group. Risk factors for IVH include prematurity, chorioamnionitis, hypotension, acidosis, respiratory distress, bicarbonate therapy, and coagulopathy.[66] A recent study of 765 neonates born at less than 32 weeks' gestational age, found that higher gestational age, antenatal steroid treatment, and cesarean section without uterine contraction were associated with a lower rate of IVH. Risk factors predisposing for IVH in this cohort included respiratory distress syndrome, pneumothorax, and use of catecholamines. **If gestational age and birth weight are excluded from the statistical analysis, early-onset sepsis and patent ductus arteriosus are associated with higher rates of IVH. Low Apgar scores have likewise been associated with IVH.[43,81]**

Physiology

Although the bleeding is regularly spoken of as *intraventricular* and *intracranial hemorrhage,* these terms do not accurately reflect its causes. Highly vascularized areas, which have relatively fragile and poorly supported blood vessels, are the source of bleeding. **In premature infants, the *germinal matrix,* in the subependymal area adjacent to the caudate nucleus, is the primary site of bleeding[11,43]** (Fig. 26.2). The anatomy of the deep venous system in this area may play a role in the pathogenesis of IVH, with preterm neonates with increased variability in subependymal vein anatomy being at higher risk for this complication.[88]

The extent of bleeding generally predicts the likelihood of complications and sequelae. Bleeding may be confined to the germinal matrix or the choroid plexus, or it may enter the ventricular system. When filled under pressure, the ventricular system may dilate. Blood may also extravasate out into the brain parenchyma.

There are several classification schemes to assess the degree of bleeding or the amount of blood present. **Volpe listed three grades of germinal matrix IVH using ultrasound scanning to identify the presence and extent of blood in the germinal matrix and lateral ventricles** (Table 26.9).

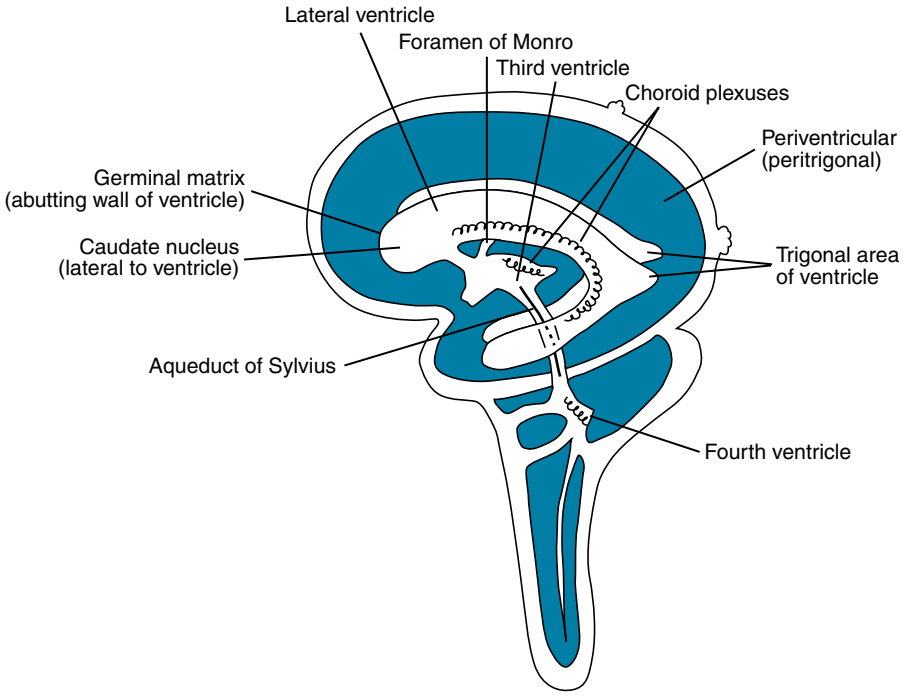

FIGURE 26.2 Central nervous system/ventricular system.

TABLE 26.9 GRADING OF SEVERITY OF GERMINAL MATRIX–INTRAVENTRICULAR HEMORRHAGE BY ULTRASOUND SCAN

SEVERITY	DESCRIPTION
Grade I	Germinal matrix hemorrhage with no or minimal intraventricular hemorrhage (10% of ventricular area on parasagittal view)
Grade II	Intraventricular hemorrhage (10%-50% of ventricular area on parasagittal view)
Grade III	Intraventricular hemorrhage (>50% of ventricular area on parasagittal view; usually distends lateral ventricle)
Separate notation	Periventricular echodensity (location and extent)

From Volpe JJ. *Neurology of the Newborn.* 5th ed. Philadelphia, PA: Saunders; 2008.

A "separate notation" is made for the existence of "periventricular hemorrhage infarction or of other parenchymal lesions." He clarified the use of this separate notation by noting that these abnormalities are not usually the result of simple "extension" of matrix or IVH hemorrhage into "normal brain parenchyma.[97]

An older classification system that grades germinal matrix hemorrhages based on CT scans (Fig. 26.3) is not used as frequently today. Because both grading systems are still cited in the literature, both are included here.

0: No bleeding
I: Germinal matrix only
II: Germinal matrix with blood in the ventricles
III: Germinal matrix with blood in the ventricles and hydrocephalus (ventricular dilation)
IV: Intraventricular and parenchymal bleeding (other than germinal matrix)

Etiology

The etiologic factors identified in infants who have experienced IVH are multiple and can be divided into prenatal, neonatal, and postnatal factors. These include asphyxia, severe respiratory distress, pneumothorax, hypoglycemia, shock, acidosis, blood transfusions, seizures, and rapid

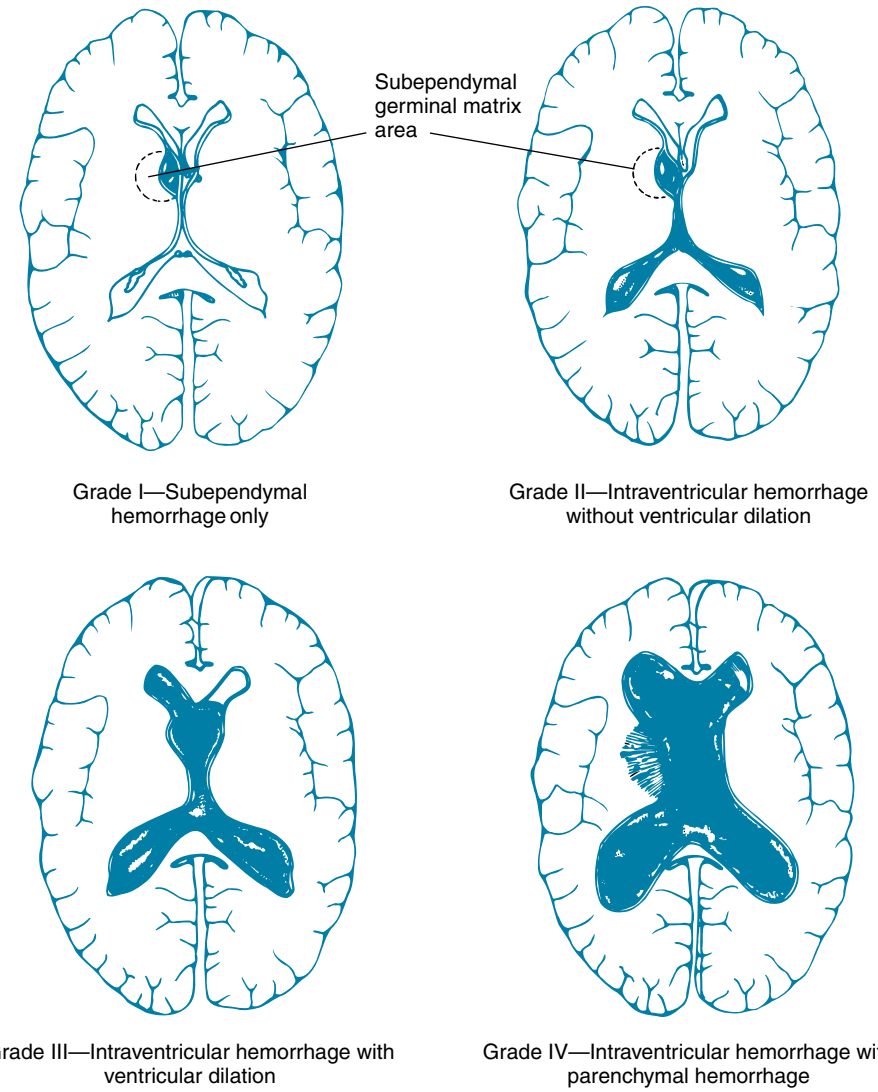

FIGURE 26.3 Periventricular-intraventricular hemorrhage, grades I to IV. (From Rozmus C. Periventricular-intraventricular hemorrhage in the newborn. *Matern Child Nurs.* 1992;17(2):79.)

volume expansion (Box 26.8). What appears to be the **common factor underlying the pathologic condition is a fluctuation/alteration in cerebral blood flow that causes the numerous and thin-walled blood vessels in the germinal matrix to bleed.**[12,46,63] Recently genetic factors have been implicated in development of IVH. Mutations of genes that can predispose to thrombophilia and collagen formation have been found to be involved in IVH.[11,12,63] **Intraventricular bleeding tends to occur in the first few hours or days of life.**

Profound physiologic changes normally seen after birth coupled with multiple problems (primarily cardiorespiratory) typically experienced by the premature infant make intraventricular bleeding common. **The degree to which the aggressive management of premature newborns has a role in the development of bleeding cannot be accurately assessed. Generally, sicker infants both**

BOX 26.8 CRITICAL FINDINGS

Factors That Predispose the Premature Infant to Intraventricular Hemorrhage

Prematurity
- Birth weight <1500 g
- Less than 34 weeks of gestation

Asphyxia (see Chapters 4 and 8)
- Before, during, after birth

Respiratory (see Chapters 8 and 23)
- Idiopathic respiratory distress syndrome
- Hypoxia
- Positive-pressure ventilation
- Pneumothorax
- Apnea

Cardiovascular (see Chapter 4)
- Rapid volume expansion
- Elevated venous pressure
- Elevated or lowered arterial pressure (shock, transfusions)

Hematologic (see Chapter 20)
- Hyperosmolarity
- Coagulation disorders
- Hyperviscosity

Metabolic (see Chapters 8, 14, and 15)
- Hypoglycemia/hyperglycemia
- Hypernatremia/hyponatremia
- Metabolic acidosis
- Rapid pH shifts

Miscellaneous
- Hypothermia (see Chapter 6)
- Acetylsalicylic acid ingestion by mother
- Neonatal pain (see Chapter 12)
- Neonatal environmental stressors (see Chapter 13)

Modified from Gardner S, Hagedorn M. Physiologic sequelae of prematurity: the nurse practitioner's role. VIII. Neurologic conditions. *J Pediatr Nurs.* 1992;6:265.

require more intervention and have a greater likelihood of bleeding.

Data Collection

HISTORY

Because premature infants, particularly those weighing less than 1500 g, tend to have multiple problems, it is not surprising that the clinical presentation of IVH may range from subtle (or even undetectable) to catastrophic.[11]

SIGNS AND SYMPTOMS

Common signs of germinal matrix hemorrhage include apnea, hypotension, drop in hematocrit, seizures, flaccidity, areflexia, full fontanel, tonic posturing, and oculomotor disturbances.[12]

LABORATORY DATA

When **intracranial** bleeding is suspected, appropriate studies of intracranial structures should be performed as soon as possible. **For IVH, ultrasonography is the study of choice.**[97] **The American Academy of Neurology practice parameter recommends screening of all neonates younger than 30 weeks of gestation. The first ultrasound should be done between 7 and 14 days looking for IVH and the second ultrasound at 36 to 40 weeks' postmenstrual age to look for a CNS lesion.** Additional follow-up imaging using MRI is indicated because MRI is better at detecting white matter changes, cysts, and bleeding lesions.[63,97]

Prevention

Strategies to prevent IVH have focused on both prenatal and postnatal interventions. Prenatal interventions such as preventing preterm delivery, maternal transport to a regional neonatal center, and prenatal glucocorticoids have been shown to be helpful in prevention of IVH.[12] Other pharmacologic agents studied, including vitamin K, phenobarbital, and magnesium sulfate, have unproven benefit.[11,12,47]

Postnatal pharmacologic treatment of IVH shows varying success in the literature. Agents

studied include phenobarbital, pancuronium bromide (Pavulon), vitamin E, ethamsylate, indomethacin, ibuprofen, and recombinant factor VIIa.[11,12,63] None of these have good data to support routine use. Postnatal prophylactic use of phenobarbital in preterm infants to prevent IVH has been one of the most widely studied therapies. However, because **phenobarbital results in a greater requirement for mechanical ventilation, it is not recommended for use in postnatal prophylactic prevention of IVH.**[11,12,44,63]

Treatment

The primary treatment of IVH is supportive care. Ventilatory support, maintenance of oxygenation, regulation of acid–base balance, suppression of seizures, and treatment of any attendant coagulopathy are all extremely important in reducing mortality and morbidity.[12] However, the role that successful management has in the amelioration or prevention of complications is unclear.

Complications

The complications from IVH relate to the underlying causes and the extent of bleeding. Massive bleeding with dilation of the ventricular system is much more likely to cause an acute change in brain function, with increased intracranial pressure, brainstem abnormalities, and apnea. Milder degrees of hemorrhage may be asymptomatic or associated with seizures, changes in muscle tone, or apnea.

When **bleeding extends into the parenchyma, porencephaly may result from liquefactive necrosis or ischemia-induced encephalomalacia.** Follow-up structural brain studies may show hypodense areas in which blood was present; later they may show areas of porencephaly.[63]

Other complications of IVH are *posthemorrhagic hydrocephalus* (PHH) and *periventricular leukomalacia* (PVL).[12,85] **Evidence of posthemorrhagic hydrocephalus should be investigated in all survivors of germinal matrix hemorrhage.** CT scanning or ultrasonography to assess ventricular size should be used because clinical signs alone are not reliable.[97] **With the hope of avoiding the necessity of placing a shunt, some attempts at control of the hydrocephalus have been made.** Various studies have evaluated intraventricular streptokinase, lumbar or ventricular punctures, and drainage/irrigation/fibrinolytic therapy, with **no interventions being effective.**[63]

The majority of infants with IVH suffer neurologic complications. In general the sickest and smallest neonates tend to have the most complications. **There is a clear correlation between the grade of bleed and the likelihood of significant neurologic complications. Over 50% of preterm children with a grade 3 to 4 IVH will have significant cognitive deficits, with 75% of these children requiring special education.**[85] The presence of white matter damage in the setting of IVH increases the risk of adverse developmental outcomes during infancy.[77] Even those with lower grade bleeds have been shown to have psychiatric and behavioral issues.[12] **The influence of other factors on neurologic outcome may be more significant than that of the actual bleed itself.** Hypoxia, hypoperfusion, and other conditions known to damage the developing nervous system cannot easily be separated as individual factors affecting outcome.

Parent Teaching

Parents of an infant with IVH should be involved with their infant's care plan. The rationale for a minimal handling protocol needs to be explained. Encouraging parents to participate in setting "timeout" and "touch me" times will facilitate their ability to visit and assist with care. **During visits, they should be encouraged to recognize signs of overstimulation and become knowledgeable about the appropriate interventions to take to calm their infant.**

The infant with IVH has both short- and long-term problems of varying degrees. If acute hemorrhage resolves without ongoing problems, possible complications such as hydrocephalus may still occur. **Teaching parents to measure head circumference and alerting them to the signs of increased intracranial pressure** such as poor feeding, posturing, eye movement difficulties, full fontanel, and lethargy enable them to participate more fully in the medical follow-up (see Box 26.3).

Parents need to understand the risk for long-term neurologic sequelae. Despite the difficulty of predicting sequelae with any degree of certainty, parents should understand that mental and motor handicaps, delays in the acquisition of milestones,

seizures, and problems associated with hydrocephalus and potential shunt placement may occur.[45] Specific preparation for these potential problems begins in the nursery, with more education as needed in follow-up visits. **Prompt and appropriate referral to medical specialists and supportive services is important in both inpatient and outpatient settings.** Parents may find support and information from national and state organizations (see "Parent Resources for Neurologic Disorders" at the end of the chapter).

PEDIATRIC STROKE

Pathophysiology

Stroke in the newborn period is defined as a group of heterogeneous conditions in which there is (1) focal disruption of cerebral blood flow secondary to arterial or cerebral venous thrombosis or embolization, (2) between 28 weeks of fetal life through the 28th postnatal day, and (3) confirmed by neuroimaging or neuropathologic studies.[82] **Perinatal stroke can be further divided into three subtypes: perinatal arterial stroke (PAS), cerebral sinovenous thrombosis (CSVT), or perinatal hemorrhagic stroke (PHS).**[39,57]

The most common stroke, PAS, affects both term and preterm infants with an estimated incidence of 1 in 2300 to 5000 births.[57,74,82] The most common site for PAS is the left middle cerebral artery.[74] Some studies have also noted male newborns affected slightly more often than females.[92]

CSVT is less common than PAS, with an incidence ranging from 40 per 100,000 live births per year.[105] As with PAS, there is a male predominance with CSVT.[105] CSVT is diagnosed as "the presence of a thrombus in a cranial venous sinus, a large deep brain vein or a smaller cortical or deep vein with partial or complete occlusion."[39] PHS is the least common type of stroke in neonates with a prevalence of 6.2 per 100,000 live births.[9] There are limited studies looking at etiology, complications, and long-term outcomes from PHS.

Etiology

The mechanisms that lead to PAS are varied and multifactorial.[82] Causes can be divided into emboli that are cardiac in origin, cerebral vessel disorders, and stasis of blood flow leading to thrombosis. **In more than half of newborns with PAS, a coagulation disorder has been identified, with thromboemboli being the most common cause.**[57,92] Newborns are especially at high risk for these emboli because of placental changes at delivery. Neonatal cardiac anatomy allows venous clots to cross the patent foramen ovale and right to left shunts also occur in cardiac disorders.[92] PHS occurs as a hemorrhagic transformation of arterial or venous infarction, from intraparenchymal hemorrhage due to vascular abnormalities or bleeding diatheses, or from unknown etiology.[9,17]

Prevention

Because PAS is multifactorial, one preventive strategy alone is not effective. Preventing any maternal risk factor (i.e., smoking, adequate weight control, and using compression stockings during periods of immobility) in women with a clotting disorder is advisable.[73] Because dehydration is a risk factor for thrombosis, attention to fluid intake during labor is indicated.[57,73]

Data Collection

HISTORY

There are numerous risk factors for PAS with no single factor as the main etiology. Risk factors may include maternal and placental disorders, perinatal asphyxia, blood disorders, cardiac disorders, infections, trauma, and drugs.[39,57,74] CSVT is also multifactorial with antepartal, intrapartal, and postpartal influences. Pregnancy factors include preeclampsia, chorioamnionitis, and gestational diabetes.[50,92] Delivery risk factors include fetal distress and birth asphyxia. The normal process of birth leading to head molding and overlapping of sutures may compress the dural sinus causing clot formation.[50,92] Postdelivery dehydration, sepsis, cardiac defects, and meningitis also may play a role.[50,92] Neonates receiving extracorporeal membrane oxygenation are at risk for CSVT because of disturbed jugular vein flow as a result of cannulation. The role of prothrombotic abnormalities in the development of CSVT in neonates is unclear. Recent studies have identified predictive risk factors for hemorrhagic stroke to be fetal distress and postmaturity of the neonate.[9,17] In addition, congenital heart disease was also a factor in another study.[17]

SIGNS AND SYMPTOMS

Most infants with PAS are normal at birth, with symptoms developing after the first day of life. Many newborns do not show signs of focal deficits; thus a high index of suspicion in at-risk neonates is warranted. Twenty-five percent of neonates with a stroke have systemic illness.[56] **Seizures, on the side opposite the infarction, are the most common presentation of neonatal stroke and occurring in 70% to 90% of cases.**[57,92] As with PAS, **neonates with CSVT present in the first day after birth to the first week of life.**[50] **Seizures are the most common presentation of CSVT.** Lethargy, irritability, poor feeding, apnea, and jitteriness are also common.[50,92] Neonates with PHS present similarly to the other stroke subtypes: seizures, apnea, respiratory distress, fever, and poor feeding are common. Diagnosis is based on CT, MRI, or magnetic resonance angiography.

LABORATORY DATA

Imaging is indicated for diagnosis of neonatal stroke. MRI, using diffusion-weighted sequences, is the imaging mode of choice for PAS, CVST, and PHS.[56,57,82] **MRI detects thrombi and infarcted areas.** Ultrasound is less useful in diagnosing PAS, and CT scan can miss small or early infarcts. CT detects hemorrhage in PHS. For CVST, Doppler flow ultrasound demonstrates decreased flow.[54,92] Pediatric stroke consensus guidelines also recommend noninvasive vascular imaging to diagnose previously undetected vessel abnormalities.[56] **Neonatal seizures require an EEG and laboratory workup for the etiology of seizures: complete blood count, CSF, cultures, and glucose, calcium, and electrolytes.** Coagulation studies are indicated with a family history of coagulopathy.[48,74] Multifocal infarcts seen on MRI or an abnormal cardiac examination (i.e., murmur) require an echocardiogram for congenital cardiac anomaly. Evaluation of the placenta is helpful in discerning sources of thromboemboli and systemic vascular abnormalities.[74,82]

MR venography is needed to evaluate for the presence of a thrombus. Doppler flow ultrasound can support a diagnosis by demonstrating absent or decreased flow.[54,92] Additional workup will depend on clinical presentation and can include laboratory testing, lumbar puncture, EEG, and echocardiography.

Treatment

Management of PAS is supportive and directed at treating any underlying condition. Maintenance of normal hydration, electrolytes, and glucose, oxygen, and pH levels are indicated.[53,86] Seizures are treated acutely with seizure medication, although most newborns do not need to be discharged on seizure medication. PAS is not routinely treated with aspirin or anticoagulation.[56,92] A congenital cardiac defect as the cause of the PAS may require treatment with antiplatelet agents or anticoagulation (i.e., heparin or low-molecular-weight heparin [LMWH]) with the consultation of pediatric cardiology.[56,58,92] If a genetic thrombophilia is diagnosed, pediatric hematology guides treatment with antiplatelet or anticoagulation agents. **Treatment of CSVT focuses on treatment of the underlying cause for thrombus formation. Antithrombotic therapy consists of the use of heparin or LMWH in neonates without significant intracranial hemorrhage,** followed by LMWH for 6 to 12 additional weeks.[69] If hemorrhage is present, radiology monitoring of the thrombus (at days 5 and 7) is followed by treatment with anticoagulation but only if the thrombus increases in size.[69] This treatment regimen is in contrast to the American Heart Association Stroke Council guideline that recommends treatment only if there is increased size of the thrombus.[50,105] Most studies have found significant variability in anticoagulation use, and more research is needed.[48]

Complications

The main complication of PAS is hemiplegic cerebral palsy, which occurs in 20% to 80% of children.[57,82,92] There is also ongoing risk of seizures, which occur in 15% to 40% of children with PAS.[57,82] Deficits in cognition, language, vision, and behavior are common and become evident in childhood.[57,58,82] **A normal or mildly abnormal neonatal neurologic examination is not predictive of future complications because of the plasticity of newborn brains and their greater ability to recover from injuries.**[58] **Neonates with CSVT have a high incidence of significant neurologic complications.** Neurologic deficits include epilepsy, cerebral palsy, and cognitive impairments.[105] Because there are few studies of PHS, long-term complications are difficult to determine. A recent

study did indicate that almost half of PHS survivors had short-term neurologic deficit.[17]

Parent Teaching

For a newborn diagnosed with any type perinatal stroke, parental education focuses on dealing with complications and associated conditions. Neonates with seizures are given antiseizure medications and may be discharged having weaned from them or still taking the medications.[56] **Parents need to learn to recognize seizures in their infant, to safely administer medications, and know the side effects of all medications.** Seizure medications may cause drowsiness/sleepiness, and parents need to know whom to contact if they are concerned about their infant's behavior.

Parents should be encouraged to use the services of multidisciplinary teams for their infant's rehabilitation needs.[58] Encouraging parents to begin early intervention services after discharge helps to lessen motor deficits. If no risk factors are identified, parents need to be reassured that the potential for recurrence of perinatal stroke is less than 1%.[58] If there is an identified cardiac or underlying abnormality, recurrence risk is higher. A small subset of newborns with underlying cardiac or hematologic risk factors will go home on antiplatelet or anticoagulant medication. These parents need to learn to dose these medications properly and know their side effects. **Parents should be aware that stroke morbidity lasts a lifetime, but their child's quality of life can be good because of the plasticity of the newborn brain.**[58]

NEONATAL NEUROINTENSIVE CARE

The advent of hypothermia as a treatment for hypoxic-ischemic injury in term infants provided the first direct therapy for modulation of neurologic injury as opposed to treatment of its symptoms. A number of additional therapies are being investigated, although none has gained the widespread acceptance of hypothermia. Therapies that remain under investigation for use in reducing the neurologic sequelae include erythropoietin, xenon, antioxidants, melatonin, topiramate, interferon-β, and stem cell transplantation.[15,26,104] As the potential for treating neurologic injury has expanded, there is increasing acceptance of the concept of the "Neuro-NICU."[15,51]

The Neuro-NICU, in its most basic form, represents a deliberate increase in communication among neurologists, neonatologists, specifically trained bedside nurses, and ancillary services to identify patients at risk for neurologic complications common to the ill or preterm neonate and to provide increased surveillance for these infants.[15,51] Although implementation strategies have differed from institution to institution, the benefits of a multidisciplinary team focused on neuro-protective strategies is beginning to be elucidated. Thus far, there is **evidence that neurointensive care services for neonates improve the detection of seizure activity and lead to decreased administration of seizure medication.**[84,102] The extent to which these efforts provide standardization of care may also yield improvements in outcomes.[2]

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PARENT RESOURCES FOR NEUROLOGIC DISORDERS

American Epilepsy Society: 342 North Main St., West Hartford, CT 06117; phone: (860) 586-7505; website: www.aesnet.org.

American Self-Help Group Clearing House: 375 E. McFarlan St., Dover, NJ, 07801; phone: (800) 367-6274 toll free; (NJ only); phone: (973) 989-1121; fax: (973) 989-1159; website: www.selfhelpgroups.org.

Epilepsy Foundation of America: 8301 Professional Place, Landover, MD 20785-2353; phone: (800) 332-1000 toll free; website: www.epilepsyfoundation.org.

Family Support Center of New Jersey: 1 AAA Drive, Suite 203, Trenton, NJ, 08691; phone: (732) 528-8080; fax: (609) 392-5621; NJ only: (800) 336-5843; website: www.fscnj.org.

Medic Alert: 2323 Colorado Ave., Turlock, CA 95382; phone: (888) 633–4298 toll free; fax: (209) 669-2450; website: www.medicalert.org.

National Hydrocephalus Foundation: 12413 Centralia, Lakewood, CA 90715–1623; phone: (888) 857–3434 toll free; phone: (562) 924–6666; website: www.rarediseases.org; e-mail: orphan@rarediseases.org.

National Organization for Rare Disorders (NORD): 55 Kenosia Ave., Danbury, CT 06813-1968; phone: (800) 999-6673 (help line); phone: (203) 744-0100; fax: (203) 798-2291; website: www.rarediseases.org; e-mail: orphan@rarediseases.org.

Spina Bifida Association of America: 4590 MacArthur Blvd, NW, Suite 250, Washington, DC 20007-4226; phone: (800) 621-3141 toll free; phone: (202) 618-4747; website: www.spinabifidaassociation.org; e-mail: sbaa@sbaa.org.

The Hydrocephalus Association: 4340 East West Highway, Suite 905, Bethesda, MD 20814; phone: (888) 598-3789 toll free; phone: (301) 202-3811; fax: (301) 202-3813; website: www.hydroassoc.org; e-mail: info@hydroassoc.org.

27 GENETIC DISORDERS, MALFORMATIONS, AND INBORN ERRORS OF METABOLISM

ANNE L. MATTHEWS AND NATHANIEL H. ROBIN

A neonate born with a malformation, a genetic syndrome, or an acute metabolic disorder presents a management challenge for the neonatal intensive care unit (NICU) staff. If these conditions are not suspected and diagnosed in a critically ill neonate, an appropriate course of action might not be taken. Thus a specific diagnosis becomes imperative. **An accurate diagnosis provides the staff with information about the cause of the condition, points the way toward appropriate treatment, and indicates the prognosis so that the most appropriate care of the infant can be initiated.** Moreover, **the broader issues of providing supportive care and counseling for the affected infant's family can be addressed.**

Genetic evaluation is a complex process that requires expertise in differentiating normal variations from abnormal findings and knowledge of the principles of embryology and dysmorphology to provide an accurate diagnosis. Skills in obtaining detailed information of prenatal and family histories may be equally important.

The field of genomics and genetic medicine has witnessed an explosion of new knowledge, much of which was generated by the efforts of the Human Genome Project.[17] Advances in understanding of the genetic basis of development and function as well as the interaction of genes and the environment, continue to provide new insights into human health.

This chapter presents a concise overview of the major categories of genetic disorders and the appropriate techniques to establish specific diagnoses. For an excellent review and detailed explanation of concepts, terminology, and specific genetic mechanisms, refer to *Thompson and Thompson Genetics in Medicine*.[51] See Box 27.1 for a comprehensive list of terms.

GENETIC PRINCIPLES

Genes

A *gene* is a segment of a deoxyribonucleic acid (DNA) molecule that codes for the synthesis of a single polypeptide and contains the hereditary information needed for development or function. DNA, which allows the storing, duplicating, and processing of hereditary information, consists of two long strands twisted around each other to form a double helix. Each strand of DNA is composed of four nucleotides: guanine (G), adenine (A), thymine (T), and cytosine (C). **The specific order of the nucleotides determines the precise information that will be encoded at that site.** Genes can (1) regulate other genes by turning them "on" or "off"; (2) specify the exact structure of proteins, which then control the activities of the cells; and (3) specify ribonucleic acid (RNA), which is necessary for protein synthesis. Dorman and colleagues[20] provide a short primer on DNA, genes, and chromosomes.

Chromosomes

Genes are packed in linear order on chromosomes. *Chromosomes* are found in the nuclei of cells. **In humans, normal somatic cells contain 46 chromosomes (diploid number), of which 44 are**

BLUE type highlights content that is particularly applicable to clinical settings.

BOX 27.1 GLOSSARY

Acrocentric chromosome A chromosome with the centromere near the end of the chromosome.
Allele One of a pair or series of alternative forms of a gene at the same locus.
Aneuploid Any chromosome number that is not an exact multiple of the haploid set.
Autosome A chromosome that is not a sex chromosome.
Centromere The primary constriction of a chromosome in which the long and the short arms meet.
Chromatid After replication of a chromosome, two subunits attached by the centromere can be seen; each is called a *chromatid,* and after separation, each becomes a chromosome of a daughter cell.
Chromosomes The microscopic structures in the cell nucleus composed of DNA and proteins that contain the genes.
Congenital Present at birth.
Copy number variant (CNV) Duplication or deletion of a section of DNA. CNVs can be benign (normal), pathogenic, or of uncertain clinical significance. The method used to detect a CNV varies based on its size (see deletion/duplication analysis).
Dermatoglyphics The dermal ridge patterns on the digits, palms, and soles.
Diploid Two copies of all chromosomes; the number of chromosomes normally present in somatic cells. In humans, this is 46 and is sometimes symbolized as *2N.*
Dominant A gene (allele) that is expressed clinically in the heterozygous state. In a dominant disorder, the mutant allele overshadows the normal allele.
Dysmorphic Morphologic abnormality, often a minor physical finding that may or may not have any cosmetic or functional significance and is present in less than 4% of the newborn population.
Fluorescence in situ hybridization (FISH) Molecular cytogenetic method for detection of microdeletions of chromosomes.
Gamete Mature reproductive cell, the egg or the sperm, containing the haploid number of chromosomes.
Gene The functional unit of heredity.
Genotype A person's genetic constitution.
Haploid One copy of all chromosomes; the number of chromosomes present in the gamete; in humans this is 23 and can be symbolized as *N.*
Hemizygous The condition in which only one copy of a gene is normally present, so its effect is expressed because there is no counterpart gene present (e.g., the genes on the X or Y chromosome of the male).
Heterozygote An individual who has two different alleles at a given locus of two homologous chromosomes.
Homologous chromosomes Members of the same chromosome pair; normally they have the same number and arrangement of genes.
Homozygote An individual who has two identical alleles at a given locus of two homologous chromosomes.
Karyotype The standard pictorial arrangement of chromosome pairs, numbered according to centromere position and length.
Locus The position or place that a gene occupies on a chromosome.
Malformation A primary structural defect that results from a localized error of morphogenesis; abnormal development.
Metacentric chromosome Chromosome with the centromere in the center of the chromosome.
Monosomy Absence of one chromosome of one pair.
Mosaicism Presence in the same individual of two or more different chromosomal constitutions.
Mutation A heritable alteration in the genetic material.
Nondisjunction Failure of two homologous chromosomes to separate equally during cell division into two daughter cells, resulting in abnormal chromosome numbers in gametes or somatic cells.
Phenotype The observable expression of traits either physically or biochemically.
Recessive A gene (allele) that is expressed clinically in the homozygous state. In a recessive disorder, both genes at a given locus must be abnormal to manifest the disorder.
Sex chromosomes The X and Y chromosomes.
Syndrome Recognizable pattern of multiple malformations that occur together and have the same cause.
Transcription The process by which complementary messenger RNA is synthesized from a DNA template.
Translation The process through which the amino acids in a given polypeptide are synthesized from the messenger RNA template.
Translocation Transfer of all or part of a chromosome to another location (i.e., on the same or another chromosome) after chromosome breakage.
Trisomy The presence of three homologous chromosomes rather than the normal two.
X-linked A gene located on an X chromosome.
Zygote A fertilized egg that develops into an embryo.

termed *autosomes* and 2 are *sex chromosomes.* Females have two X chromosomes (XX), and males have an X and a Y chromosome (XY). Gametes—eggs or sperm—contain 23 chromosomes (haploid number). In the zygote and somatic cells, chromosomes are paired (homologs). In each pair, one homolog is maternal and the other is paternal in origin. Each chromosomal pair has unique morphologic characteristics that allow it to be distinguished from other chromosomes, such as size, position of the centromere, and the unique banding pattern that is demonstrated by special staining techniques (Fig. 27.1).[25] To pass on the genetic information to daughter cells, the chromosomes must replicate and then divide correctly. Somatic cells undergo *mitosis,* in which cells replicate and then divide chromosomal

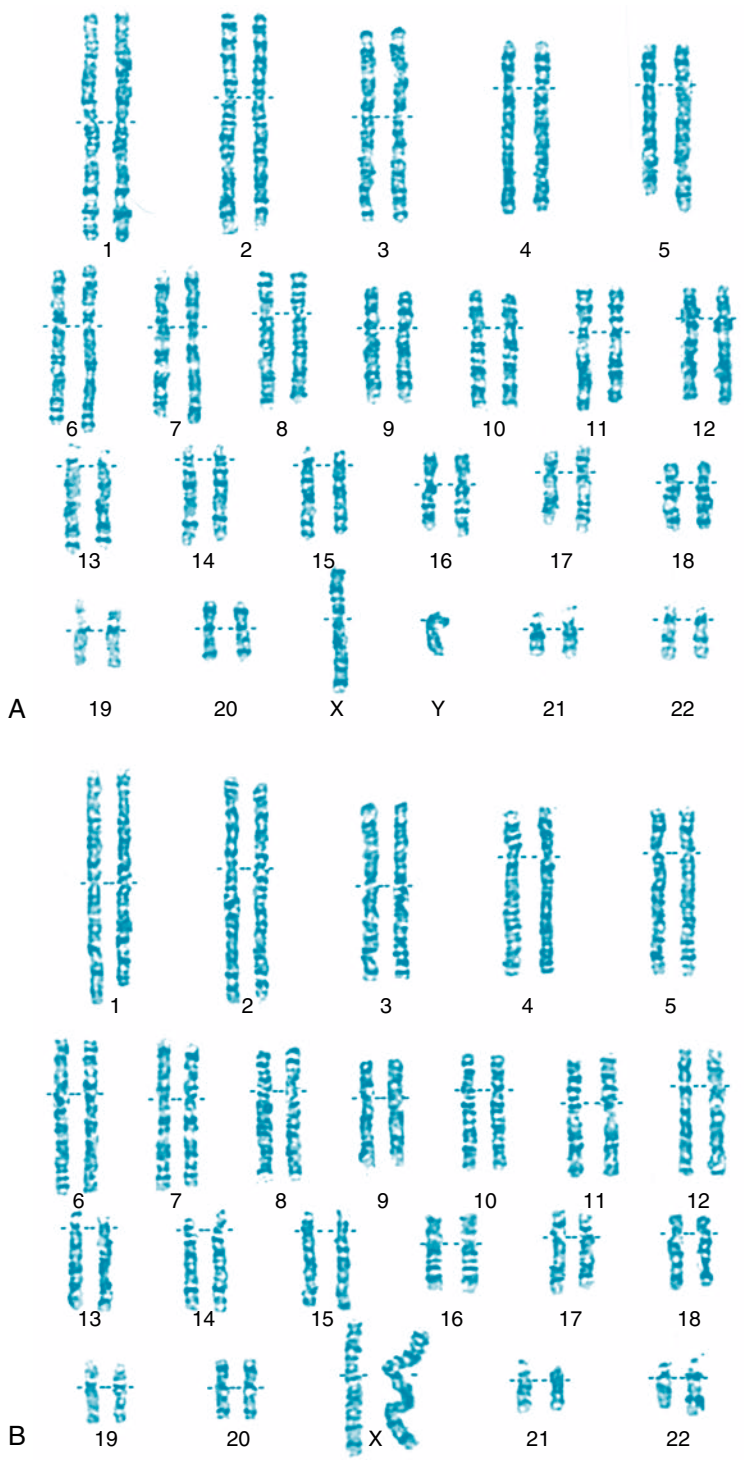

FIGURE 27.1 **A**, Normal male karyotype. **B**, Normal female karyotype. Each karyotype contains 46 chromosomes (44 autosomes and 2 sex chromosomes: XY, male; XX, female). The autosomes are numbered from 1 to 22. Note banding pattern, unique for each chromosomal pair. (Courtesy Dr. Loris McGavran, PhD, Cytogenics Laboratory at the University of Colorado at Denver and Health Sciences Center, Denver.)

material into two genetically identical daughter cells with 46 chromosomes each. In gametes, the process is known as *meiosis,* which is different from mitotic division in that daughter cells contain the haploid number of chromosomes (23) and crossing over or recombination between two homologs occurs, thus facilitating genetic variation in offspring.[51]

An individual's chromosome constitution can be determined by examining dividing body cells under certain laboratory conditions from any accessible tissue such as blood lymphocytes or skin fibroblasts. The resulting *karyotype* (see Fig. 27.1), or pictorial arrangement, demonstrates the number and structure of that individual's chromosomes.

ETIOLOGY

Malformations and genetic disorders caused wholly or partly by genetic factors can be categorized into four major areas: (1) chromosomal disorders caused by **numeric or structural abnormalities of chromosomes;** (2) **single-gene or Mendelian disorders,** which are secondary to single-gene mutations; (3) complex or multifactorial disorders resulting from **interaction of genes and environmental influences;** and (4) abnormalities caused by **environmental exposures of the fetus during development.**

More recently, better understanding of molecular processes has allowed the identification of additional genetic mechanisms contributing to genetic disorders: germline mosaicism, genomic imprinting, and uniparental disomy.

Chromosomal Disorders

Chromosomal abnormalities are relatively common. Approximately 0.5% to 0.7% of all live newborns have a chromosomal abnormality, and 4% to 7% of perinatal deaths result from a chromosomal abnormality. Moreover, it is estimated that at least 50% of all recognized first-trimester miscarriages are caused by a chromosomal aberration.[45] Current cytogenetic and molecular techniques, such as high-resolution banding, fluorescence in situ hybridization (FISH), microarray-based comparative genomic hybridization (array-CGH), and single nucleotide polymorphism (SNP) arrays have increased the detection rate of chromosomal aberrations. Submicroscopic deletions, duplications, or other abnormal rearrangements of chromosome material that may not have been identified a few years previously are now being detected in children with congenital malformations or intellectual disability.

Chromosomal aberrations should be suspected in any of the following situations:

- **Small for gestational age** for weight, length, or head circumference
- Presence of one or more **congenital malformations**
- Presence of **dysmorphic features**
- **Neurologic or neuromuscular dysfunction (i.e., hypotonia)**
- **Family history of multiple miscarriages or siblings with intellectual disability or birth defects** along with one or more of the previous other situations listed here

Chromosomal abnormalities can be classified into two major categories: (1) abnormalities of chromosome number (aneuploidy), in which there is an extra or missing chromosome and **(2) abnormalities of chromosome structure** that result in the loss or duplication of part of the chromosomal material resulting in a loss or gain of genomic DNA (copy number variation). Abnormalities of autosomes usually have more significant deleterious effects on the development of the infant than those seen with sex chromosome abnormalities.

ABNORMALITIES OF CHROMOSOME NUMBER

Numeric chromosomal abnormalities occur as a result of nondisjunction in which aberrant segregation leads to loss or gain of one or more chromosomes. Nondisjunction can occur during either meiosis or mitosis, resulting in an abnormal gamete (egg or sperm) or abnormal somatic cell, respectively (Fig. 27.2). **Fertilization of an aneuploid gamete by a normal gamete produces a zygote with an extra chromosome *(trisomy)* or missing chromosome *(monosomy).* Aneuploidy in somatic cells results in *chromosomal mosaicism* (i.e., the presence of some cells with the normal number of chromosomes and other cells with an abnormal number of chromosomes)** (Fig. 27.3). Although nondisjunction may affect any chromosomal pair, the **most commonly recognized trisomies in liveborn infants are trisomy 21 (Down syndrome), trisomy 18 (Edward syndrome), and trisomy 13 (Patau syndrome).** Conversely, full trisomy 16 has been found exclusively in

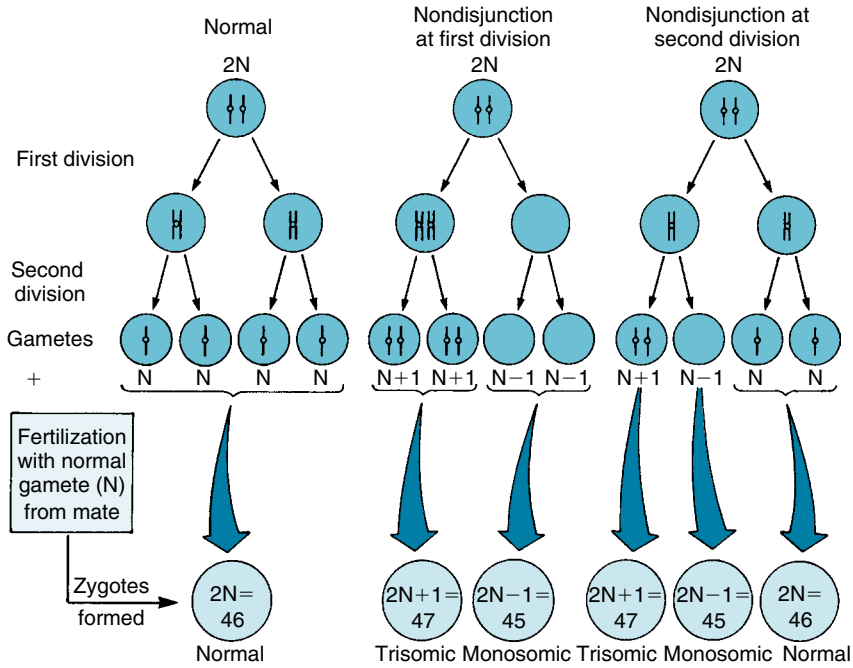

FIGURE 27.2 Nondisjunction. During formation of gametes, errors of nondisjunction can occur during either first or second meiotic division.

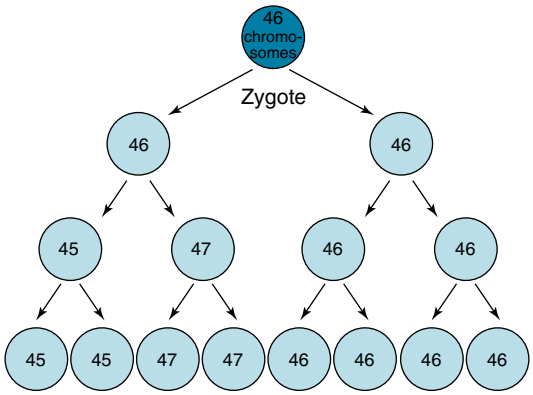

FIGURE 27.3 Mosaicism. Nondisjunction occurring after fertilization and zygote formation results in some cells containing the normal 46-chromosome complement and other cells having an abnormal number of chromosomes.

spontaneous abortions.[45] **The most common monosomy is 45,X, Turner syndrome.** As a rule, numeric chromosomal abnormalities are associated with intrauterine growth restriction (IUGR), dysmorphic features, malformations, and intellectual disability. Physical abnormalities may be milder or absent in the newborn with mosaicism.

ABNORMALITIES OF CHROMOSOME STRUCTURE

Structural abnormalities have been described in all chromosomes. These include deletions, translocations, duplications, and inversions (Fig. 27.4). A *deletion* is a loss of chromosome material and results in partial monosomy for the chromosome involved. Loss of material from the end of a chromosome is known as a *terminal deletion,* as seen in 5p-, or cri du chat syndrome. An *interstitial deletion* involves a loss of chromosomal material that does not include the ends of the chromosome. A terminal deletion of both arms of a chromosome may result in reattachment of the remaining arms, leading to a formation of a ring chromosome. The presence of additional chromosome material results in *duplication* or partial trisomy of a chromosome. **A *translocation* is the detachment of a chromosome segment from its normal location and its attachment to another chromosome.** The translocation is balanced if the cell contains two complete copies of all chromosomal material, although in different order. In an unbalanced translocation, the rearrangement results in partial trisomy or monosomy.

Translocations can be reciprocal or Robertsonian. **A reciprocal translocation involves exchange of**

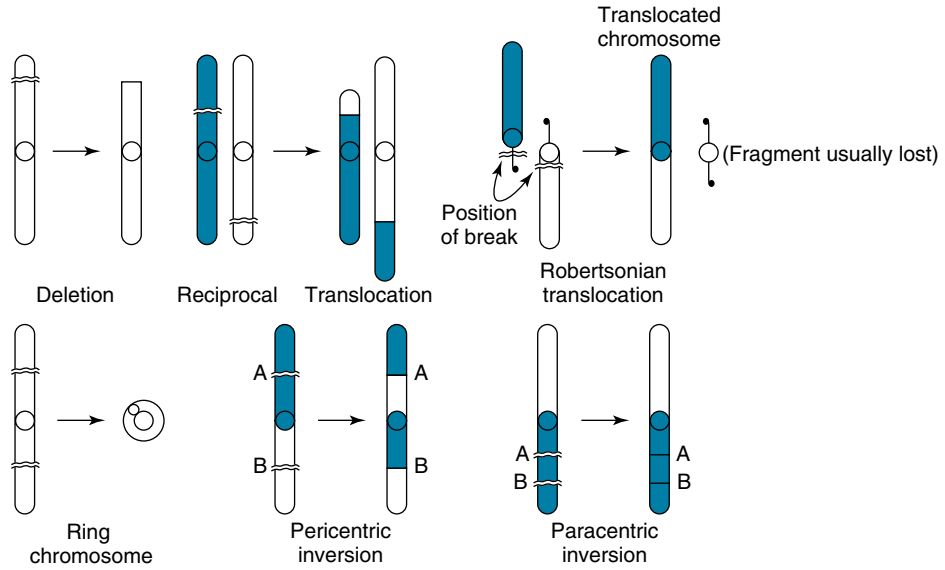

FIGURE 27.4 Schematic example of structural chromosomal abnormalities. (From Hathaway WE, Groothius J, Hay W, eds. *Current Pediatric Diagnosis and Treatment.* 10th ed. Norwalk, Conn: Appleton & Lange; 1991.)

segments between two chromosomes (e.g., part of the short arm of chromosome 4 trades place with a part of chromosome 10). **Robertsonian translocations involve rearrangements between two acrocentric chromosomes** (chromosomes 13, 14, 15, 21 and 22) fused at their centromeres. The most common Robertsonian translocations are formed between chromosomes 13 and 14 as well as 14 and 21.[45]

***Inversions* are the result of a double break in a single chromosome and reinsertion of the chromosomal material that has been inverted.** Inversions are either pericentric (including the centromere) or paracentric (without the centromere). The most common inversion is a small pericentric inversion of chromosome 9, which is considered to be a normal variant, found in approximately 1% of the general population.[51] All other inversions may produce gametes that result in an individual with an unbalanced rearrangement (i.e., having both a duplication and a deletion of some chromosome material, such as that seen in recombinant 8 syndrome).

MICRODELETIONS AND SYNDROMES

At times, structural chromosomal abnormalities are submicroscopic and therefore cannot be detected by conventional cytogenetic techniques. **FISH is a molecular cytogenetic method that facilitates the detection of microdeletions.** FISH uses segments of fluorescently labeled DNA called *probes,* constructed so that each probe can attach only to a specific segment of a chromosome, which then will be fluorescent during a microscopic visualization. In the case of a deletion of that chromosome segment, the probe cannot attach to the chromosome; thus the fluorescent segment is missing from the deleted segment of that chromosome.[67]

The most recent advances being used to detect very small submicroscopic deletions and duplications are array-CGH and SNP array.[60] These technologies blend molecular techniques with cytogenetics and allows the genome to be scanned at a higher resolution than conventional techniques. For CGH arrays, DNA from a patient sample and DNA from a control sample are differentially labeled, mixed in equal proportions, and hybridized to DNA substrates fixed on an array platform (i.e., bacterial artificial chromosomes [BACs] or oligonucleotides [short segments of DNA usually 8 to 50 base pairs]). This technique can measure the difference between two different DNA samples in copy number (dosage) of a particular segment of DNA. Thus, microscopic gains and losses from a patient sample can be quantified.[18] Similar to CGH arrays, SNP arrays label patient DNA, which hybridizes to DNA substrates fixed on an array platform; however, no control DNA is needed to identify dosage of segments of DNA.

Microdeletions result in phenotypic abnormalities. A number of well-recognized microdeletion syndromes may be suspected in the NICU. *Prader-Willi syndrome,* caused by an interstitial deletion of chromosome 15 (q11q13), usually manifests in a newborn as severe hypotonia, feeding difficulties, and micropenis or hypoplastic labia.[14] In fact, Prader-Willi syndrome should be considered in the differential of any neonate with severe hypotonia. *Williams syndrome* is caused by an interstitial deletion or mutation of the elastin gene *(ELN)* on the long arm of chromosome 7 (7q11).[49] The condition is often first seen in an affected newborn in the postterm period; the infant is small for family size. There may be a congenital heart defect, in particular, supravalvular aortic stenosis or peripheral pulmonic stenosis; hypotonia; failure to thrive with gastroesophageal reflux; poor suck and swallow; and vomiting and irritability or colic. Infantile hypercalcemia is seen in approximately 20% of these infants. Subtle dysmorphic facial features may be noted in the newborn.[49]

One of the **most commonly seen microdeletion syndromes is 22q11.2 deletion syndrome (22q11DS),** which is characterized by cleft palate or velopharyngeal insufficiency, hypernasal speech, learning disabilities, conotruncal heart defects, and characteristic facies. 22q11DS actually represents one of a spectrum of clinical disorders all known to be caused by a deletion in chromosome 22q11 (del22q11). These include *velocardiofacial syndrome* (VCFS; palatal anomalies, congenital heart disease, characteristic facial features, and developmental delay or learning difficulties), *DiGeorge syndrome* (DGS; conotruncal heart defect, hypocalcemia, and thymic hypoplasia), and *conotruncal anomaly face syndrome* (CTAF; conotruncal heart defects and typical facies). In addition, del22q11DS has been found in 11% to 16% of cases of nonsyndromic congenital conotruncal heart disease and has been reported to present as apparently isolated neonatal hypocalcemia or learning problems.[43] Overall, del22q11DS has an estimated incidence of 1 in 2000 to 4000 newborns. The availability of molecular cytogenetic testing by FISH and chromosomal microarray (CMA) has led to appreciation of both the high incidence of the del22q11DS, as well as the increasing variety of clinical presentations that can be seen even within a single family.[43,44]

In the newborn period, the characteristic facial features are seldom obvious. However, most affected individuals manifest some of these findings by early childhood. Most prominent is the nose, which is described as long, with a "built up nasal bridge, squared off nasal root, and bulbous nasal tip."[63] The eyes appear narrow and slit-like, the mala (cheeks) are flat, and the jaw is recessed. The ears usually are small and in some way abnormally formed. There may be an overt cleft of the secondary palate, a bifurcated uvula, a subtle submucosal cleft, or cleft lip with or without cleft palate. Other nonstructural palatal abnormalities can be seen, most commonly velopharyngeal insufficiency. In an older child or adult, this presents as hypernasal speech; in a newborn, one sees excessive nasal regurgitation. Congenital heart disease (CHD) is seen in 74% of del22q11DS patients. The type of CHD is fairly specific and includes those lesions classified as "conotruncal heart defects" (truncus arteriosus, interrupted aortic arch, tetralogy of Fallot, left-sided aortic arch, vascular rings, and some types of ventricular septal defects [VSDs]). Additional nonspecific findings include abundant scalp hair, hypospadias, renal abnormalities that can include renal agenesis, tortuous retinal vessels, ectopic/aberrant/unilateral absence of carotid and vertebral artery, microcephaly, and microdontia (there are 166 findings to date).[63]

Developmental delay, learning disabilities, or mental retardation is common and quite variable. Behavioral and psychiatric problems are common but underappreciated findings in VCFS. These individuals have a characteristic personality, marked by a flattened affect and abnormal social interaction, ranging from being intermittently withdrawn to socially precocious. A host of other psychiatric diagnoses have been seen in patients with 22q11DS.

More than 85% of cases of 22q11DS are deleted for a large 3-Mb region of chromosome 22 encompassing approximately 40 genes, including the *TBX1* gene.[43] Point mutations in *TBX1* have also been found when no deletion was identified.[71] Although 93% of cases are de novo, it is important to obtain family histories and examine parents for subtle features of the syndrome because approximately 7% of infants have inherited the abnormality from a parent.[43] Guidelines for the clinical diagnosis and management of patients with the 22q11DS deletion have been published.[9]

CLINICAL EXAMPLES OF CHROMOSOMAL ABNORMALITIES

Down Syndrome. Down syndrome has an incidence of approximately 1 in 600 live births. Approximately 95% of cases are caused by

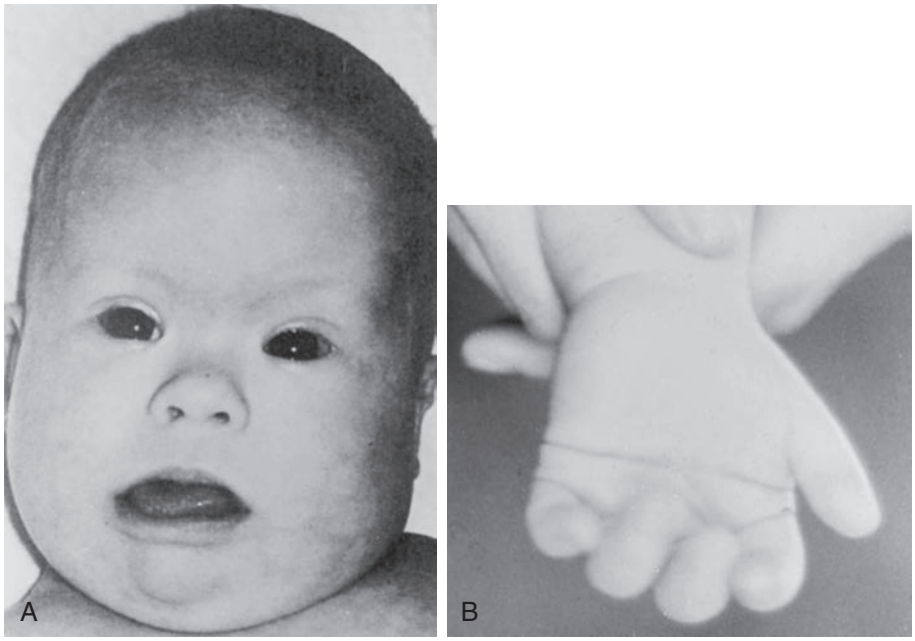

FIGURE 27.5 Infant with Down syndrome. **A**, Note midface hypoplasia, epicanthic folds, and depressed nasal bridge. **B**, Single palmar crease. (**A** from Cohen MM. *The Child With Multiple Birth Defects.* 2nd ed. New York, NY: Raven Press; 1997. **B** courtesy Dr. Eva Sujansky, Genetic Services at The Children's Hospital, Denver, Colo.)

nondisjunction involving chromosome 21, 4% are caused by a translocation, and 1% are mosaic. **Down syndrome may manifest with marked hypotonia; a number of major malformations, most commonly congenital heart defects, duodenal atresia, and tracheoesophageal fistula; and a characteristic pattern of dysmorphic features.** The classic phenotype seen in Down syndrome includes a flattened occiput, midfacial hypoplasia, depressed nasal bridge, upward-slanting palpebral fissures, epicanthic folds, grayish speckling of the iris (Brushfield spots), micrognathia, excess nuchal skin, single palmar creases (simian creases), single flexion creases and in-curving of the fifth fingers (clinodactyly), and increased distance between the first and second toes (Fig. 27.5).

In full-term infants with the classic phenotype of Down syndrome, the clinical diagnosis is usually not difficult. However, it is imperative that cytogenetic studies be done to confirm the diagnosis and to differentiate a nondisjunctional trisomy from a translocation. This distinction has important implications for recurrence risks (see discussion in "Prevention" section). **In premature infants, the classic facial phenotype is frequently missing, making clinical diagnosis more difficult.** The presence of an atrioventricular (AV) canal or duodenal atresia with minor malformations, such as abnormal dermatoglyphics, should alert the clinician to the possibility of Down syndrome.

Trisomy 18. Trisomy 18 has an incidence of 1 in 6000 live births. The major phenotypic features include prenatal growth restriction, complex cardiac malformations, abnormal muscle tone, microcephaly, prominent occiput, short sternum, low-set and malformed ears, corneal opacities, micrognathia, peculiar hand posturing with the second and fifth digits overlapping the third and fourth, hypoplasia of fingernails, abnormal dermatoglyphics, prominent calcanei, and deep plantar furrows between the first and second toes (Fig. 27.6). **The prognosis is poor, and the majority of infants with trisomy 18 die within the first few months of life.** Those who survive into childhood are profoundly intellectually disabled.

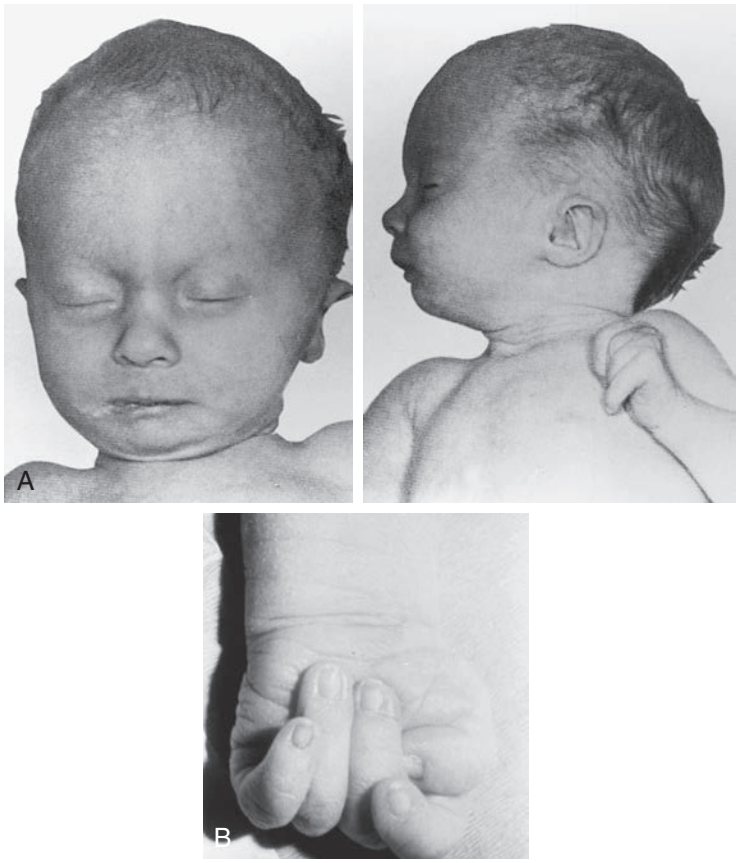

FIGURE 27.6 Infant with trisomy 18. **A**, Typical facies with small chin, abnormal pinna, and prominent occiput. **B**, Typical hand posturing with overlapping fingers. (From Paerregaard P, Mikkelsen M, Froland A, et al. Trisomy no. 17–18: report of two cases. *Acta Pathol Microbiol Scand.* 1966;67:479.)

Trisomy 13. Trisomy 13 is seen in approximately 1 in 15,000 live births. Phenotypic features include prenatal and postnatal growth restriction, microcephaly, sloping forehead, coloboma of the iris, microphthalmia or anophthalmia, low-set or malformed ears, cleft lip and palate, postaxial polydactyly, and abnormal palmar creases and dermatoglyphics (Fig. 27.7). Internal abnormalities may include a number of central nervous system (CNS) malformations, such as holoprosencephaly, cardiac malformations, omphalocele, renal malformations, and urogenital abnormalities such as cryptorchidism in males and uterine malformations in females. The prognosis is extremely poor for these infants, with most dying within the first few months of life.

Although it is well recognized that there is variability in the presentation of findings for infants and children with Down syndrome, it is also important to recognize that there can be variability in the phenotypes of infants with trisomy 18 and 13. Because some infants do survive the neonatal period and may live well into childhood, it is important to include parents along with other members of the management team in ensuring the complex needs of these infants are addressed. Moreover, there are a number of support groups available to families whose child is diagnosed with one of the classic trisomies.[38]

Turner Syndrome. The only monosomy to be seen in live births is that of Turner syndrome—females

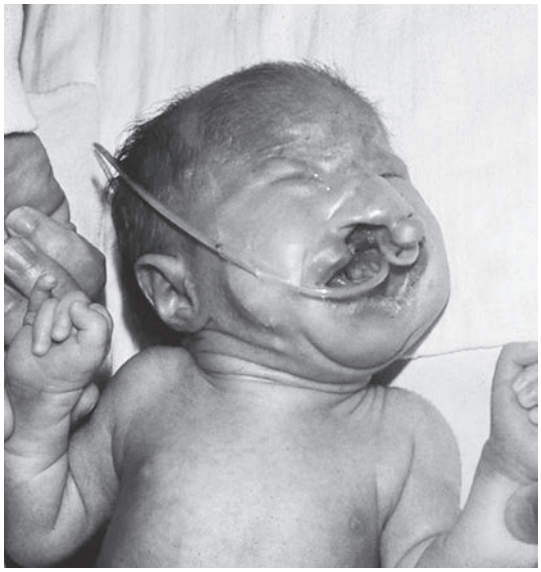

FIGURE 27.7 Infant with trisomy 13. Facial clefts and microcephaly; abnormal positioning of the hands. (From Hathaway WE, Groothuis J, Hay W, eds. *Current Pediatric Diagnoses and Treatment.* 10th ed. Norwalk, Conn: Appleton & Lange; 1991.)

with a 45,X karyotype. In addition, it is the only numeric abnormality of the sex chromosome that may be identifiable at birth. Turner syndrome has an incidence of 1 in 5000 female births.[58] Clinical features that may be evident in the newborn period are a short, webbed neck or redundant skin on the back of the neck and marked lymphedema of the dorsum of the hands and feet (Fig. 27.8). Congenital heart defects are seen in approximately half of the patients, with 30% having a coarctation of the aorta. Renal anomalies also may be present.[32] Prognosis is usually excellent but depends on the presence and severity of the congenital heart defect. Intelligence is within normal parameters; however, some females with Turner syndrome have been noted to have learning disabilities in spatial perception or fine motor abilities.[58] Guidelines for the management of infants, children, and women with Turner syndrome have been published recently following an international consortium meeting of the International Consortium Turner Syndrome Group.[26]

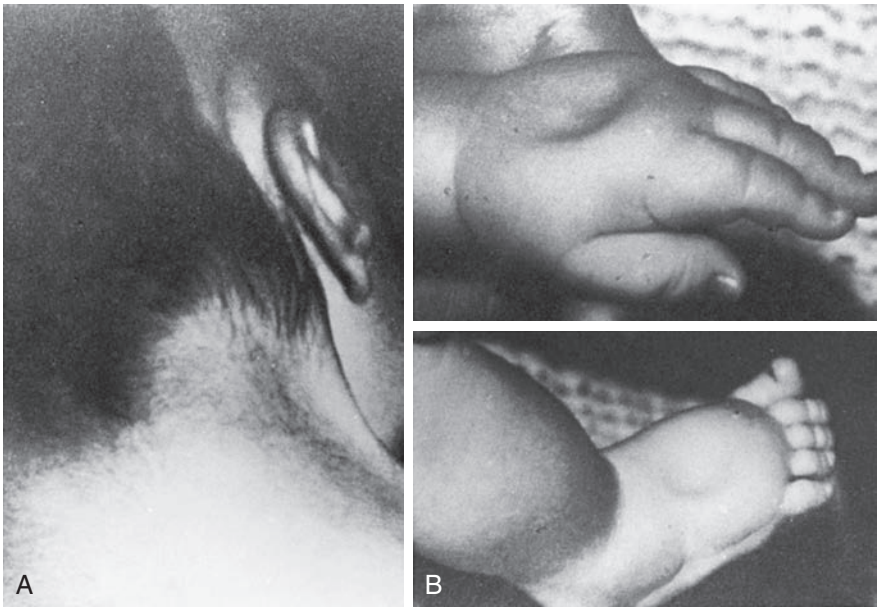

FIGURE 27.8 Female infant with Turner syndrome. **A**, Webbed neck with low posterior hairline. **B**, Lymphedema of the dorsal surfaces of the hands and feet. (From Knuppel R, Drukker JD, eds. *High Risk Pregnancy: A Team Approach.* Philadelphia, Pa: Saunders; 1988.)

Cri du Chat. Cri du chat, or "cat cry" syndrome, is the result of loss of the terminal end of the short arm of chromosome 5 (5p-). The name of the syndrome reflects the unusual catlike, weak cry these infants have in the neonatal period. These infants are usually small for gestational age, hypotonic, and microcephalic and may have ocular hypertelorism, epicanthic folds, downward slant of the palpebral fissures, low-set ears, and micrognathia. They are significantly intellectually disabled.

San Luis Valley Syndrome. *Recombinant 8,* or *San Luis Valley, syndrome,* named for the area in which many of these individuals were first identified, is an example of an unbalanced pericentric inversion with both duplication and a deletion of chromosome 8 material.[65] The pericentric inversion of chromosome 8 found in a parent and other relatives of a child with recombinant 8 syndrome have no phenotypic consequence because it is a balanced rearrangement. However, a carrier is at risk for producing unbalanced gametes during meiosis. In recombinant 8 syndrome, there is a deletion of chromosomal material of the short arm of chromosome 8 and a duplication of chromosome material of the long arm of 8. The phenotype is characterized by unusual facial features, including a wide face, depressed nasal bridge, hypertelorism, down-slanting palpebral fissures, upturned nose, long philtrum, low-set and malformed ears, cleft lip or cleft palate, congenital heart disease, and renal abnormalities.[65]

PREVENTION

The identification of chromosomal abnormalities in the newborn is important, not only for management issues about the infant but also because of the recurrence risks the abnormality carries for the family. In general, numeric chromosomal abnormalities carry low recurrence risks (approximately 1% to 2%).[45] In the presence of structural abnormalities, recurrence risks depend on whether one of the parents carries a balanced rearrangement. **If parental chromosomes are normal, the recurrence risk is minimal. However, if a parent carries a balanced chromosomal rearrangement, the recurrence risk is significantly increased.** The exact risk figure varies with the nature of the specific chromosomal rearrangement and, in some cases, the sex of the carrier parent. In either situation, **prenatal diagnosis for chromosome analysis is available for parents and families concerned about recurrence risk.**

Single-Gene Disorders

McKusick's Online Catalog of Mendelian inherited disorders currently lists almost 25,000 entries, approximately 16,000 genes and approximately 7800 disorders with known patterns of inheritance.[53] Many of these disorders are singularly rare; however, collectively, they affect about 1% of the population. Single-gene disorders are the result of either a single or double dose of an abnormal gene. **Single-gene disorders are classified as autosomal dominant, autosomal recessive, X-linked dominant, and X-linked recessive.** Humans have two copies of each gene located at identical places (gene loci) on homologous chromosomes. In a single-gene disorder, an abnormal or mutated allele (an alternative form of a gene) is found on one or both members of a pair of chromosomes.[51] Individuals with identical alleles at a particular locus are homozygous for the gene. Individuals with different alleles are heterozygous for the gene. Because males have only one X chromosome and most genes located on the Y chromosome do not correspond to those located on the X, males are hemizygous for the genes on the X chromosome. Abnormal genes located on one of the 44 autosomes are the cause of autosomal disorders: **disease-causing genes located on the X chromosome are the cause of X-linked disorders. Disorders are *dominant* when the phenotype is expressed in the presence of only one copy of the mutated gene. In *recessive disorders,* the phenotype is expressed only when both chromosomes carry the mutated gene.**

AUTOSOMAL DOMINANT DISORDERS

Autosomal dominant disorders are ones in which the disorder is expressed in the heterozygous state. Major characteristics include (1) multiple generations are affected (i.e., an infant would have an affected parent); (2) both males and females are affected, and both sexes can transmit the disorder to their offspring (i.e., male-to-male transmission can occur); (3) there is a 50% risk for each offspring to inherit the gene from an affected parent; and (4) individuals who do not have the gene cannot transmit the disorder to their offspring.

A negative family history does not rule out the presence of an autosomal dominant disorder. Possible explanations for a negative family history are (1) the infant's disorder is a result of a new mutation; (2) a parent has a very mild expression

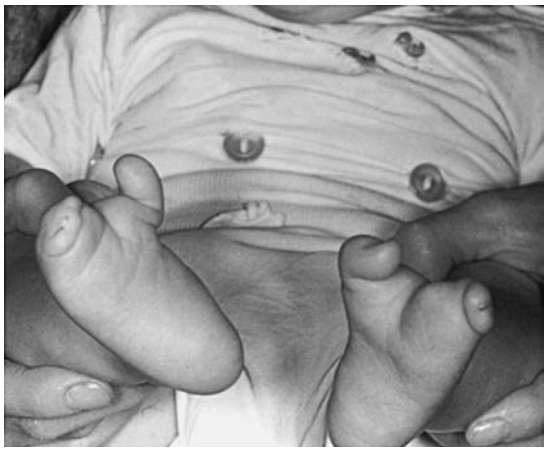

FIGURE 27.9 Ectrodactyly (lobster claw deformity) of the feet. (Courtesy Dr. Eva Sujansky, Genetic Services at The Children's Hospital, Denver, Colo.)

(variable expressivity) of the disorder and may not have been previously diagnosed; (3) nonpaternity; (4) decreased penetrance (i.e., not all individuals with the gene have phenotypic abnormalities, i.e., skipped generation); and (5) germline mosaicism for the mutation (see the "Nontraditional Inheritance" section).

Examples of dominant disorders that may be seen in the NICU include skeletal dysplasias, such as *achondroplasia* (abnormality in the *FGFR3* gene), *osteogenesis imperfecta (OI)* (abnormality in *COL1A1* or *COL1A2*), *Apert and Crouzon syndromes* (abnormality in the *FGFR2* gene), *Treacher Collins syndrome* (abnormality in *TCOF1, POLR1C, or POLRID* genes; mutations in *TOCF1* are responsible for approximately 93% of cases), and ectrodactyly (Fig. 27.9).[51]

AUTOSOMAL RECESSIVE DISORDERS

Autosomal recessive disorders are expressed only in the homozygous state. Thus, to be affected, an individual usually inherits an abnormal gene from each parent. The parent who is heterozygous for a disease-causing gene is usually phenotypically normal and is called a *carrier.* Major characteristics of autosomal recessive inheritance include (1) phenotypically normal parents, (2) affected siblings, (3) both males and females affected, (4) offspring of two carrier parents (25% risk for being affected), (5) unaffected siblings have a two-thirds chance of being carriers, and (6) possibly an increased incidence of consanguinity (mating between blood relatives). **Autosomal recessive disorders that may be identified in the neonatal period include many of the metabolic disorders** (e.g., *phenylketonuria [PKU], galactosemia,* and isovaleric acidemia) and some of the *multiple-malformation syndromes* (e.g., Meckel-Gruber syndrome), *cystic fibrosis presenting with meconium ileus, Zellweger* (cerebrohepatorenal) *syndrome* (Fig. 27.10), and skeletal dysplasias such as achondrogenesis. The specific gene(s) or biochemical defect for many of these disorders is now known.

As noted earlier, **one of the characteristics that may be seen in autosomal recessive disorders is a family history that includes consanguinity.** Thus, it is important to inquire from parents of the neonate whether they are related by blood. In many areas of the world, marriage between blood relatives is a common practice; thus, this becomes a risk factor for such couples because they are more likely to carry similar deleterious mutations that can be passed on to offspring and lead to disease or major birth defects.[50]

X-LINKED DISORDERS

X-linked disorders are caused by an abnormal gene (or genes) located on the X chromosome. Most X-linked disorders are recessive. The X-linked recessive disorders are phenotypically expressed in hemizygous males; heterozygous females are generally phenotypically normal and are called *carriers.* **Affected fathers do not have affected sons (no male-to-male transmission); however, all daughters of affected males are carriers. A carrier female has a 50% chance of having an affected male offspring.**

Occasionally, heterozygous females may be phenotypically affected, although usually less severely than males. If females are severely affected, other mechanisms, including homozygosity for the X-linked gene, may be responsible for the phenotype. **X-linked recessive disorders that may be recognizable in the newborn period include factor VIII and IX deficiency** (classic hemophilia A and B), X-linked hydrocephalus, and Opitz syndrome.

X-linked dominant disorders occur when the abnormal gene located on the X chromosome is expressed in both the hemizygous and heterozygous states. As in X-linked recessive conditions, there is no male-to-male transmission, because the affected male passes his Y chromosome and not his X chromosome to his sons; however, all of the daughters of an affected male will inherit his X chromosome and thus

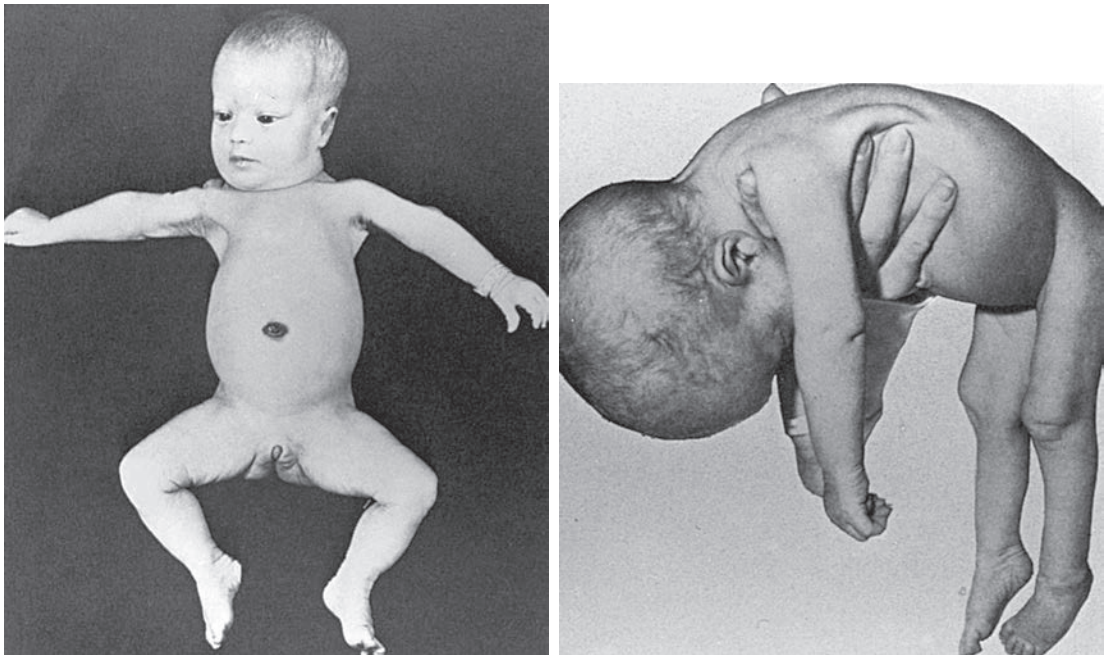

FIGURE 27.10 Infant with Zellweger syndrome, an autosomal recessive disorder. Note the high forehead, narrow facies, and extreme hypotonia. (*Left* from Jan JE, Hardwick DF, Lowry RB, et al. Cerebro-hepato-renal syndrome of Zellweger. *Am J Dis Child.* 1970;119:274. *Right* from Passarge E, McAdams AJ. Cerebro-hepato-renal syndrome: a newly recognized hereditary disorder of multiple congenital defects, including sudanophilic leukodystrophy, cirrhosis of the liver, and polycystic kidneys. *J Pediatr.* 1967;71:691.)

be affected. **Each son and daughter of an affected female has a 50% risk for being affected; males usually are more severely affected than females.** Only a few disorders are known to be inherited as an X-linked dominant, such as incontinentia pigmenti, hypophosphatemia (vitamin D–resistant rickets), and ornithine transcarbamylase (OTC) deficiency. Early diagnosis of OTC deficiency is important because, if untreated, it leads to neonatal hyperammonemia and death in affected males. In affected females, the clinical picture can be variable, ranging from an asymptomatic infant to one who presents in the first week of life with lethargy, vomiting, and protein avoidance, ending in seizures and coma.

Complex and Multifactorial Disorders

Complex, common non-Mendelian disorders, often called *multifactorial disorders,* are the result of both environmental and genetic factors.[27] Most isolated single malformations, including congenital heart defects, neural tube defects, cleft lip and palate, pyloric stenosis, and club feet, are inherited in this manner. In addition, the more complex, common familial disorders, such as diabetes mellitus, coronary artery disease, affective disorders, and mild intellectual disability are the result of multifactorial inheritance. In contrast to single-gene inheritance, multifactorial disorders recur within families without a characteristic pedigree pattern and recurrence risks are based on empirical data.[51]

Multifactorial inheritance is explained as a liability model with a threshold effect.[27] The general population as a whole has an underlying genetic predisposition for multifactorial traits and disorders that follow a normal distribution curve; only in those individuals in whom the genetic predisposition exceeds the threshold will the malformation actually be expressed (Fig. 27.11).

- Major characteristics of complex/multifactorial inheritance include the following: (1) no consistent pedigree pattern exists between families

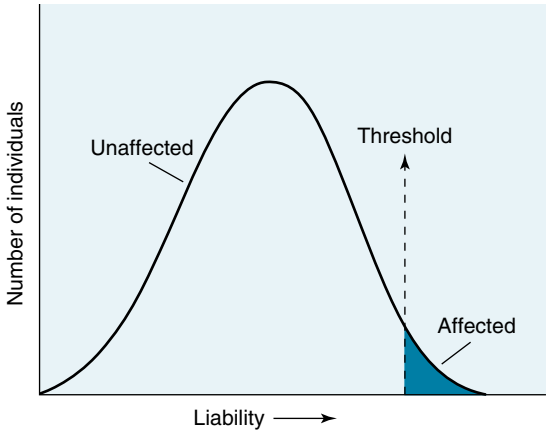

FIGURE 27.11 Multifactorial inheritance. Liability curve with a threshold beyond which the trait is expressed.

(i.e., there may be only an isolated occurrence, or the disorder may be seen among siblings, in multiple generations, or scattered throughout the family); and (2) recurrence risks are not constant, as in single-gene disorders, but are influenced by a number of factors. **These factors include the following:**

- **The number of family members affected** (i.e., the more family members affected, the higher the recurrence risk becomes)
- **The degree of relatedness to those affected** (i.e., first-degree relatives are at higher recurrence risk than second- or third-degree relatives)
- **The severity of the defect** (i.e., the more severely affected an individual is, the higher the recurrence risk)
- **The frequency of the disorder, which may vary with ethnic background** (e.g., neural tube defects have a higher incidence among English and Irish populations)
- **The gender of the individual** (for disorders in which one gender is more commonly affected than the other [e.g., pyloric stenosis is more common in males]; if the less commonly affected gender has the defect, the recurrence risk is higher)

With the increasing sophistication of ultrasound diagnosis during pregnancy, a number of these isolated malformations can now be diagnosed before delivery. Moreover, in the case of neural tube defects, it has been shown that folic acid supplements may decrease the incidence of spina bifida by as much as 70% in women of reproductive age.[48]

NONTRADITIONAL INHERITANCE

Germline Mosaicism. Spectacular growth in the field of molecular genetics and its technologies in only the past few years has enabled the clarification of the inheritance patterns of many genetic disorders and birth defects that were previously unknown or unclear. For example, the lethal form of OI occurring in multiple offspring of unaffected parents was thought to be the result of autosomal recessive inheritance. However, improved molecular techniques have documented that it is an autosomal dominant disorder in which germline mosaicism can result in having more than one affected child. That is to say, the mutation occurs in the gonad (egg or sperm) of one of the parents, who then has some gametes with and others without the OI mutation. This distinction alters the recurrence risks and is important for genetic counseling.[51]

Genomic Imprinting. In the past, little notice was given to whether the sex of the parent who transmitted an abnormal gene to offspring had any effect on the expression of genes. It is **now recognized that maternally and paternally derived genes may function differently, and this is called *genomic imprinting*.**[69] For example, offspring who inherit a mutation in the imprinted region of chromosome 15q, if it results in a loss of the paternal allele the child will have Prader Willi syndrome; the loss of expression of the maternal allele will result in Angelman syndrome.[21]

Uniparental Disomy. Uniparental disomy is the result of inheriting both copies of a chromosome from one parent and none from the other.[69] It is assumed that for normal growth and development, a child must receive both maternal and paternal genes; if both copies of a gene originate only from one parent, the development is abnormal. Uniparental disomy has been seen in cystic fibrosis with short stature and in the Prader-Willi, Angelman, and Beckwith-Wiedemann syndromes. The parental origin of a child's chromosomes can be identified only by molecular analysis; routine chromosome analysis usually is not helpful.

Trinucleotide Repeat Disorders. Trinucleotide (triple) repeat disorders are disorders that result from an unstable expansion of a segment of DNA that consists of three or more nucleotides adjacent to each

other. If a mutation occurs in a gene that contains a segment of repetitive trinucleotide sequences, it can cause the normal number of repeats to increase such that the expansion interferes with the expression or function of the gene.[51] **Repeat disorders have been found to be the cause of more than 20 disorders, including myotonic dystrophy** (an expanded CTG triple repeat in the *DMPK* gene) **and fragile X syndrome** (an expansion of CGG in the *FRAXA* gene). What is important to note is that **the abnormal number of repeats can expand through each generation and lead to a more severe phenotype in the next generation (known as *anticipation*).** The sex of the parent who passes on the mutation that causes the abnormal expansion can also affect the phenotype. For example, the repeat expansion in myotonic dystrophy is often larger in offspring of affected mothers.[33]

The possibility of a nontraditional pattern of inheritance makes genetic counseling more complex than previously thought. Thus, it is imperative that health care providers be aware of such complexities and refer families to a geneticist or genetic counselor for a more detailed discussion when appropriate.

INHERITED METABOLIC DISORDERS

Genetic disorders in which defects of single genes cause clinically significant blocks in metabolic pathways, regulatory proteins, and transport mechanisms are known as *inherited metabolic disorders and include inborn errors of metabolism*.[23] Recognition of inherited metabolic disorders has increased rapidly in recent years, and they are now recognized as important causes of disease in the newborn and pediatric age groups.[66] **Inborn errors of metabolism include defects of carbohydrate, amino acid, organic acid, and purine metabolism; disorders of fatty acid oxidation; lysosomal storage diseases; and disorders of peroxisomes.** Remember that metabolic diseases can present at any time and may affect almost any organ system. Specific disorders that should be considered in symptomatic newborns include galactosemia, PKU, OTC deficiency, and carbamoyl-phosphate synthetase (CPS) deficiency, maple syrup urine disease, nonketotic hyperglycinemia, propionic and methylmalonic acidemias, isovaleric acidemia, carnitine uptake deficiency, glutaric acidemia type II, and mitochondrial disorders, to name a few.[34,46]

Although the majority of infants are not found to have an inborn error of metabolism as the etiology of their illness, early recognition is imperative and may be considered a medical emergency if appropriate treatment is to be initiated. Many of these disorders can be treated effectively; if untreated, they can be lethal in the newborn period. Moreover, without the appropriate diagnosis, parents would not be aware of recurrence risks in future offspring.

Inherited metabolic disorders should be included in the differential diagnosis for any critically ill newborn in the following instances: (1) suspicion of neonatal sepsis; (2) recurrent vomiting or altered consciousness; (3) clinical findings of hypoglycemia, seizures, parenchymal liver disease, unusual odor, hyperammonemia, or unexplained acidosis; or (4) a family history of a sibling affected with similar symptoms, intellectual disability, or sudden infant death syndrome.[34]

In general, laboratory analysis depends on the presenting symptoms seen in the newborn. Laboratory studies that should be obtained before any treatment is begun are electrolytes, ammonia, glucose, urine pH, urine-reducing substances, and urine ketones. Neuroimaging can also provide clues to specific diagnoses.[56] **Clues to a possible metabolic abnormality are (1) hypoglycemia and ketonuria in the newborn, (2) acidosis with recurrent vomiting and hyperammonemia, and (3) acidosis that is difficult to correct and is out of proportion to the clinical state.** If other underlying disorders are not readily apparent, additional laboratory tests that may be appropriate are serum and urine amino acids and urine organic acids.[66] Moreover, molecular (DNA) testing is available for most disorders.[37] In addition, consultation with a metabolic specialist should be included in any evaluation of a neonate with a suspected inherited metabolic disorder.[46]

NEWBORN SCREENING

Inherited metabolic disorders, when unrecognized and untreated, may lead to severe consequences, including intellectual disability and death in some instances. Thus, the goal is to identify, treat, and prevent major sequelae whenever possible. Newborn screening accomplishes this goal for a growing number of disorders (Box 27.2). Screening criteria that should be met are relatively high frequency of the disorder, severity of symptomatology in untreated

BOX 27.2 PARTIAL LIST OF DISORDERS SCREENED FOR IN NEWBORN SCREENING PROGRAMS

Defects Identifiable by Tandem Mass Spectrometry (MS/MS)

Amino Acid Disorders and Urea Cycle Disorders

- Phenylketonuria
- Homocystinuria
- Hypermethioninemia
- Argininosuccinic acidemia
- Citrullinemia
- Argininemia
- Tyrosinemia types I and II

Organic Acid Disorders

- Maple syrup urine disease
- Isovaleric acidemia
- Methylmalonic acidemia
- Propionic acidemia
- Glutaric acidemia type I
- Isobutyryl-CoA dehydrogenase deficiency
- 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency
- 2-Methylbutyryl-CoA dehydrogenase deficiency
- 3-Methylcrotonyl-CoA carboxylase deficiency

Fatty Acid Oxidation Disorders

- Medium-chain acyl-CoA dehydrogenase deficiency
- Short-chain acyl-CoA dehydrogenase deficiency
- Very-long–chain acyl-CoA dehydrogenase deficiency
- Long-chain hydroxyacyl-CoA dehydrogenase deficiency
- Glutaric acidemia type II
- Carnitine palmityl transferase deficiency type II
- Carnitine/acylcarnitine translocase deficiency
- Multiple CoA carboxylase deficiency
- Trifunctional protein deficiency

Disorders Screened by Other Methodologies

- Congenital adrenal hyperplasia
- Galactosemia
- Sickle cell disease and hemoglobinopathies
- Hypothyroidism (congenital)

Data from the National Newborn Screening and Genetics Resource Center; website: http://genes-r-us.uthscsa.edu.
CoA, Coenzyme A.

individuals, availability of treatment, simplicity of obtaining tissue for testing, and availability of a simple screening test with high sensitivity and specificity at reasonable cost. There have been major changes in the laboratory technologies available for newborn screening—specifically, the introduction of tandem mass spectrometry (MS/MS).[15] **Using MS/MS technology, a single blood spot from a newborn can detect more than 60 metabolic disorders.**[10] Although many of the disorders detectable by MS/MS are rare, screening has been instituted in most states because screening remains inexpensive and a variety of disorders can be identified in a single assay. In most instances, additional testing adds approximately $25 to $60 to the cost of the newborn screen.[42]

MS/MS has been used for many years to measure metabolites in blood and urine. The technology is now applied to newborn screening programs. A mass spectrometer is an instrument that separates and quantifies ions based on their mass/charge ratio (m/z). In MS/MS, there are two spectrometers in a series. After sample preparation from the dried blood spot, the process of tandem mass is automated and the analysis is computerized. The process takes only a few seconds, and an entire screen takes less than 2 minutes.[42] The MS/MS system is capable of handling a high volume of samples; thus, it is an excellent technology for use in newborn screening. Currently the false-positive rate is 0.3% for all disorders.[72]

Screening for metabolic disorders is mandated by individual states, and all states require screening for PKU, hypothyroidism, congenital adrenal hyperplasia, sickle cell disease, s-beta thalassemia, and galactosemia.[7] However, the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) has worked with the Secretary of Health and Human Services to formulate the Recommended Uniform Screening Panel (RUSP), which recommend that all states screen for a panel of 35 core conditions and an additional 26 secondary conditions that may be detected by screening.[7] These recommendations are also supported by the American Academy of Pediatrics (AAP) and the American College of Medical Genetics.[5,6] The additional disorders most often screened for include amino acid disorders (homocystinuria, maple syrup urine disease), organic acids (glutaric, methylmalonic, and propionic acidemias), disorders of fatty acid metabolism (medium-chain and very-long–chain acyl-coenzyme A (CoA) dehydrogenase deficiency), hemoglobinopathies including sickle cell anemia, and others such as biotinidase deficiency, congenital adrenal hyperplasia, and cystic fibrosis.[5]

Each state decides individually what will be included in its newborn screening program.

Although some states require all of the tests on their list to be mandatory, other states offer a supplemental program in addition to the mandated program, often called *expanded newborn screening.* Testing for disorders listed on the mandated program is necessary, and only parents objecting on religious grounds may decline the mandated screen (e.g., Ohio Revised Code 3701.501). **In those states offering a supplemental program, parents can choose whether to screen their child for the disorders listed.** The program is optional, and no extra blood or additional tissue is necessary.[36] In most situations, parents are asked to sign a participation form to opt in to the supplemental program. With states now using MS/MS in their newborn screening process,[7] state legislators are constantly changing and updating their screening practices. It behooves the clinician to periodically check with the state newborn screening program for updates. The "Baby's First Test" resource provides up-to-date information for health professionals as well as educational and family resources about newborn screening at the local, state, and national levels.[7]

Any screening test may give both false-positive and false-negative results; this includes those identified by MS/MS. **Thus, a positive screen result must be followed by a confirmatory diagnostic test.**[5] Moreover, if there is clinical suspicion of a particular disorder despite a negative screening result, further diagnostic testing is warranted. **In addition to confirming positive screens, clinicians may have to deal with the concern for increased parental anxiety based on false-positive screens.** Waisbren and colleagues found in a prospective interview study of 254 mothers and 153 fathers that stress levels of parents whose infants had false-positive screening results were significantly higher than those with normal results.[68] Thus, for clinicians in the NICU setting, being cognizant of the potential for an increased number of positive newborn screening results is important for the care of the neonate, as well as for parent teaching. (For an in-depth review of those disorders that may be part of the newborn screening program, refer to the AAP's newborn screening recommendations.[5])

Newborn Hearing Screening. **Newborn hearing screening tests are now available that have high sensitivity when administered properly.**[6] Hearing loss is present in approximately 1 to 2 per 1000 infants. **Research has demonstrated that there are both genetic and nongenetic causes of deafness.** Eighty percent of prelingual deafness has a recognizable genetic etiology, and, of these, the most common cause of autosomal recessively inherited nonsyndromic hearing loss results from mutations in the connexin 26 *(Cx26)* gene, a member of the connexin family of gap junction proteins.[61] Commercial DNA–based screening tests are now available to detect common genetic forms of deafness including *Cx26* and mitochondrial deafness.[1] The AAP recommends that all newborns be screened for hearing loss before the age of 3 months.[4] The American College of Medical Genetics has recommended, in addition to screening and subsequent confirmation of hearing loss by diagnostic tests, that protocols be developed to ensure that appropriate genetic counseling be provided if diagnostic testing includes genetic testing.[1,30] This would provide families with accurate information about causes and recurrence risks for parents, siblings, and other family members.

ABNORMALITIES RESULTING FROM ENVIRONMENTAL EXPOSURES

Environmental exposures may have adverse (teratogenic) effects on fetal development, resulting in malformations and functional neurodevelopmental abnormalities in infants and children. The four major prerequisites needed for teratogenic action are[2]:

1. The agent must have the **potential to be teratogenic.** Few conclusive data are available about the teratogenicity of most chemicals and drugs in humans. Animal studies provide most of the currently available data on the teratogenicity of agents; however, not all are always applicable to human situations. To prove that an agent is teratogenic, a causal relationship between the exposure and presence of a malformation must be documented; just the history of an exposure to an agent is not sufficient. **Although very few agents have been documented to be teratogenic in humans, a few stand out, such as alcohol, cocaine, anticonvulsants, and ISOtretinoin (Accutane)** (Fig. 27.12).
2. The **timing of the exposure** during pregnancy is of major importance. **For the agent to adversely affect the fetus, it must be present during organogenesis or histogenesis.** Exposures occurring within the first 2 weeks

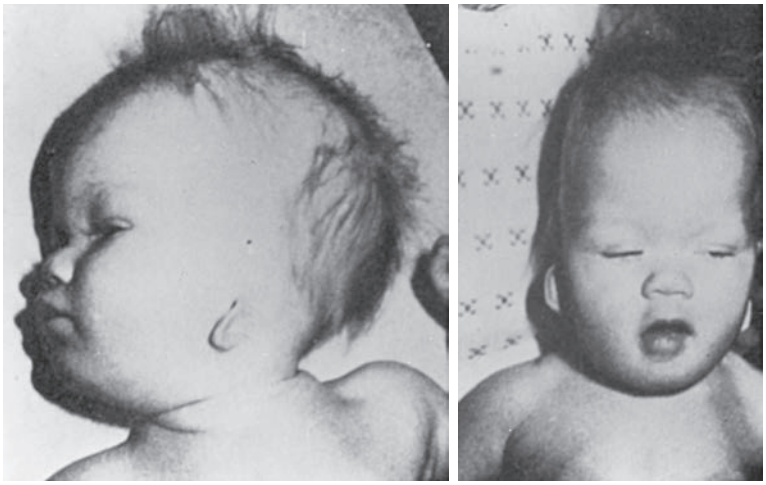

FIGURE 27.12 Infant exposed to Accutane in utero. Note dysmorphic face and auricles with atretic ear canal. (Courtesy Dr. Eva Sujansky, Genetic Services at The Children's Hospital, Denver, Colo.)

after conception, before cell differentiation, will either cause no damage or result in fetal wastage. **Exposures occurring from 2 to 12 weeks of gestation (period of organogenesis) may result in major malformations.** After completion of development of the major organ systems, harmful exposures usually do not result in malformations but can be responsible for organ dysfunction. However, some agents may morphologically disrupt previously intact organs.[16] Conversely, it has been shown that if the harmful exposure to an agent such as alcohol has been discontinued, the damage is less severe than if the exposure continues throughout the pregnancy.

3. **Dosage of the teratogen is related to the severity of the teratogenic effect;** the higher the dose, the more severe the effect and the higher the frequency of affected fetuses.
4. Finally, **genetic makeup or genetic susceptibility of the mother and fetus** may affect the metabolism, as well as tissue sensitivity to the teratogen.

Teratogenic agents may be divided into four categories: (1) infectious agents, (2) chemical agents (drugs and environmental agents), (3) radiation, and (4) maternal factors (such as maternal diabetes or maternal PKU). Chapter 2 provides excellent overviews of most of these exposures.

Traditionally, only maternal exposures to teratogens have been implicated in malformations. There has been a concern that some paternal exposures also may be teratogenic. Theoretically, a teratogen excreted in the semen could be introduced into the fetal environment and potentially be teratogenic to the developing fetus.[2]

Teratogenic exposures should be considered in the differential diagnosis of congenital malformations and CNS dysfunction if one can document fetal exposure and the phenotype is compatible with the known effects of the suspected teratogen. The recognition of exposures is important for genetic counseling; if they can be avoided during subsequent pregnancies, recurrence risk is not increased. Frequently there is phenotypic overlap between the fetal abnormalities caused by specific teratogens and other syndromes. The family should be referred to a genetics clinic to rule out chromosomal, single-gene, and sporadic syndromes with overlapping phenotypes.

DATA COLLECTION

A genetic evaluation consists of the same components found in any medical evaluation; however, the emphasis may be different. Moreover, **to make an accurate diagnosis and assessment, medical information about extended family members may have to be obtained.** For an overview of the

evaluation of the neonate with single or multiple congenital anomalies see the chapter by Jones and Jones[31] on a clinical approach to the dysmorphic child or the article by Jones and Adam[30] on the evaluation of the dysmorphic infant.

History

Prenatal and perinatal histories, from a genetic standpoint, should elicit information about potential teratogenic exposures, including maternal disease and acute illness. Fetal growth and behavior (e.g., fetal movement, swallowing) provide important clues for the assessment of fetal neuromuscular function. Thus, **information about fetal position, movement, and amount of amniotic fluid should be obtained.** Perinatal history should include the duration of gestation; anthropometric birth measurements, including head circumference; and information about perinatal adaptation. In a newborn with abnormal CNS functioning, it may be difficult to differentiate between primary maldevelopment and dysfunction caused by perinatal complications. **An abnormal newborn with a genetic disorder may present with signs suggestive of birth asphyxia (i.e., hypoxia, acidosis, hypotonia, seizures).** Moreover, because many a priori abnormal newborns have an increased frequency of perinatal complications, **a documented birth injury does not rule out the presence of a genetic cause.**

Family history may be extremely helpful in clarifying the causes and risk for recurrence. The information obtained from the parents may have to be complemented by physical examination of the parents and other family members and review of the medical records. This may be necessary because parents may not be aware that different defects in family members may be an expression of the same disorder. For example, an autosomal dominant gene may cause mild hypoplasia of thumbs in one family member and complete absence of thumb and radii in another.

A three-generation pedigree also should be obtained that includes health information about parents, siblings, grandparents, aunts, uncles, and cousins. Specifically, information about miscarriages, stillbirths, childhood deaths, relatives born with congenital malformations and birth defects or who have intellectual disability and other disorders that "run in the family" should be obtained.[11]

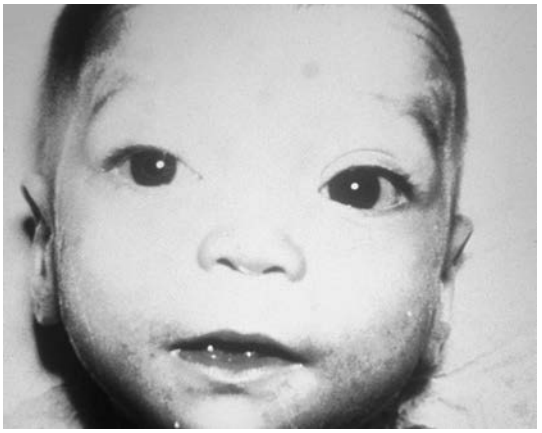

FIGURE 27.13 Dysmorphic feature of hypertelorism. Note wide-spaced eyes. (From Gilbert-Barness E, Kapur RP, Oligny LL, et al. *Potter's Pathology of the Fetus, Infant, and Child.* 2nd ed. St Louis, Mo: Mosby; 2007.)

Information about ethnic background and consanguinity also should be collected.

Physical Examination

A physical examination should enable the examiner to detect major and minor malformations (dysmorphic features). *Minor malformations* **are defined as structural variations found in less than 4% of the general population and that have no significant medical or cosmetic effect.** This is in contrast to structural variations that are found in more than 4% of the newborn population and represent a normal variation, such as a Mongolian spot or a capillary hemangioma on the forehead. Minor malformations may provide important clues to the identification of a specific syndrome. **None of the minor malformations as an isolated finding are clinically significant; however, a combination or pattern of minor malformations may indicate a specific disorder.** For example, dysmorphic features such as up-slanted eyes, epicanthic folds, hypertelorism (Fig. 27.13), and abnormal dermatoglyphic pattern (Fig. 27.14) in an infant with a congenital heart defect are suggestive of Down syndrome. **Minor malformations also may alert the clinician to the presence of major malformations.** For example, preauricular ear tags are associated with an increased frequency of inner ear malformations and hearing impairment. In addition, **the greater the number of minor malformations an infant has, the higher the chance is of finding one or more major malformations.**[30,39]

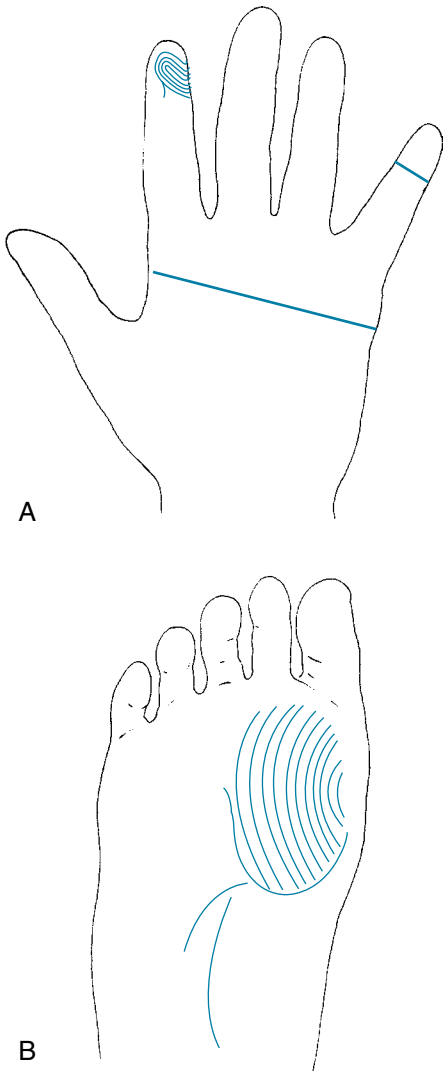

FIGURE 27.14 Dermatoglyphics commonly seen in infants with Down syndrome. **A**, Ulnar loop on the second digit, single flexion crease on the fifth digit, and single palmar crease (simian line). **B**, Tibial arch pattern on hallucal area of foot.

If minor malformations are identified, the parents of the infant should be examined. **Presence of the same minor malformation in one of the parents may indicate a benign familial feature.** Alternatively, **finding the same dysmorphic features in other family members may represent an inherited genetic disorder.** A mild syndactyly between the second and third toes is frequently an isolated, inherited finding without clinical significance. However, syndactyly associated with craniosynostosis may represent an autosomal dominant disorder with variable expression and significant clinical sequelae.

If an infant looks dysmorphic, documentation of specific features should be recorded. Actual measurements compared with age-related norms should be used to measure body proportions, length of extremities, and such facial features as distance between eyes, length of eye fissures, size of ears, and length of philtrum. Description of the other features, such as the shape of the neck (webbed) or the chest size (widely spaced nipples), or a specific description of any skin lesions, including size, shape, location, and color (hyperpigmented or hypopigmented), may provide important clues for a specific diagnosis. **Dermatoglyphic analysis—the analysis of the dermal ridges on the digits, palms, and soles—may prove useful for determining the timing of a fetal insult.**[70] Development of ridges begins during the thirteenth week of gestation and is complete by the nineteenth week. Thus, **many chromosomal and genetic disorders have disruptions of the dermal ridge patterns.** For example, an infant with Down syndrome may have a single palmar crease (simian crease), a single flexion crease of the fifth digit, and an open field pattern (tibial arch) on the hallucal area of the foot.[70] Moreover, specific descriptors or, even more useful, photographs, should be used to describe dysmorphic findings (e.g., as noted in Fig. 27.13).

Photographs are particularly important if the infant is critically ill and the constellation of findings does not immediately suggest a specific syndrome. Thus, the patient's findings may be more accurately shared with other clinicians in the future. Jones and Adam[30] provide a concise review of the evaluation of a dysmorphic newborn.

Smith's Recognizable Patterns of Human Malformation[32] and other texts document a large number of syndromes, some of which are rare and may not be immediately recognized by neonatal staff. It also may be very helpful and important to **consult a clinician who is familiar with dysmorphology and syndromology to help establish a diagnosis.**

Laboratory Data

When a genetic disorder is suspected, a number of diagnostic studies may be useful in delineating a diagnosis, including chromosome analysis; CGH array, which is now considered the first-tier test for

the evaluation of a dysmorphic newborn[47]; molecular DNA testing; biochemical studies to rule out inborn errors of metabolism; radiographs; organ imaging; and, when appropriate, autopsy. Not all of these studies are routinely used in all patients, but selection of studies is based on clinical suspicion of a particular disorder.

CHROMOSOME ANALYSIS

As mentioned, chromosome microarray is now considered the first-line genetic test for neonates and infants with dysmorphic features and/or malformations that are not specific to a well-recognized genetic syndrome per ACMG guidelines.[47,62] **As with a karyotype, results may not be available for 2 or 3 weeks;** however, if results are urgently needed for clinical management, a chromosome analysis from bone marrow can be available within a few hours and preliminary results from blood lymphocyte culture can be obtained in 48 hours. Indications for chromosome analysis and microarray analysis have been listed previously. **Regardless, blood for a microarray and/or karyotype should be obtained in all critically ill infants for whom there is no plausible explanation for their grave clinical course, before death occurs.** For postmortem examination, chromosomes or DNA for a microarray also may be obtained from any tissue—in particular, intracardiac blood, thymus, skin, and gonad. Under sterile conditions, these tissues should be obtained as soon as possible after the infant's demise. Tissue should be transported to the laboratory in a tissue culture medium or sterile saline solution, not in formalin.

MOLECULAR DNA ANALYSIS

There is a **growing list of disorders for which the gene has been identified, and thus molecular diagnostic tests are commercially available.** Although the Genetic Alliance, an international coalition comprising 10,000 organizations, of which 1200 represent disease-specific advocacy groups, research, and health care organizations, has access to databases with over 10,000 conditions at their website *(www.geneticalliance.org),* not all those disorders are amenable to DNA testing. Moreover, often a clinical diagnosis of a recognized syndrome does not require additional diagnostic testing.[30] **However, if the diagnosis is not clear, if there is a need to confirm a diagnosis for management issues, or if additional information about a clinically recognized disorder is needed for family planning and genetic counseling, then DNA testing may be extremely helpful.**[30]

Whenever the health care professional has a reasonable suspicion of a specific diagnosis based on clinical phenotype, it is reasonable to suggest molecular testing if it is available to confirm the diagnosis and provide appropriate genetic counseling. However, **the clinician must remember that mutational analysis is complex, and, although it can confirm a diagnosis when the test result is positive, a negative result may not determine conclusively that the neonate is not affected.**[3] Some disorders (listed with their gene symbol or chromosomal locus) that might be seen in the neonate for which molecular gene testing is available are listed in Table 27.1.

BIOCHEMICAL STUDIES

A critically ill neonate who has a condition suggestive of an inborn error of metabolism or who has no specific diagnosis should have blood and urine sent for appropriate biochemical studies (specified in the "Inborn Errors of Metabolism" section). If such studies have not been obtained, postmortem tissue such as liver should be obtained and frozen for later biochemical analysis. **Care providers should request detailed instructions from a laboratory specializing in testing for inherited metabolic disorders about which tissue is appropriate and how it should be obtained, stored, and shipped to the laboratory.**

RADIOGRAPHS

X-ray examination should be obtained if a skeletal dysplasia or other skeletal abnormality is suspected or if the differential diagnosis includes a genetic syndrome that has skeletal defects as part of the phenotype. Moreover, **if a localized skeletal defect is found, a skeletal survey should be obtained to identify other possible skeletal defects.**

ORGAN IMAGING

Organ imaging by **ultrasonography, magnetic resonance imaging (MRI), and computed tomography (CT) scan should be used to rule out structural abnormalities of major organs** such as the brain, heart, and kidneys. Malformations may be suspected on the basis of clinical symptoms such as anuria or on the basis of known nonrandom associations of certain birth defects, such as the vertebral/anal/tracheoesophageal fistula/renal/radial (VATER) association. In addition, some dysmorphic features are associated with major malformations, and one must rule out these features. For example, there

TABLE 27.1 PARTIAL LIST OF DISORDERS SEEN IN THE NEWBORN PERIOD WHERE DNA MOLECULAR TESTING IS AVAILABLE CLINICALLY

SYNDROME	GENE	CHROMOSOMAL LOCATION
Apert and Crouzon	*FGFR2*	10q26
Achondroplasia and thanatophoric dysplasia	*FGFR3*	4p16
Cystic fibrosis	*CFTR*	7q31
Congenital myotonic dystrophy	*DMPK*	19q13
Miller-Dieker	Microdeletion	17p13.3
Osteogenesis imperfecta	*COL1A1* or *COL1A2*	17q21.3-q22
Pfeiffer	*FGFR1*	10q26
Prader-Willi and Angelman	Uniparental disomy, imprinting, deletion	15q11.3-q13
Smith-Lemli-Opitz	*DHCR7*	11q12-q13
Treacher Collins	*TCOF1* *POLR1C* *POLR1D*	5q32-q33 6p21.1 13q12.2
22q11.2 deletion syndrome	Microdeletion	22q11.2
Waardenburg type 1	*PAX3*	2q35
Waardenburg type 2	*MITF*	3p14.1-p12.3
Williams	*ELN* (elastin)	7q11.2
Wolf-Hirschhorn	Microdeletion	4p16.3

is an increased incidence of underlying midline brain defects associated with some facial dysmorphic features.

AUTOPSY

In the event of a neonate's death, **an autopsy may provide crucial information for the establishment of a correct diagnosis.** As outlined, chromosome analysis, microarray, DNA testing, biochemical studies, x-ray examination, and photographs should all be included. **In the absence of a specific, confirmed diagnosis, the family should be strongly encouraged to consent to an autopsy, and a tissue sample should be frozen for further testing.** Without this valuable information, subsequent genetic counseling of the parents, including clarification of the causes and recurrence risks, becomes impossible.

TREATMENT AND INTERVENTION

For most genetic disorders and malformations, there are no "cures" and only symptomatic **treatment is available; that is, conventional medical and surgical interventions are instituted, although the basic genetic defect is not corrected.** Surgical intervention for specific malformations will depend on the malformation, its cause, and prognosis. For example, surgical repair of a cleft lip and palate usually has an excellent outcome, although the underlying genetic cause has not been altered. In other instances, the diagnosis may provide direction and guidance to the health care professionals and family as to the appropriate course of action. An infant born with a hypoplastic left side of the heart may be considered a candidate for a heart transplant. However, if the cardiac malformation is the result of a chromosomal abnormality with an extremely poor prognosis, such as trisomy 13, the management of that infant may be palliative rather than corrective depending on the health care team's expertise and family wishes.

With the diagnosis of a metabolic disorder, treatment may be one of a nutritional or pharmacologic approach, such as the restriction of phenylalanine in an infant with PKU or the replacement of a deficient hormone, such as thyroid supplements in hypothyroidism. For some conditions,

such as OI, the best approach may be educating the parents on specific techniques of holding and caring for an infant to prevent further fractures. In some disorders, organ or tissue transplantation may be appropriate. **Hematopoietic stem cell transplantation has been found to be effective in treating select genetic disorders,** including a few lysosomal storage disorders[10] and beta-thalassemia.[8] Because specific treatment leading to a cure is not available for most genetic disorders, the use of genetic counseling and available reproductive alternatives, such as prenatal diagnosis, in vitro fertilization, preimplantation diagnosis, and artificial insemination by donor, are acceptable alternatives for some families.

THE HUMAN GENOME PROJECT

The year 2000 marked the announcement that the vast majority of the human genome had been sequenced.[17] This international effort, funded in part by the National Institutes of Health (NIH), began in 1990 with the development of genetic and physical maps of the human genome and completed its initial goals in 2000 with a draft of the sequencing of the 3 billion base pairs of the human genome. Defining the sequence of the human genome is only the beginning of the application of that knowledge to current and future research opportunities that will provide avenues for innovative therapies. With the introduction of massively parallel DNA sequencing (often referred to as NextGen sequencing), the ability to examine the entire genome is now a reality. Tests based on next-generation sequencing (NGS) technologies are rapidly replacing many single gene–sequencing tests. These tests use disease-targeted exon capture, whole-exome sequencing (WES), or whole-genome sequencing (WGS) strategies. *WES* allows for all the exomes in the genome (the coding portion of DNA) to be examined and to identify disease-causing mutations. *WGS* investigates an individual's entire genome (all components of genes such as introns, regulatory elements, etc.) and is available clinically in some instances.[28,64] Moreover, some institutions are using a rapid turnaround time approach with WES and WGS in the neonatal setting, which have been found to provide increasing clinical utility and demonstrate improved outcomes.[1,22,54] **These new powerful technologies for understanding gene expression are also being applied to designing drugs that will moderate disease pathways.** Moreover, the field of genomics is providing opportunities to predict responsiveness to drug therapies, because reactions to drugs often are based on individual genetic variations.[64] With the identification of common gene variants involved in drug action or metabolism, health care professionals might be able to predict an infant's response—good or bad—to a particular drug regimen.[17]

With the numerous advances in molecular genetics, it is predicted that many genetic disorders and malformations may be amenable to treatment in utero or after birth. **In utero correction of such birth defects as urinary tract malformations, myelomeningocele, and diaphragmatic hernia has been successful.**[12,19,52] In 1990, the first human trial of gene therapy was undertaken at the NIH. The treatment was somatic gene replacement in a 4-year-old child with adenosine deaminase deficiency, a rare inherited disorder that destroys the immune system.[40] Successful efforts using improved gene therapy techniques continue with this disorder.[13] Since that time, a number of gene therapy trials for other genetic disorders have been done. Although the arena of gene therapy in general has been somewhat disappointing, the results have led to new areas of research and experimentation with new promising techniques.[59] The development of safer and more effective vectors based on technologies spearheaded by the Human Genome Project should provide significant improvements in gene therapy, such as that seen in an application of gene therapy with hemophilia B.[35] Finally, newer gene editing technologies have provided researchers and clinicians the ability to change the DNA of organisms by altering their genetic make-up. One such technique is CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9).[24] These technologies are the "wave of the future" in potentially successfully treating and perhaps curing some genetic disorders. In fact, the NIH has approved clinical trials involving humans using CRISPR-Cas9 technology to treat cancers.[57]

PARENT TEACHING

The birth of any infant with a malformation or genetic disorder is a devastating event for any family. Members of the neonatal staff are on the front lines helping families deal with the infant's problems and providing the best environment for both the critically ill newborn and his or her family.

BOX 27.3 PARENT/CAREGIVER TEACHING GENETIC CONSIDERATIONS

- Genetic diagnosis is essential not only for management of the neonate's condition but also for counseling.
- Genetic counseling assists parents and care providers in addressing management issues such as cause and diagnosis, prognosis, treatment and interventions, short-term and long-term care, and follow-up.
- Genetic counseling assists parents in decisions about future pregnancies or the use of assistive reproductive technologies.

In general, the most difficult factor for most parents and families to deal with is the unknown. Thus, once again, the need for an accurate diagnosis becomes paramount (Box 27.3). **Moreover, even when the diagnosis carries a poor prognosis, parents would prefer having the information so they can realistically anticipate and prepare for what is to come.**[29] Currently, many parents obtain information about their infant's malformation or genetic disorder through prenatal screening and diagnosis and have already begun the process of anticipatory grief by the time the infant is admitted to the NICU. **Parental feelings of disbelief, shock, anger, or despair may already have been replaced with a "sense of relief" about confirmation of the abnormalities and a need to deal with the situation at hand.**[41]

Chapter 30 provides an excellent review of the grief and mourning process that parents will experience when their anticipated "perfect baby" is born with a malformation or genetic disorder.

From a genetic counseling standpoint, a number of principles should be incorporated into the plan of care for the neonate and his or her family. First—and it cannot be overstated—**an accurate diagnosis is essential if genetic counseling is to be provided.** Even with what appears to be an isolated malformation, a genetics consultation may be appropriate to rule out other causes, such as single-gene disorders or chromosomal abnormalities. After establishing the diagnosis, one can realistically address the prognosis, treatment, and other management issues with the family. **Finally, at the appropriate time for the family, recurrence risks and options for future pregnancies can be addressed** (see the American College of Medical Genetics practice guideline regarding when a genetic consult may be helpful).[55]

Certainly, the busy and stressful environment of the NICU is not the most conducive atmosphere for obtaining and providing detailed information. **However, it is appropriate for the geneticist to make an initial contact with the family in the NICU, where basic information about the pregnancy and perinatal and family histories can be obtained that will aid in diagnosis and defining the cause.** The neonatal staff and geneticist can then address diagnosis and management. Later, at a time appropriate for the family, such issues as recurrence risks can be addressed. Eventually the family should receive a written summary of all the issues discussed for their own documentation.

The genetic evaluation is a complex and multifaceted process that cannot be done in isolation; it requires a team approach. The geneticist can assist the NICU staff in determining the diagnosis, cause, and prognosis so that appropriate management of the infant can be implemented and aid in future counseling of the families they serve. **The neonatal staff should use the genetics team as a resource for consultation and assistance in providing infants and families with the most appropriate and complete health care available.**

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RESOURCES FOR PARENTS

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Resources for Professionals

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Resource Materials

Gene Reviews: (http://www.genereviews.org). *Gene Reviews* is an online peer-reviewed database developed and maintained by the University of Washington. Gene Reviews currently lists 730 chapters regarding genetic disorders that have information authored by experts for a particular disorder. A wealth of information is presented, including (1) major clinical features of the disorder, (2) what is known about the genetics and inheritance, and (3) suggestions about a differential diagnosis for the findings. Each entry has an extensive reference list and information about support groups and is updated on a regular basis. The site also includes educational materials about genetics, genetic disorders, and genetic testing including an illustrated glossary.

Genetic Alliance: (www.geneticalliance.org). The Genetic Alliance is a coalition of hundreds of genetic advocacy organizations, health professionals, clinics, hospitals, and companies. Type in a disorder and be transported to that support group's website for information about the disorder and resources for people with the disorder.

Genetics Home Reference: (http://ghr.nlm.nih.gov). The *Genetics Home Reference* is the National Library of Medicine's website for consumer information about genetic conditions and the genes or chromosomes responsible for those conditions. Summaries are provided about hundreds of genetic disorders. Each summary also contains information and Web links to other resource materials.

Genetic Testing Registry (http://www.ncbi.nlm.nih.gov/gtr). The Genetic Testing Registry is an online database maintained by the National Institutes of Health as a central repository of genetic tests. The registry lists more than 55,935 tests for 11,437 conditions, 16,451 genes, and 518 laboratories. Information included for laboratories includes the test's purpose, methodology, validity, evidence of the test's usefulness, and laboratory contacts and credentials.

OMIM: (http://www.ncbi.nlm.nih.gov). *Online Mendelian Inheritance of Man* database is a catalog of genetic disorders and human genes. It is overseen by its originator, Dr. Victor A. McKusick, and maintained by the National Center for Biotechnology Information (NCBI). The database contains information about known inherited disorders, including information about the genes responsible for the disorder, a clinical synopsis, and references.

28 NEONATAL SURGERY

MARGARET E. GALLAGHER, ANNETTE S. PACETTI, HAROLD N. LOVVORN, III, AND BRIAN S. CARTER

Congenital malformations may be found in up to 3% of all newborns and are an important cause of morbidity, early infant death and chronic disability.[13] Although overall infant mortality has declined, the **mortality attributable to birth defects has increased, and up to 20% of neonatal deaths have been attributed to congenital malformations.**[2,70] In the last decades, improvements in prenatal imaging and perinatology have allowed earlier diagnosis and intervention for surgically correctable malformations. Because of the complexity of accurate prenatal imaging and diagnosis, many anomalous conditions continue to escape early detection and present to the neonatology and surgical teams with advanced developmental consequences. **The care of a neonate having a major congenital malformation therefore may be resource intensive and costly.** In a study of one regional neonatal intensive care unit (NICU), newborns having major congenital malformations accounted for 27% of NICU referrals, 32% of total NICU days, and 40% of NICU costs. Moreover, **surgery was more frequent in newborns having major malformations and one third required ongoing medical support at the time of discharge.**[62] A more recent study by Centers for Disease Control and Prevention (CDC) researchers found that costs for care for birth defects among infants were the highest, at $9 billion, or 35% of hospitalizations for all children under 1 year of age.[14] **Early diagnosis, comprehensive neonatal care, and a multidisciplinary approach are necessary to ensure an optimal outcome for both parent and child.** This chapter briefly describes the embryology, clinical history, diagnostic evaluation, and therapeutic intervention of common neonatal surgical conditions.

DIAPHRAGMATIC HERNIA

Physiology and Etiology

Congenital diaphragmatic hernia (CDH) is a defect in closure of the diaphragm that occurs in 1 in 4000 live births. A posterolateral defect, or Bochdalek diaphragmatic hernia (Fig. 28.1), accounts for nearly 95% of all CDHs and may be left (95%) or right sided (5%). Much less common is the Morgagni diaphragmatic hernia (Fig. 28.2), which results from a failure of anteromedial closure and resides in a substernal location. Several theories have been proposed to explain the mechanism for how this **malformation of the diaphragm occurs, but currently the most widely accepted theory is failure of the pleuroperitoneal canal to close completely during the 8th week of gestation.** If a patent pleuroperitoneal canal persists through the 11th week of gestation, a period when the intestine returns from its normal herniation into the umbilical cord, the stomach, bowel, and spleen may be forced into the chest. **Resultant compression of the developing lung leads to a variable extent of pulmonary hypoplasia.** Despite many studies in both animal models and infants over the past four decades, the causes of the pathophysiologic changes that occur in the underdeveloped lung are not well understood and are likely multifactorial. Recognition of the associated abnormal physiologic mechanisms has failed to define these alterations as cause or effect for the malfunctioning lung.

In addition to alveolar hypoplasia, abnormal development of the pulmonary vasculature is a major contributor to the clinical challenges in managing CDH and its inherent risk for pulmonary hypertension. Postnatal blood flow through

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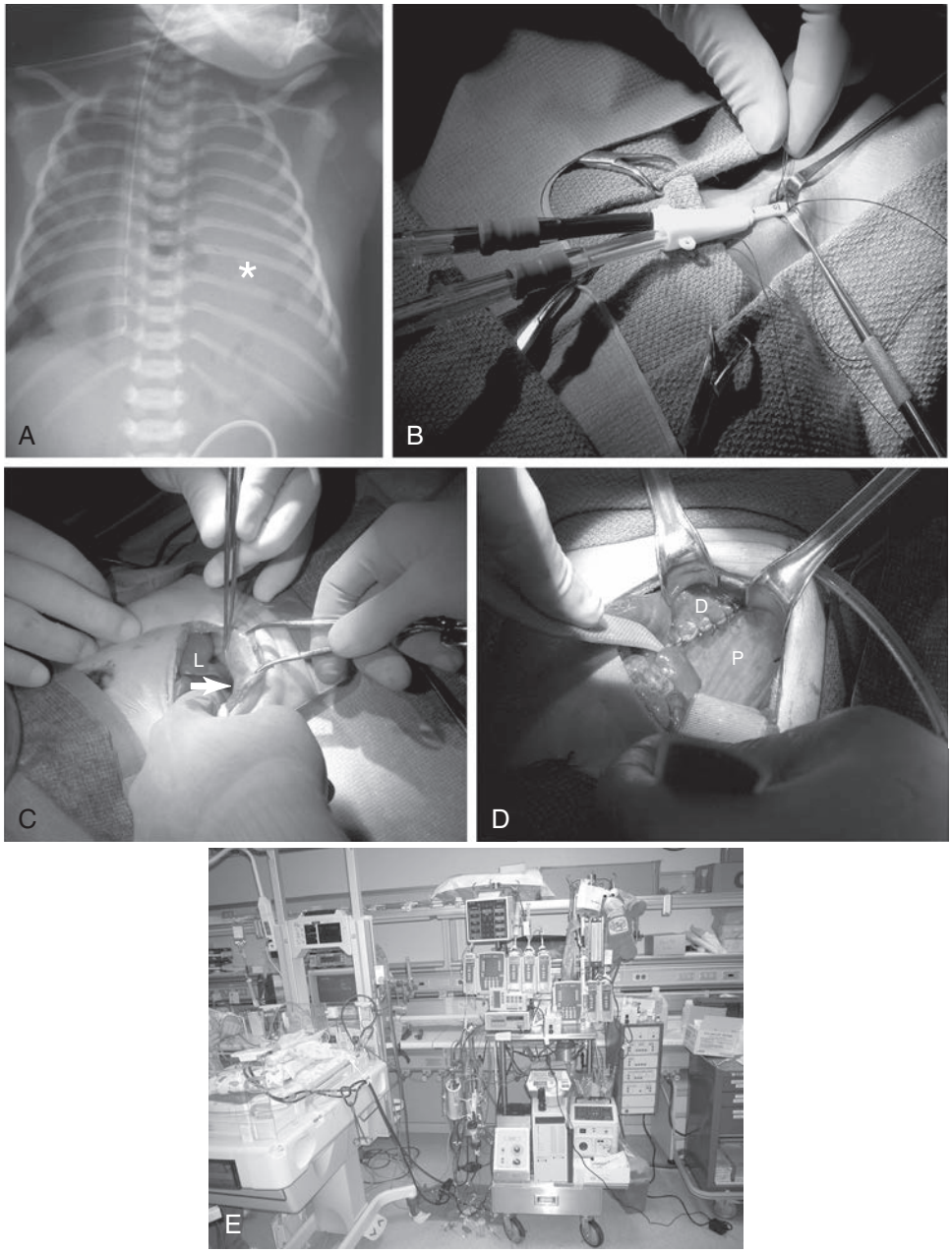

FIGURE 28.1 Newborn with left congenital diaphragmatic hernia (CDH), or Bochdalek hernia. **A**, Chest radiograph shows liver herniation *(asterisk)* into the left chest. Note displacement of heart and orogastric tube to right and minimally aerated lung on left. **B**, Dual-lumen venovenous cannulation via right internal jugular vein for extracorporeal life support (ECLS). **C**, Four days later, baby had stabilized on ECLS, so repair was performed in the neonatal intensive care unit (NICU) on ECLS. Note left lobe of liver *(L)* herniating beneath a diminutive anterior leaflet of the left diaphragm (in forcep). Left lobe of liver is between forcep and surgeon index finger. **D**, Defect required a biosynthetic patch (*P; D,* anterior leaflet of diaphragm). **E**, Panoramic view of neonatal ECLS equipment, which aids in bedside operative planning.

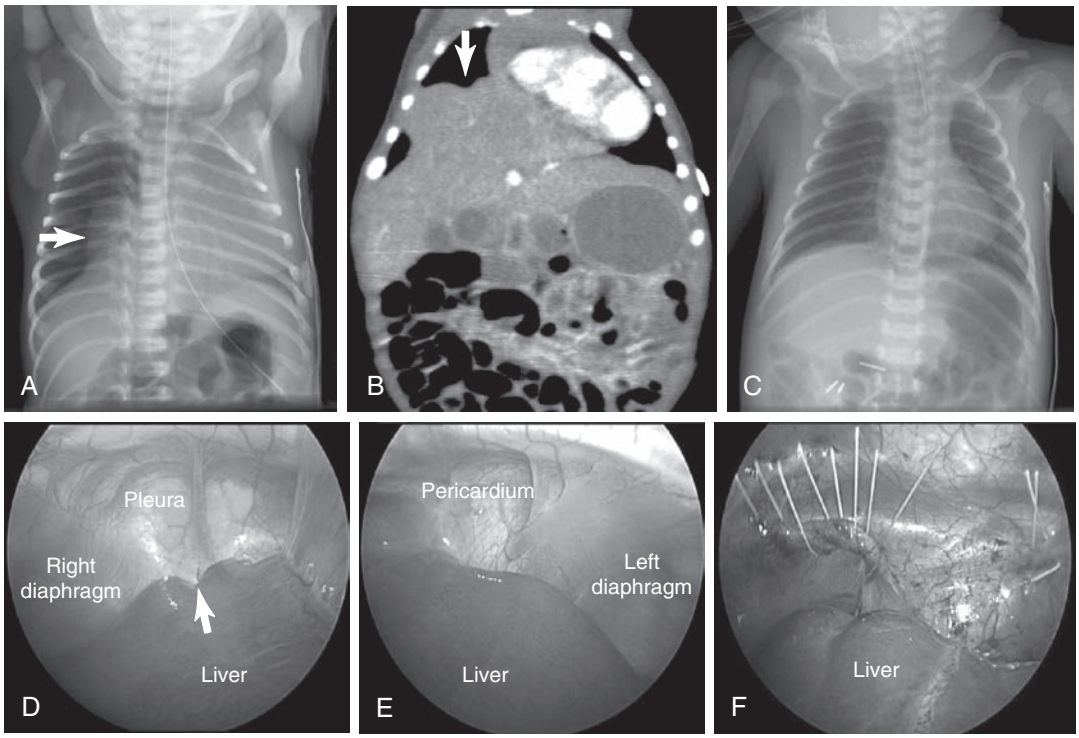

FIGURE 28.2 Newborn with anterior Morgagni diaphragmatic hernia. **A, B,** Chest radiograph and CT scan, respectively. *Arrows* show liver herniation. **C,** Postoperative chest radiograph shows complete reduction of liver and correction of hernia. **D–F,** Laparoscopic technique to repair large anterior defect: Right and left diaphragms are sutured to abdominal wall anteriorly; sutures are passed through the entire wall of abdomen, and knots are secured below skin level. *Arrow* shows groove in liver corresponding with CT scan image.

these hypoplastic lungs is compromised by both a reduced total number of pulmonary arterioles and an increased muscularization of the arteriolar bed. As a result, pulmonary vasculature capacitance is reduced and responsiveness to signals for smooth muscle relaxation may be lost. **Persistent pulmonary hypertension after birth maintains patency of and blood flow through natural fetal shunts. Resultant pulmonary hypoperfusion and systemic hypoxemia may be extreme and is often irreversible and recalcitrant to conventional therapy.**

Data Collection

HISTORY

Technologic advances in ultrasonography have facilitated earlier and more accurate antenatal diagnosis of diaphragmatic hernias, permitting planning of intervention and counseling of parents, as appropriate. High-quality prenatal ultrasound can diagnose a CDH early in pregnancy and also identify high-risk infants who may have worse outcomes. Prenatal lung-to-head ratio (LHR) is a widely accepted prognostic tool that is measured at 28 weeks of gestation using ultrasound. **An LHR of less than 1.2 can identify infants who have a higher risk of requiring extracorporeal membrane oxygenation/extracorporeal life support (ECMO/ECLS) and/or death. An observed-to-expected LHR can be calculated throughout gestation as it normalizes for gestational age. An observed-to-expected ratio of less than 25%, especially late in gestation, portends a poorer prognosis. Identification of the left lateral segment of the liver in the thoracic cavity also identifies infants who have worse outcomes.**[5] Recently, fetal magnetic resonance imaging (MRI) to identify incomplete pulmonary baseline, liver up and retrocardiac stomach[45] and fetal lung volume and lung-to-head

ratio[51] have been shown to be a useful prognostic tool in infants with CDH. **Prenatal identification of high-risk infants with CDH allows the mother to deliver in a high-risk perinatal center with the appropriate level of neonatal and surgical support on standby.** Although in utero surgical techniques to promote lung growth and passive reduction of the herniated abdominal contents seemed promising initially, after a moratorium on fetal surgery, there is now a global trial being conducted into fetoscopic intraluminal tracheal occlusion.[94] At this time, fetal intervention for severe CDH is still investigational. Some fetal surgery centers, particularly European, continue to explore minimally invasive means to promote lung growth in utero and thereby reduce the herniated abdominal contents. The Achilles' heel of fetal intervention, however, is the risk of preterm labor and the consequent morbidity of prematurity, risks which collectively must be weighed against a term delivery but with profound compromise in lung development.

SIGNS AND SYMPTOMS

Respiratory distress may develop immediately after birth or after an initial period of relative stability. If significant pulmonary hypoplasia is present and fetal circulation persists, the newborn may become rapidly symptomatic, heralded by profound respiratory distress and circulatory shock. Because much of the bowel is herniated into the chest, the **abdomen appears scaphoid and the anteroposterior diameter of the chest may enlarge as the bowel distends with air. Breath sounds are diminished or absent on the affected side,** and the mediastinum may be displaced toward the contralateral side. **Associated anomalies of the cardiovascular system** may include patent ductus arteriosus (PDA), aortic coarctation, and hypoplastic left heart syndrome, which require detailed echocardiographic evaluation. Other associated **anomalies requiring evaluation include central nervous system (CNS) malformations, genitourinary anomalies, esophageal atresia, omphalocele, cleft palate, and cardiovascular defects.**[105]

LABORATORY DATA

A chest radiograph is obtained and shows bowel herniated into the ipsilateral thoracic space with contralateral displacement of the heart. An **echocardiogram is necessary to assess cardiac function, degree of pulmonary hypertension, and presence of significant congenital cardiac anomalies. Lung ultrasound at the point of care** enables prompt diagnosis and may assist in decisions about surgical stategy.[21,47] Nonrotation of the intestine is an understood feature of CDH and does not require specific evaluation as a newborn. **Arterial blood gas analysis may reflect a profound degree of hypoxemia and mixed acidemia** (elevated Pco_2 and very negative base excess). **Whole blood lactic acid may rise after birth in concert with the degree of hypoxemia and circulatory shock.**

Treatment

PREOPERATIVE CARE (STABILIZATION)

As soon as a diaphragmatic hernia is suspected, an orogastric tube should be placed to prevent further distention of the stomach and bowel and alleviate consequent compression of the lung. The **newborn having CDH requires endotracheal intubation and mechanical ventilation to reduce swallowed air during spontaneous respirations and to maintain adequate respiratory gas exchange.** Because cardiac function also may be compromised, a combination of **pressor medications such as dopamine, dobutamine, and milrinone may need to be administered** (see Chapter 23). The earlier the infant becomes symptomatic, the more severe the respiratory compromise and the poorer the prognosis may be. **Despite the primary defect in the diaphragm, the major determinants of outcome are pulmonary hypertension and lung hypoplasia.**

A significant number of CDH newborns may have such severe pulmonary hypertension refractory to conventional or alternative (e.g., high-frequency oscillation or jet; inhaled nitric oxide [iNO]) ventilation that ECLS (venovenous or venoarterial) may be required to establish effective gas exchange and end-organ perfusion. The first population-based study of CDH infants found that only 13% were on ECLS preoperatively.[127] After ECLS therapy the simultaneous use of iNO and intravenous (IV) milrinone improves oxygenation and survival.[56] The overriding principle in stabilizing CDH newborns is to reduce barotrauma and oxygen toxicity to the lung that result in chronic lung disease. Strategies now emphasize *gentle ventilation* and *permissive hypercapnia,* so long as arterial pH does not drift significantly low (less than 7.25).[59]

OPERATIVE INTERVENTION

Surgical repair does not alter early outcome. Therefore, the baby's condition should be stabilized and efforts directed toward management of the

associated pulmonary hypoplasia and hypertension. **Early repair within the first 72 hours of life is indicated only in infants having little or no pulmonary dysfunction.** If **severe pulmonary insufficiency is present, medical therapies of conventional or high-frequency mechanical ventilation, iNO, or ECLS is instituted.** If these modalities are successful in stabilizing the baby, surgical repair is generally performed between 4 and 14 days of life.[71] The first population-based study of CDH found that the median age at surgery was 5 days.[127] If ECLS has been needed to stabilize the newborn having CDH, some centers advocate herniorrhaphy while on bypass, whereas other centers recommend repair after decannulation (see Fig. 28.1).

Most commonly through a subcostal transabdominal approach, the surgeon reduces the stomach, intestine, and spleen from the chest to the abdominal cavity and repairs the diaphragmatic defect. **If the defect is large, a prosthetic patch may be required to complete closure of the hernia.** Closure of the abdominal wound also may be difficult because of underdeveloped abdominal wall musculature and loss of abdominal domain. In these circumstances, **if abdominal closure is not possible or may result in abdominal hypertension, simple skin closure or prosthetic silo placement may be necessary to cover the abdominal contents,** leaving a large ventral hernia for future repair when abdominal domain is more adequate and the baby is more stable. Chest tube placement depends on risk for bleeding, which may be significant if repair is performed on ECLS (because of anticoagulation during ECMO therapy) or if risk of pneumothorax is anticipated. Minimally invasive techniques to repair CDH, both Bochdalek and Morgagni types, also may be used in newborns[120] (see Fig. 28.2), but may not be well tolerated in fragile neonates. Appropriate patient selection is a premium. Thoracoscopic and laparoscopic techniques to repair CDH have been described and may be better suited for infants who present out of the newborn period and without physiologically significant pulmonary hypoplasia or hypertension.

POSTOPERATIVE CARE

The principal postoperative concern remains effective ventilation and oxygenation while imparting the least amount of barotrauma and toxicity. If conventional mechanical ventilation fails, high-frequency oscillation and iNO are employed.[38] ECLS is reserved in this setting as a salvage therapy for babies who revert back to fetal circulation and who do not respond to these less invasive modalities.[71]

Complications and Prognosis

The survival rate for newborns having CDH and who require mechanical ventilation in the first 18 to 24 hours of life is approximately 64%. The first population-based study of CDH outcomes found that the 30-day mortality rate postoperatively was 9%.[127] If an infant with a diaphragmatic hernia does not present with respiratory distress in the first 24 hours of life, survival approaches 100%. As improvements in *gentle ventilation* **strategies have emerged, a gradual, albeit small, increase in survival has been realized. The primary, early pathophysiologic consequence of CDH is pulmonary hypertension. Late complications include chronic lung disease with deterioration in exercise capacity,**[115] **recurrent diaphragmatic hernia, gastroesophageal reflux (GER), musculoskeletal deformities (including scoliosis), growth restriction, and protracted need for medical equipment/home health services.**[36,79] Long-term neurologic outcomes have recently become important to evaluate, as perinatal mortality has decreased. **Survivors of CDH continue to have impaired neurologic development as evidenced by hearing impairment, hypotonicity, psychomotor dysfunction,** and the need for special education,[36] **affecting collectively 30% to 50% of children with CDH.** Basic and clinical research continue in an effort to identify improved therapies for the complex pulmonary dysfunction associated with CDH, not only to close the persistent and large survival gap but also to optimize quality of life among survivors.

ESOPHAGEAL ATRESIA AND TRACHEOESOPHAGEAL FISTULA

Physiology and Etiology

Esophageal atresia (EA) occurs in 1 in 3000 to 4500 live births and represents a **spectrum of anomalies that arise early in gestation (3 to 6 weeks) when the trachea normally buds from the primitive foregut.** Failure in the normal development of the esophagus and in complete separation of the

trachea from the esophagus gives rise to EA and distal tracheoesophageal fistula (TEF) in 85% of cases, isolated EA in 8%, TEF without EA in 5%, or EA with proximal or proximal and distal fistulas in 2%. Etiologies for this collection of defects remain unclear, but it is suspected that **genetic alterations in and environmental insults on rapidly proliferating foregut stem cells during this critical period of organogenesis account for such diverse yet predictable esophageal malformations.** Aberrations at the cellular level in muscle fibers of the distal esophagus may help explain the **nearly universal symptoms of dysmotility and GER after operative repair.**[30,34] Because other developing organs are vulnerable to the same insults in this critical period of gestation, associated anomalies are common (46%), particularly vertebral, anorectal, cardiac, CNS, genitourinary, limb, gastrointestinal (e.g., duodenal atresia), VACTERL and CHARGE syndromes.[106] **In 11% to 33% of infants with EA and distal TEF, concurrent and severe tracheomalacia is present and is manifested by stridorous breathing.**[101] Although EA with or without TEF has not been associated with a single-gene defect, a high incidence has been observed in children having trisomy 21, or Down syndrome.[106]

Data Collection

HISTORY

Maternal polyhydramnios may suggest EA or other conditions in which the fetus does not swallow amniotic fluid normally or has a gastrointestinal obstruction.

SIGNS AND SYMPTOMS

Babies having EA are identified soon after birth because of excessive salivary secretions and inability to swallow feedings. Upon feeding, these babies quickly cough, regurgitate undigested formula or breast milk, and may exhibit cyanosis. When attempting to pass an **orogastric tube, obstruction is typically encountered between 8 and 12 cm from the lips, and the diagnosis of EA is established.** If a distal TEF is also present, air passes into the stomach and bowel and is present on plain abdominal radiographs. **Respiratory distress may arise if gastric secretions reflux through the TEF and into the lungs, which may incite a profound chemical aspiration pneumonitis.** Symptoms of an "H"-type fistula in the absence of EA are less obvious and require a high index of suspicion. **Coughing and choking with feedings, or recurrent pneumonia over the first months of life, suggest the presence of an occult TEF** (Box 28.1).

BOX 28.1 CRITICAL FINDINGS
ESOPHAGEAL ATRESIA AND TRACHEOESOPHAGEAL FISTULA

Critical assessment findings for esophageal atresia and tracheoesophageal fistula are:

- Excessive secretions
- Feeding intolerance
- Inability to pass orogastric tube
- Abdominal distention
- Other findings associated with VACTERL (Vertebrae, Anus, Cardiac system, Trachea, Esophagus, Renal [urinary tract], and Limbs)

PHYSICAL EXAMINATION

Once EA has been established, the infant should be carefully examined to exclude other anomalies of the **VACTERL** association, a variable sequence of anomalies affecting the **V**ertebrae, **A**nus, **C**ardiac system, **T**rachea, **E**sophagus, **R**enal (urinary tract), and **L**imbs.[106] Echocardiography permits both the identification of significant cardiac anomalies and the presence of a right- or left-sided aortic arch, which have important implications in the operative approach.

LABORATORY DATA

After obstruction is met with passing of an orogastric tube, a plain radiograph of the chest and abdomen should be obtained with the tube left in place, which is visualized usually at the second or third thoracic vertebra and above the carina. The stomach and intestines may contain luminal air if a distal TEF is present. If no distal fistula exists, the abdomen on radiograph will appear gasless. **In the rare setting of EA, distal TEF, and duodenal atresia, the abdominal gas pattern may show the classic "double bubble" sign, as gas fills the stomach and proximal duodenum only.**

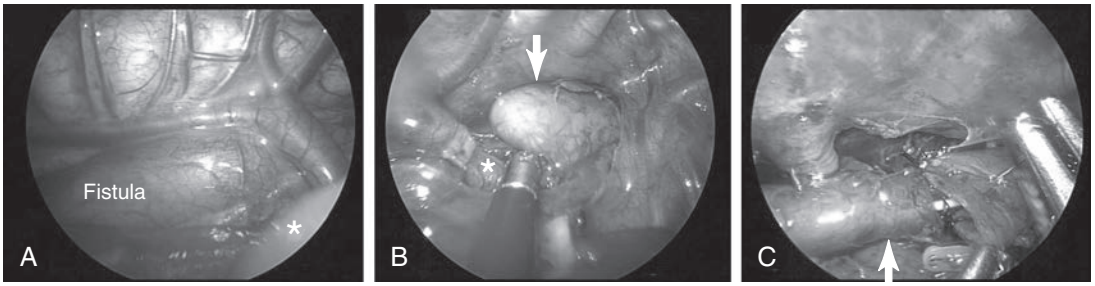

FIGURE 28.3 Thoracoscopic repair of esophageal atresia with distal tracheoesophageal fistula (TEF) in a newborn. **A**, View of TEF (fistula), which is distended from ventilation. Azygous vein is obscuring connection to trachea. **B**, After division of azygous vein, one can visualize the fistulous connection *(asterisk)* of the distal esophagus to the posterior trachea. Upper atretic pouch has been mobilized and is being elevated with instrument. **C**, Suturing of upper esophagus to distal esophagus. Replogle tube has been advanced through anastomosis after approximation of posterior row initially. For perspective of small working space, 3- and 5-mm instruments are used for this procedure.

Treatment

PREOPERATIVE CARE

Once the diagnosis of EA is established, a 10-Fr Replogle tube is placed in the upper esophageal pouch and set to low continuous suction to prevent aspiration of oral secretions. While awaiting operation, the **neonate should be kept in the head-up position and initiated on antireflux medication to minimize GER and the consequent risk of acid-induced pneumonitis.** Operative repair, in general, is not an emergency procedure. Patients first should be **evaluated thoroughly for other associated anomalies by physical examination, echocardiography to delineate the anatomy of the heart and great vessels, abdominal ultrasound of the kidneys and genitourinary tracts, and plain radiographs of the spine and limbs.** Newborns having cyanotic congenital heart disease may require a palliative cardiac procedure before reconstruction of the esophagus.

If babies having EA and distal TEF are born prematurely and have respiratory distress syndrome (i.e., "stiff lungs"), a significant portion of mechanical tidal volumes, delivered under positive pressure, may be shunted preferentially through the fistula and into the stomach. As a result, effective ventilation is lost and critical gastric distention ensues, further restricting diaphragmatic excursion. Emergent ligation of the TEF with gastrostomy tube insertion is necessary in such instances to restore effective ventilation.

OPERATIVE INTERVENTION

The type of esophageal malformation dictates the surgical approach. **Surgical repair of EA with or without TEF is generally not an emergency but should be carried out as soon as the patient is stable.** If the infant is in otherwise good health and the gap between esophageal elements is not too large, primary anastomosis is indicated through a right thoracotomy and retropleural approach. To reduce the pain and potential morbidities associated with a thoracotomy, some surgeons recommend repairing thoracoscopically in appropriately selected patients (Fig. 28.3).

Unfortunately, in isolated EA, the gap distance is generally too long to allow early primary repair. If the gap length is considered too great, with or without TEF, or if the child is too ill, a delayed or staged repair is planned. **An early gastrostomy is placed for decompression and feeding, and the TEF if present is divided to prevent reflux into the tracheobronchial tree.** After a variable period of time to allow resolution of pneumonitis or maximum growth of the distal esophagus, a second operation completes the repair. To promote lengthening and growth of the distal esophagus in cases of isolated EA, dilation and stretch of the proximal and distal esophagus may be performed via the oropharynx and a mature gastrostomy tract, respectively, using Bakes dilators under fluoroscopic guidance (Fig. 28.4).

Multiple options for long gap atresia exist. One strategy is first, after a period of growth in early infancy, to suture and approximate the two ends

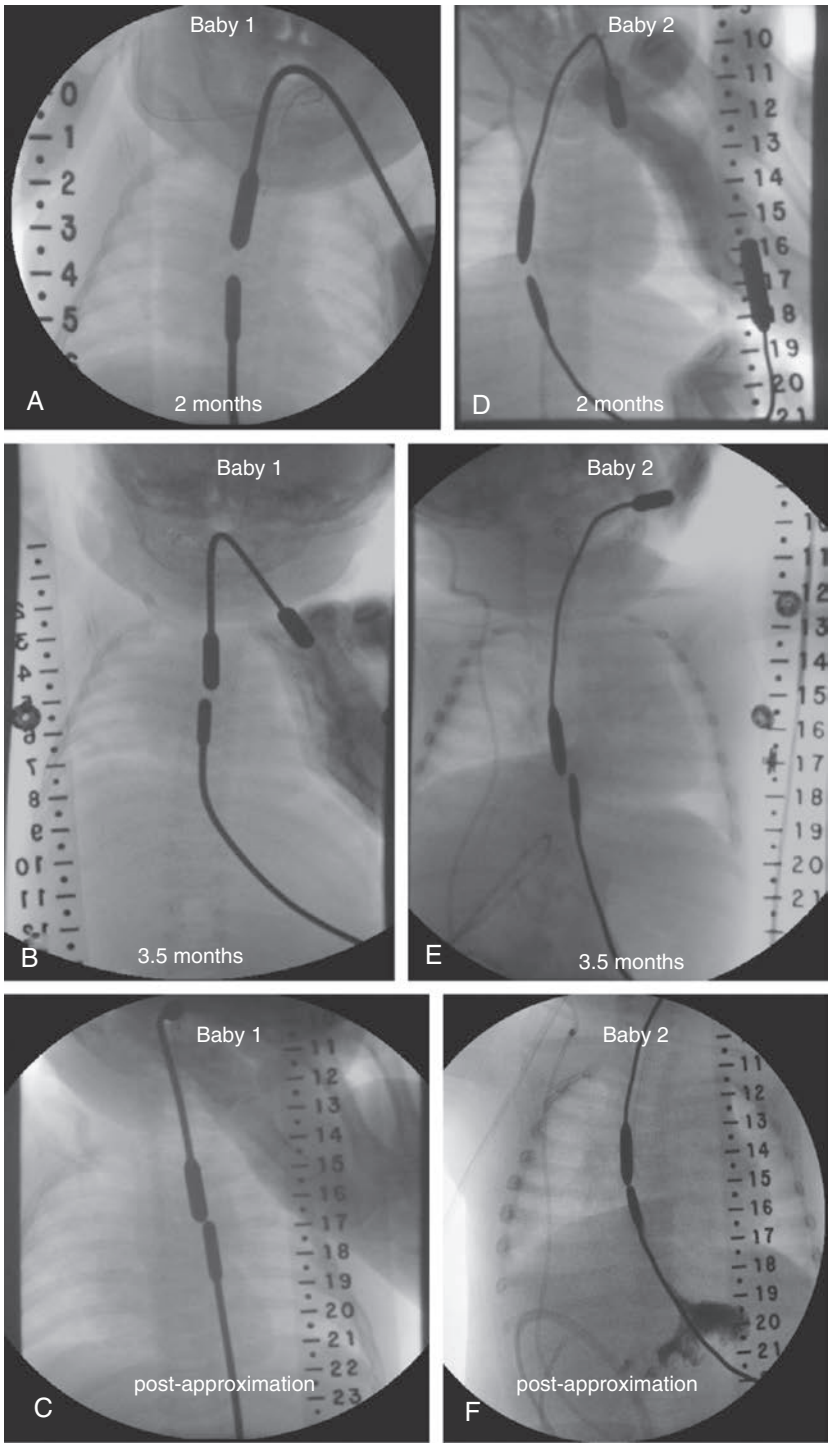

FIGURE 28.4 Representative fluoroscopic images to assess the distance between esophageal pouches (i.e., gap length) for both babies. ***A*** and ***B*** (Baby 1) and ***D*** and ***E*** (Baby 2) show placement of Bakes dilators per os and per gastrostomy in both babies before suture approximation at 2.0 and 3.5 months of age, respectively. ***C*** (Baby 1) and ***F*** (Baby 2) show repeat gap length assessment using Bakes dilators 2 months after suture approximation of the esophageal pouches.

without creating an anastomosis, then perform a repeat thoracotomy 6 to 8 weeks later to establish luminal continuity once tension between the esophageal ends has resolved. An alternative approach is to use magnetic fistulization to create luminal continuity to preserve length and prevent the need for an additional thoracotomy. When this approach is used, the magnetic compression creates a leak-free anastomosis typically within 4 to 7 days. The placement and removal of the catheter-based magnets is simple and well tolerated without general anesthesia (Fig. 28.5). Importantly, when using "magnamosis," the coupling surface of the magnets is only 10 Fr, so the surgeon should anticipate several procedures to dilate the anastomosis to a size compatible with that of the infant to restore appropriate oropharyngeal ingestion and swallowing (Fig. 28.6). To date, our two patients using this magnamosis technique each has her complete esophagus without requiring an interposition, such as colon, stomach, or jejunum, and both are oral feeders.[66]

If delayed or staged repair is planned, secretions must be controlled. Suction catheters placed in the upper pouch are maintained to reduce the risk of aspiration. In rare cases, reconstruction using the native esophagus is not possible. In these circumstances, esophageal replacement using gastric or colon transposition is necessary. If the infant is not a candidate for early operation because of a lethal chromosomal defect or severe congenital heart disease, cervical esophagostomy and gastrostomy are performed to palliate the infant, and esophageal replacement is performed later, as indicated.

POSTOPERATIVE CARE

Postoperative care includes appropriate pain control and pulmonary care, parenteral nutrition, and a brief course of systemic antibiotics. Tracheal and esophageal suction catheters should *not* come in contact with the newly repaired esophagus and trachea, because suture line disruption may cause a leak or recurrent fistula, both potentially catastrophic complications. Antibiotic therapy is continued based on surgeon preference. A chest tube and/or retropleural drain is placed to control an anastomotic leak, should it occur. **Before initiating oral feedings, an esophagram is usually obtained 5 to 7 days after repair to verify complete anastomotic healing and absence of leak. All EA babies have some degree of esophageal**

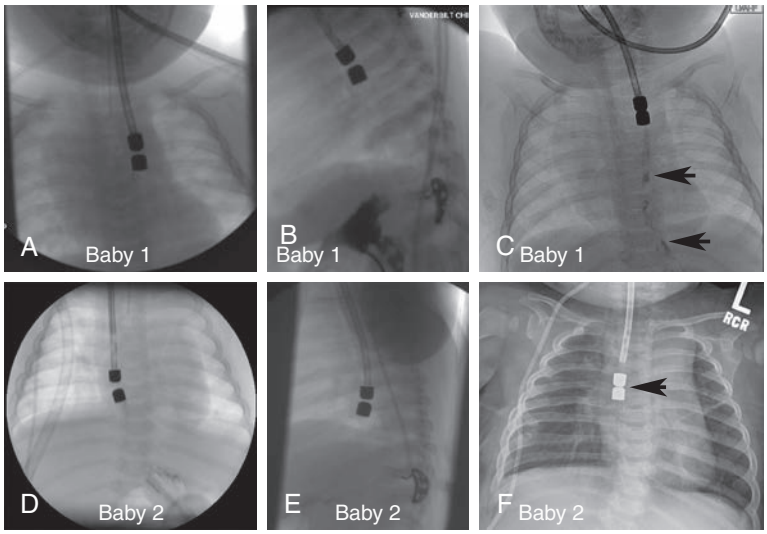

FIGURE 28.5 Fluoroscopic images taken at time of catheter-based magnet placement for both babies. **A** and **D** show anteroposterior projections, and **B** and **E** show lateral projections. **C** shows Baby 1 on magnet day 6; the baby was taken to the fluoroscopy suite to assess canalization of the esophageal lumens. Free flow of contrast through the upper catheter is shown *(arrows)*. The magnets were removed and an orogastric tube was placed under fluoroscopic guidance. **F** shows Baby 2 on magnet day 10; the magnets migrated proximally but were still coupled (*arrow,* note lower position of magnets compared to **D** and **E**). The catheters were removed completely at the bedside, and an 8-Fr orogastric tube was placed until dilation could be initiated the next day.

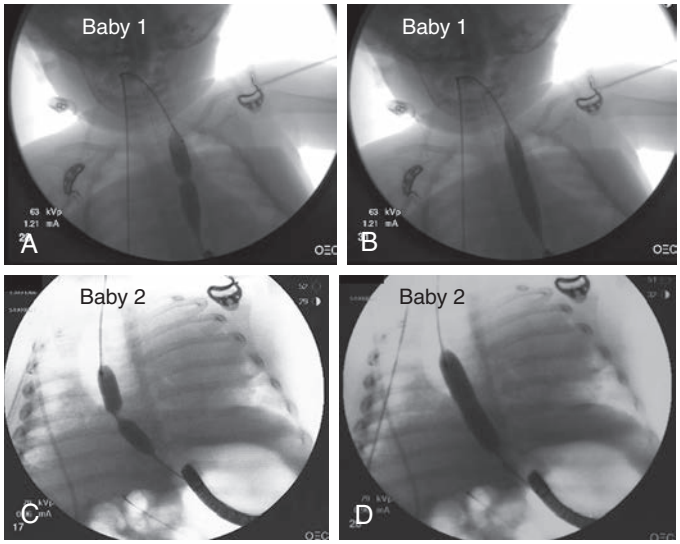

FIGURE 28.6 Fluoroscopic images taken after magnetic compression anastomosis for both babies. **A** and **B** show an anastomotic stricture before and after 12-mm balloon dilation, respectively, in Baby 1 at 6 weeks after magnetic compression anastomosis. After magnetic catheter removal, Baby 2 self-removed her nasogastric tube the day after its placement (11 days after magnetic compression anastomosis). **C** and **D** show her anastomotic stricture before and after 10-mm balloon dilation, respectively.

dysmotility and GER after repair.[30,34] Elevating the head of the bed 30 to 45 degrees, administering histamine (H2) antagonists or proton pump inhibitors, and slow feeding may help control reflux symptoms.

Complications and Prognosis

Postoperative complications include anastomotic leak and/or stricture, as well as esophageal dysmotility. Anastomotic leaks may occur in up to 20% of patients and generally are treated conservatively with chest tube drainage, parenteral nutrition, antibiotics, and tincture of time. **The vast majority of leaks close without operative intervention but tend to heal with some degree of stricture, commonly amenable to dilation. Anastomotic strictures are the most common postoperative complication after EA-TEF repair occurring in 30% to 50% of infants** with EA-TEF. In the **majority of infants who develop a postoperative esophageal stricture, esophageal dilation is an effective therapy to maintain esophageal patency, and only a minority of infants (2% to 10%) require reoperation and reconstruction of the esophageal anastomosis.** Esophageal strictures often are associated with or exacerbated by GER and may be treated successfully by esophageal dilation. **If GER complicates a stricture and is refractory to maximal medical therapy, a fundoplication procedure may be necessary.[34]** Some degree of esophageal dysmotility usually exists because of poor peristalsis in the distal esophagus. In a recent study the rate of dysmotility was 85% at 1 year of age and 100% at 10 years of age.[34] The child may adapt to a poorly functioning esophagus by altering his or her feeding habits or using anti-reflux medications (47% in a recent study).[34] However, **in infancy, gastrostomy feeding may be necessary to prevent vomiting and aspiration. Postoperative airway complications include tracheobronchomalacia and recurrent laryngeal nerve injury with vocal cord dysfunction.**

A recent study of postoperative complications found a mortality rate of 4.2%.[34] With modern neonatal care and surgical techniques, **long-term survival after repair of EA and TEF is excellent.** Prognosis depends on largely two factors: the presence and type of cardiac anomalies and the presence of prematurity and respiratory distress syndrome. **A useful system to predict survival is the Spitz**

classification, which stratifies infant survival by birth weight and major cardiac anomaly[103]:

I: Birth weight greater than 1500 g, no major CHD, survival is greater than 97%
II: Birth weight less than 1500 g or major CHD, survival is 59%
III: Birth weight less than 1500 g and major CHD, survival is 22%

CONGENITAL CHEST MASSES

Physiology and Etiology

The most common congenital chest masses requiring surgical intervention in the newborn period are congenital pulmonary airway malformations (CPAM, also formerly known as congenital cystic adenomatoid malformation or CCAM), pulmonary sequestrations (both intralobar and extralobar types), bronchogenic cysts, and congenital lobar emphysema (CLE). Each of these malformations may exist alone or in combination with other anomalies.

CPAM lesions are thought to arise from focal interruption in coordinated pulmonary progenitor cell growth, resulting in abnormal development of pulmonary tissues and structural distortion. Histologically, CPAM is associated with increased cell proliferation and decreased apoptosis when compared with normal lung tissue. The CPAM lesion receives its blood supply from the pulmonary system but does not communicate with normally formed bronchial structures.

Anomalous development of the foregut is the accepted underlying etiology of both bronchogenic cyst and pulmonary sequestration. Bronchogenic cysts are lined by ciliated columnar and/or cuboidal epithelium. The surrounding tissues resemble those of the normal bronchus and are generally, although not exclusively, located within the mediastinum along the tracheobronchial tree. Extralobar sequestrations are masses of primitive pulmonary parenchyma with no bronchial connection and are supplied by and drain into the systemic and not pulmonary vasculature. Intralobar sequestrations on the other hand are supplied by systemic vasculature, but drain into the pulmonary venous system. They too do not have a bronchial connection. CLE presents in the newborn period as a fluid-filled, overdistended lobe that, under positive pressure ventilation, may trap air and generate tension physiology. In many cases, although not all, CLE is associated with the absence or hypoplasia of cartilaginous rings of the major and segmental bronchi. These structurally underdeveloped bronchi are prone to collapse on expiration, thereby trapping air.

Data Collection

HISTORY, SIGNS, AND SYMPTOMS

Although rare, congenital lung malformations may lead to considerable morbidity, such as infection, hemorrhage, respiratory failure, and pulmonary hypoplasia and may even prove lethal. Some lesions may escape prenatal detection and appear later in development. Failure to recognize a malformation may lead to inappropriate intervention. For example, placement of a chest tube to manage suspected tension pneumothorax in a baby having congenital lobar emphysema may lead to lung injury and loss of tidal volume through the thoracostomy tube instead of into the remaining healthy lung.

Congenital Pulmonary Airway Malformation. CPAMs are increasingly detected prenatally and are nicely characterized on fetal ultrasound, but if not, may be further delineated by fetal MRI, as indicated. In utero, many of these lesions may reduce in size throughout a normal gestational period and cause no respiratory symptoms for the newborn at birth. In such an instance, a simple chest radiograph and clinical assessment is all that is necessary. However, other **such lesions may cause a variety of problems, from pulmonary hypoplasia (both ipsilateral and contralateral) to nonimmune hydrops fetalis with congestive heart failure. Polyhydramnios also may be present if the lesion compresses the esophagus and compromises fetal swallowing of amniotic fluid.** Fetal intervention may be indicated if the gestation has not yet reached 34 weeks, in which case premature delivery might be planned. Large fluid-filled cystic lesions may be amenable to thoracoamniotic shunt placement while in utero to relieve compression of intrathoracic structures and to restore hemodynamic status. Solid CPAM lesions arising early in gestation and causing similar complications have been resected in fetuses with promising results. If these lesions do not manifest with in utero pathophysiology, yet are of sufficient size, the neonate may develop respiratory distress shortly after birth. This process

is responsible for the cystic appearance on radiographs. Babies may have mediastinal shift and large air spaces, easily confused with a pneumothorax or diaphragmatic hernia. **Sonography may be helpful to delineate a solid or cystic mass and should establish the diagnosis. CPAM may result in recurrent infections because mucociliary clearance is poor.** Rarely, malignancy may arise in a CPAM in the form of pulmonary pleuroblastoma, rhabdomyosarcoma, or bronchoalveolar carcinoma.

Pulmonary Sequestration. Pulmonary sequestration accounts for less than 10% of all congenital lung malformations and mostly occurs in the lower lobes. **A sequestration represents a mass of disorganized bronchopulmonary tissue without a normal bronchial communication and has a systemic vascular supply.** Because of the systemic vasculature, large lesions can shunt blood away from other organs and lead to cardiac overload and heart failure. The abnormal sequestered lung tissue may be intralobar or extralobar and is classified according to pleural coverage, either within the pleural investment of the whole lung itself and with pulmonary venous drainage (intralobar) or outside of this normal pleural lining with drainage back into the systemic vasculature (extralobar). Sequestrations rarely may have some sort of communication with the foregut. Infants having an intralobar sequestration not detected prenatally may present outside of the newborn period and often with recurrent respiratory problems, such as chronic cough, or with recurrent pneumonias, either in the lesion or in the surrounding normal but compressed lung tissue. **Plain radiographs may show simply consolidation. Anomalies associated with extralobar sequestration include diaphragmatic hernia and eventration, bronchogenic cysts, pericardial problems, duplication cysts, and may share a similar dysregulated embryologic event because approximately 95% of extralobar lesions are left-sided.**[9] Extralobar lesions may reside either above or below the left diaphragm. Older children may have exercise intolerance if a large systemic arteriovenous shunt exists. Systemic arterial flow through the lesion may produce a murmur, and may lead to congestive cardiac failure. Squamous cell carcinoma, adenocarcinoma, and rhabdomyosarcoma may rarely arise in the sequestration. These lesions are often removed later in infancy because of the risk of recurrent infection and potential malignancy.

Bronchogenic Cyst. Bronchogenic cysts may be considered a foregut duplication and arise from an abnormal budding of the ventral foregut. Approximately 85% are mediastinal and 15% are intrapulmonary. Bronchogenic cysts may be filled with air or fluid and may show air-fluid levels on plain radiographs. As a result, **bronchogenic cysts may become infected or simply grow over time, and so may behave as a space-occupying and compressive lesion.** Many cysts are asymptomatic or have vague symptoms and are discovered on routine chest radiographs. Infection, hemorrhage, and, in rare cases, late malignancy may occur. **Associated respiratory symptoms include stridor or wheezing.** Chronic air trapping may lead to emphysema, atelectasis, or both. Dysphagia, chest pain, and epigastric discomfort may also occur.

Congenital Lobar Emphysema (or Congenital Lobar Hyperinflation). Although generally not discovered in utero, **congenital lobar emphysema typically manifests in neonates as hyperinflation of one or more lung lobes.** Causes include intrinsic absence or abnormality (bronchomalacia) of cartilaginous rings or external compression of a segmental bronchus by a large pulmonary artery that predisposes to air trapping. **Hyperinflation of a pulmonary lobe develops after birth, as inspired air enters the affected lobe but cannot exit, because the positive pressure of expiration collapses the nonrigid airway.** Congenital lobar emphysema most commonly involves the upper lobes. **The left upper lobe is involved in roughly 41% of patients, the right middle lobe in 34%, and the right upper lobe in 21%.** Involvement of the lower lobes is rare, occurring in fewer than 5% of patients. **Neonates may present with mild-to-moderate respiratory distress. Mediastinal shift may develop with progressive air trapping, and decreased breath sounds are noted on the involved side. Infants who have a milder form of lobar emphysema will present with nonspecific findings, including cough, wheezing, respiratory distress, and cyanosis.** Older children may present with recurrent chest infections. **On plain radiographs obtained in neonates, the affected lobe may be hyperlucent or slightly opacified if alveoli remain fluid-filled.** Associated cardiac anomalies may occur in as many as 10% of patients.

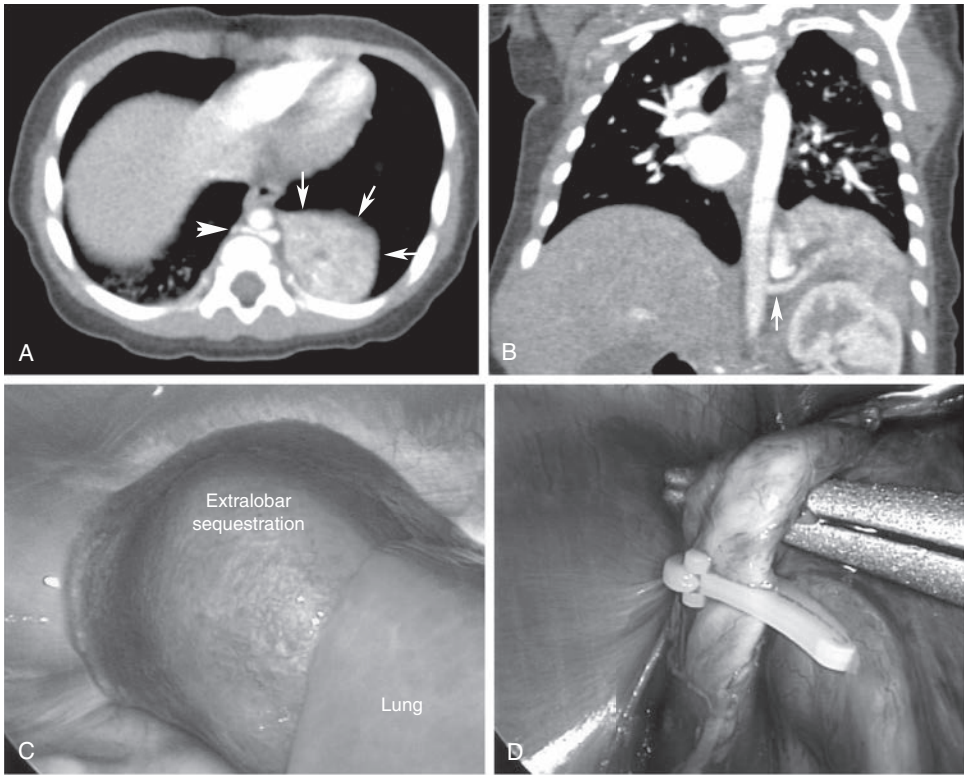

FIGURE 28.7 Thoracoscopic resection of a left-sided extralobar pulmonary sequestration (ELPS) in a newborn. **A, B,** CT scan shows ELPS at base of left chest (*arrows* in **A**). Note large vein coursing behind aorta in **A** *(arrowhead)* and large artery supplying lesion directly from aorta in **B** *(arrow)*. **C,** Thoracoscopic view of ELPS (looking toward diaphragm). **D,** Clipping of large artery and vein. Lesion is then removed through one of the port sites.

LABORATORY DATA

Routine chest radiograph is the initial evaluation tool in distinguishing congenital chest masses and is the principle study to establish the diagnosis of diaphragmatic hernia and congenital lobar emphysema in newborns. Sonography and/or computed tomography (CT scan) of the chest are useful means to evaluate CPAM, sequestrations, bronchogenic cysts, and lobar emphysema in older infants and children. The differential diagnosis of a hyperlucent hemithorax with mediastinal shift on chest x-ray in the newborn includes tension pneumothorax, cystic CPAM, diaphragmatic hernia with air-filled stomach or intestine in the chest, and congenital lobar emphysema.

Treatment

Surgical resection of these congenital chest masses is curative. Some small, asymptomatic lesions of sequestration or CPAM may be followed expectantly, as reports of spontaneous regression may be found in the literature. However, most lesions may be removed with little morbidity in an effort to minimize long-term complications of the various lesions. Operative approach to these lesions may be by either thoracotomy or thoracoscopy, depending on the suitability of the baby and the skill set of the surgeon (Figs. 28.7 and 28.8).

Special consideration to resection of the pulmonary lobe involved with congenital lobar emphysema should be given (Fig. 28.9). Extreme caution must be exercised upon induction of general anesthesia and endotracheal intubation with positive pressure ventilation. Because of the malacic airway and the propensity for air-trapping in congenital lobar emphysema, rapid development of tension physiology may ensue, compromising the well-being of the baby and necessitating emergent decompressive

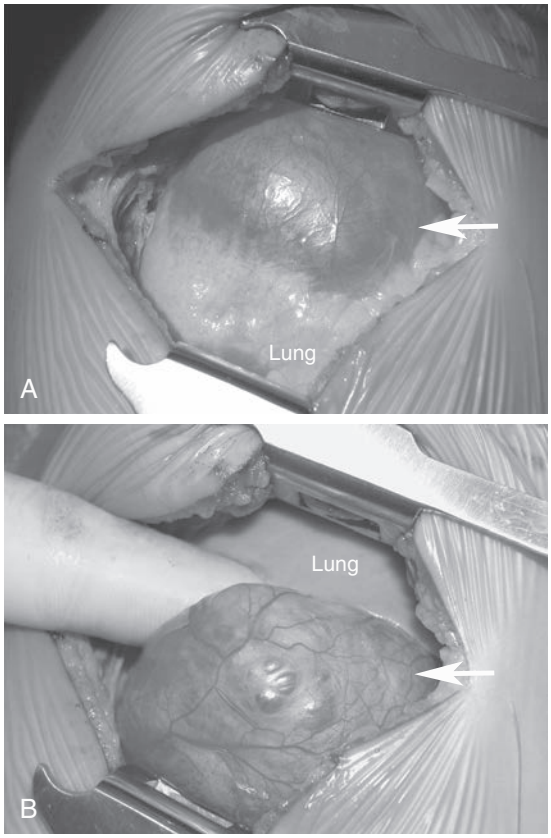

FIGURE 28.8 Thoracotomy in a newborn for congenial pulmonary airway malformation (CPAM). Views of anterior **(A)** and undersurface **(B)** of cystic lesion *(arrows)*.

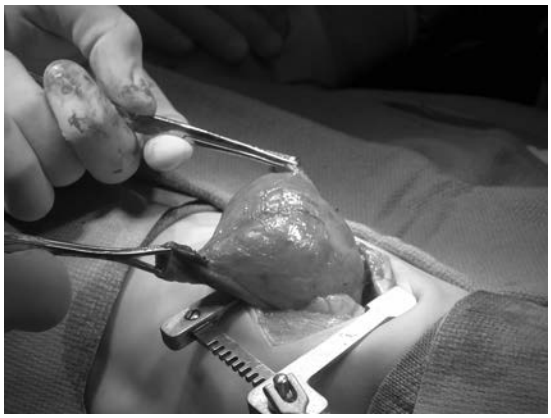

FIGURE 28.9 Thoracotomy in a newborn for congenital lobar emphysema. Note overdistended nature of emphysematous lobe compared with normal lobe just peering out from inferior aspect of wound.

thoracotomy. Such pathophysiology is possible in any neonate having congenital lobar emphysema and requiring positive pressure ventilation.

INTESTINAL MALROTATION AND VOLVULUS

Physiology and Etiology

In the 4th week of gestation, the midgut exists as a straight tube deriving its blood supply from the superior mesenteric artery (SMA). The proximal limb of primitive intestine, representing the future duodenum, jejunum, and proximal ileum, lie in the midline and anterior to the SMA. The distal limb, destined to become the terminal ileum and ascending and transverse colon, lies posterior to the SMA. During the 6th week of gestation, these segments of bowel, known collectively as the midgut, are able to lengthen rapidly by herniating through the incompletely closed abdominal wall and into the umbilical stalk. While lengthening outside of the coelomic cavity, the midgut undergoes a 270-degree counterclockwise rotation around the SMA axis. On return to the abdominal cavity, the duodenojejunal junction comes to rest in the left upper quadrant and becomes fixed in this location by the ligament of Treitz. At the end of the 11th week of gestation, midgut rotation is completed and the cecum resides anterior and to the right of the SMA and is fixed in the right lower quadrant. Because of the counterclockwise nature of this intestinal rotation, the ascending and transverse colon lie to the right of the SMA. The hindgut (splenic flexure of the colon to the rectum) then fixes in the left hemiabdomen and derives its blood supply largely from the inferior mesenteric artery (IMA).

Failure of this rotation and fixation results in the clinical condition termed malrotation, which covers a wide spectrum of rotational anomalies. **Complete nonrotation is characterized by the entire small bowel existing on the right side of the abdomen and the colon principally to the left.** Partial malrotation involves the improper fixation of a single segment. Complete malrotation is thought to occur from a lax umbilical ring allowing the gut to return en masse to the abdomen. Because proper rotation does not occur, the root of the mesentery is not anchored in the left upper quadrant, and the SMA and vein loosely suspend the entire bowel without

fixation. **This unfixed, narrow mesenteric pedicle predisposes the midgut and its tenuous blood supply to twisting or volvulus. If volvulus occurs, the blood supply to the midgut may be compromised, leading rapidly to ischemia and bowel infarction.** The majority of patients with midgut malrotation are diagnosed in the first month of life, but may be seen with decreasing frequency in the older child or rarely the adult.[54]

By definition, malrotation also exists in gastroschisis, omphalocele, and CDH, as the midgut is trapped and unable to rotate and fix properly in these conditions.

BOX 28.2 CRITICAL FINDINGS
MALROTATION AND VOLVULUS

Critical assessment findings for malrotation and volvulus are:
- Lethargy
- Bilious emesis
- Abdominal distention
- Abdominal radiograph suggestive of intestinal obstruction
- Acidosis, leukocytosis, and shock suggest volvulus

Data Collection

HISTORY

Malrotation may manifest in the newborn simply as a proximal mechanical bowel obstruction caused by abnormal attachments, or Ladd bands, between the cecum and porta hepatis. **These babies typically show some degree of feeding intolerance early on with or without bilious emesis.** A more worrisome presentation of malrotation may arise acutely, should the bowel volvulize around its unfixed, narrow vascular pedicle. These babies present with an acute, high-grade proximal bowel obstruction. **In a neonate who develops midgut volvulus, the first few days of life usually are unremarkable, but then the baby develops acute feeding intolerance and bilious emesis in the absence of abdominal distention.** If a delay in diagnosis occurs, **intestinal ischemia sets in, and the symptoms may progress rapidly to an acute abdomen and profound shock as a result of gangrenous bowel. Abdominal wall erythema and distention are usually present in advanced stages of intestinal ischemia and are ominous findings.**[114]

SIGNS AND SYMPTOMS

The symptoms of nonvolvulized malrotation mimic those of duodenal stenosis or atresia, proximal jejunal atresia, or other conditions resulting in proximal intestinal obstruction and result from Ladd bands compressing the proximal duodenum. **These babies develop feeding intolerance followed by bilious emesis and typically have a scaphoid abdomen on examination. Midgut volvulus presents with a more sudden onset of symptoms in a neonate or infant who had been previously feeding normally, suggesting acute proximal intestinal obstruction.** If **diagnosis is delayed, symptoms of intestinal ischemia become evident and include abdominal distention, lethargy, hypovolemic shock, and anuria.** Therefore, **any episode of bilious emesis in a neonate should prompt an urgent evaluation for malrotation and volvulus. The presence of bloody emesis or stools suggests intestinal ischemia with mucosal injury or necrosis.** In this setting, rapid diagnosis and prompt surgical intervention is essential to avoid extensive bowel loss or death (Box 28.2).

LABORATORY DATA

Plain abdominal radiographs may show a dilated stomach and proximal duodenum, or rarely pneumoperitoneum in the presence of advanced intestinal necrosis. However, the **definitive study is an upper gastrointestinal series, which shows both abnormal rotation of the duodenum (malrotation) and partial obstruction** (from Ladd bands), or complete obstruction with a bird's beak, suggesting midgut volvulus. A contrast enema may show an abnormal location of the cecum but is not diagnostic alone of malrotation and provides no information about the presence or absence of midgut volvulus.[64] **Abdominal ultrasound, although user dependent, can be used to identify a midgut volvulus without the need to expose the infant to radiation and reveals a twisting** (i.e., target sign) **of the mesentery, a "whirlpool sign," and abnormal relationship of the mesenteric vessels.**[29,37,43] However, this modality is less sensitive for malrotation without volvulus. **Laboratory data are generally unremarkable, unless bowel ischemia is present, as suggested by leukocytosis, anemia, and metabolic acidosis.**

Treatment

PREOPERATIVE CARE

Although distinguishing between symptomatic malrotation with obstruction (e.g., Ladd bands) and volvulus in its early stages may be difficult, these conditions should be managed similarly. **Gastric decompression, fluid resuscitation, correction of electrolyte and acid–base abnormalities, and parenteral antibiotics are instituted in the preoperative period. Emergent abdominal exploration should be considered in any infant with suspected or confirmed volvulus, because the bowel will be irreparably damaged in as little as 4 hours.** In this setting, prompt surgical intervention with continued intraoperative resuscitation is indicated to maximize the chances for bowel salvage and survival.

OPERATIVE CARE

Operative correction of malrotation without midgut volvulus includes division of Ladd bands (to relieve duodenal obstruction), correction of the malrotation (by placement of the small bowel in the right of the abdominal cavity and the colon on the left), broadening the base of the mesentery by dividing its peritoneum and adhesions, and appendectomy (the appendix and cecum will reside in the left upper quadrant). **This procedure is best performed via laparotomy, and a laparoscopic approach has limited utility in the newborn.** The long-term results of the laparoscopic approach are unknown, and preliminary results are conflicting. More recent studies comparing laparoscopy and open laparotomy found better short-term results (i.e., shorter time to full feedings and shorter length of stay) in the laparoscopy group.[32,49,104] However, there is a higher incidence of postoperative volvulus recurrence in the laparoscopic group (30% recurrence of symptoms versus 40% in the laparotomy group) and a 100% need for surgery to be redone compared to 50% in the laparotomy group.[11,32] Although researchers conclude that laparoscopic surgery is a safe, acceptable option, all agree that more research is needed.[11,32,49,63,104]

If volvulus is present, the bowel is detorsed and allowed to reperfuse (Fig. 28.10). Necrotic segments of bowel are resected and stomas created as indicated. **In selected instances, substantial resection may result in short bowel syndrome.** In these cases, **marginal intestine may be left in place rather than removed and a planned reoperation performed within 24 to 36 hours to re-evaluate the need for additional bowel resection.** The **objective of a second look laparotomy is to allow continued resuscitation and marginally viable intestine the necessary time to recover.** Bowel that is nonsalvageable will become more obviously nonviable within this time window but should not have perforated in this short period. This approach is designed to minimize the amount of total intestine resected and the late risk for short bowel syndrome.

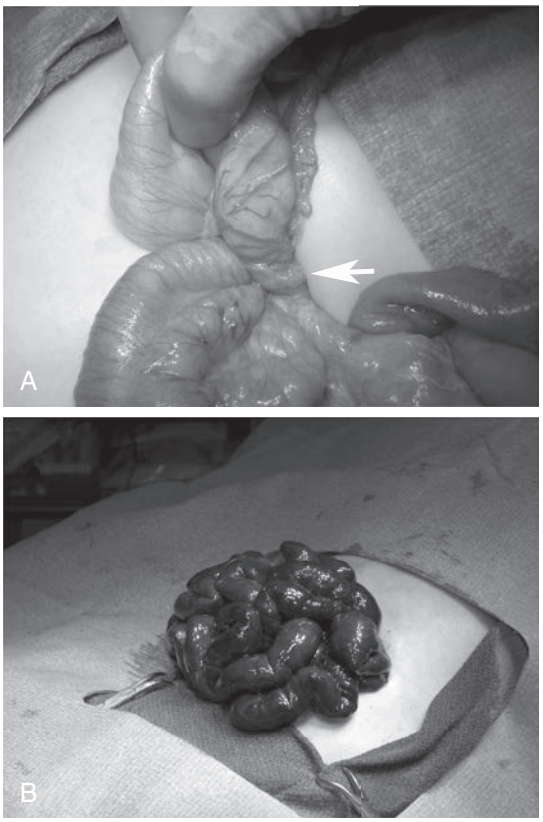

FIGURE 28.10 Two extremes of malrotation with midgut volvulus in newborns. **A,** Volvulus that presented before intestinal ischemia set in. *Arrow* shows 720-degree volvulus. Bowel is entirely viable. **B,** Delayed presentation of midgut volvulus with complete necrosis of intestine, a nonsurvivable injury.

Complications and Prognosis

Proximal obstruction related to Ladd bands is corrected by the Ladd procedure, and recurrent

obstruction is rare. **The risk for subsequent volvulus is greatly reduced with the Ladd procedure but is not entirely eliminated.** Adhesive small bowel obstruction may occur later in life at the same rare incidence as after any other laparotomy.

The **immediate postoperative care from a Ladd procedure consists of nasogastric decompression and IV fluid therapy until the return of gastrointestinal function (4 to 6 days on average).**[31] Conversely, the outcome after malrotation with midgut volvulus is predicated on the degree of intestinal resection.[73] **Midgut volvulus is a leading cause of short bowel syndrome in infants and may render the infant TPN dependent if extensive intestinal necrosis has occurred.** Long-term sequelae of the Ladd procedure include the risk of adhesive small bowel obstruction and a failure to prevent recurrent midgut volvulus, albeit exceedingly uncommon.

INTESTINAL ATRESIA

Physiology and Etiology

Any segment of the bowel may be narrowed (stenosis) or become discontinuous (atresia). Duodenal atresia is the most commonly involved bowel segment, occurring in 1 in 7000 pregnancies,[111] **followed by ileum, jejunum, colon, and stomach.**[55,98]

Sporadic duodenal atresia is thought to result from failure of vacuolization (5 to 6 weeks of gestation) and recanalization (8 to 10 weeks of gestation) of the intestinal lumen; however, a genetic component may also exist.[12] A vascular accident or segmental volvulus occurring later in utero is thought to give rise to jejunal, ileal, or colonic atresia.[92] **Duodenal atresia associated with syndromes is increasingly recognized as having a strong genetic component related to fibroblastic growth factor.**[12,111] **Duodenal atresia is associated with a high incidence (30%) of anomalies that include trisomy 21 (61% in a recent cohort),**[55] **congenital heart disease, and VACTERL association.**[41] **Conversely, intestinal atresia occurs later in gestation and so is rarely associated with significant anomalies.** Atresias are classified as membranes (type I), fibrous cords (type II), gap defect including mesentery (type IIIa), and "apple-peel" atresia (type IIIb).[118] Multiple atresias are classified as type IV.

BOX 28.3 CRITICAL FINDINGS
INTESTINAL ATRESIA

Critical assessment findings for intestinal atresia are:
- Maternal polyhydramnios
- Emesis (nonbilious versus bilious depending on location of atresia)
- Abdominal radiograph suggestive of intestinal obstruction
- Abdominal radiograph with "double bubble" suggests duodenal atresia

Data Collection

HISTORY AND PHYSICAL EXAMINATION

Commonly, a history of maternal polyhydramnios may be provided and the affected neonate may appear small for gestational age (SGA). The more proximal the site of intestinal atresia, the more likely is the history of maternal polyhydramnios. **Newborns having a proximal atresia (duodenum or jejunum) present with early feeding intolerance and emesis and also a scaphoid abdomen. Bilious emesis is present when the obstruction is distal to the ampulla of Vater, as is the case in approximately 85% of duodenal atresias.** However, in **15% of cases, duodenal atresia occurs proximally to the ampulla of Vater and therefore the baby does not show bile-stained emesis or gastric aspirates.**

The more distal the site of atresia and obstruction, the more likely it is that the infant will manifest significant abdominal distention. Babies having a **distal intestinal atresia (ileum or colon) show typical features of a distal intestinal obstruction and develop abdominal distention often with visible intestinal loops.** If the **atresia occurs early in gestation, the infant fails to pass meconium and only mucus is passed after birth** (Box 28.3).

LABORATORY DATA

Initial evaluation of **suspected duodenal atresia begins with a plain abdominal radiograph (flat and left lateral decubitus views), which classically shows a dilated air-filled stomach and proximal duodenum in the double bubble pattern.** A contrast study is not indicated unless air is present in the distal bowel, in which case malrotation with midgut volvulus cannot be excluded. Ultrasound is an adjunctive diagnostic test.[10]

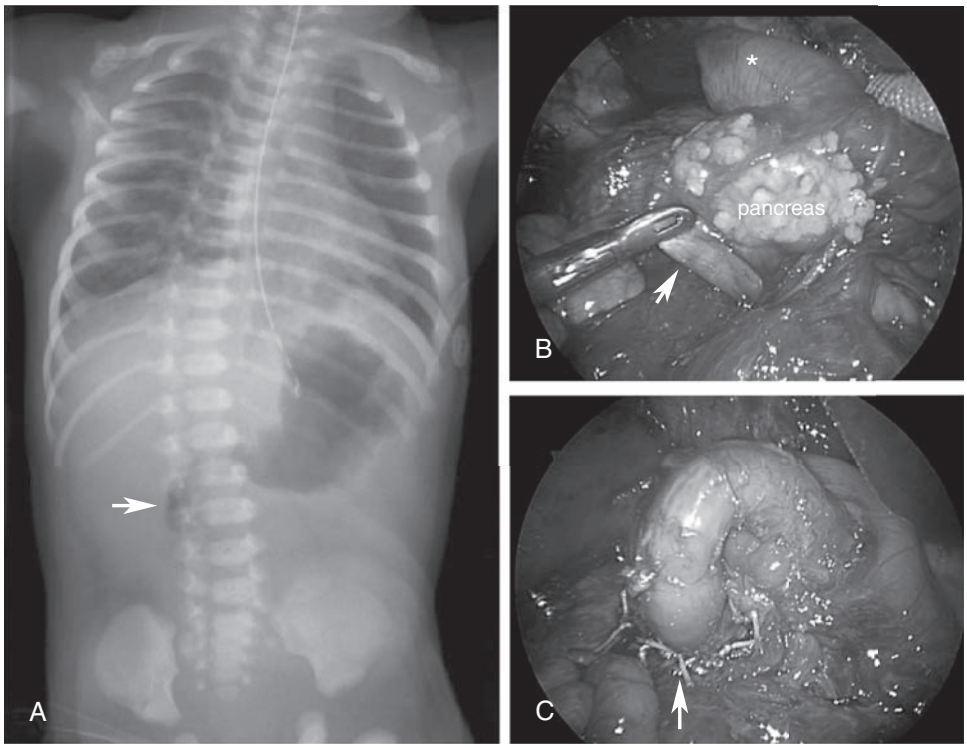

FIGURE 28.11 Duodenal atresia in a newborn. **A,** Abdominal radiograph shows classic "double bubble" sign. Orogastric tube is in stomach, and *arrow* shows air-filled proximal duodenum. **B,** Laparoscopic view of duodenal atresia. *Asterisk* depicts proximal dilated duodenum (compressed by instrument) and *arrow* shows small distal duodenum being elevated by a 3-mm bowel grasper. **C,** Completed anastomosis *(arrow)*.

Abdominal x-ray films that show multiple distended loops of bowel suggest a distal intestinal obstruction. In the setting of **atresia of the small intestine or colon, abdominal x-ray films demonstrate dilation of intestinal segments proximal to the site of obstruction with absence of air in the distal bowel.** For intestinal atresia distal to the duodenum a contrast enema (i.e., per rectum) is generally performed[10] and typically shows a microcolon or unused colon, and no reflux of the contrast agent into the proximal bowel is observed.

Treatment

PREOPERATIVE CARE

Preoperative care includes **orogastric tube decompression to reduce the risk of vomiting and aspiration, fluid resuscitation, and correction of electrolyte abnormalities. Preoperative antibiotics are administered to cover enteric organisms.**

OPERATIVE INTERVENTION

All forms of intestinal atresia require surgical correction to restore gastrointestinal tract continuity. Duodenal atresia is repaired through a diamond-shaped, end-to-end anastomosis of the proximal and distal duodenum, and care must be exercised to prevent injury to the bile and pancreatic ducts. Repair of duodenal atresia may be performed either through a standard transverse right upper quadrant incision or laparoscopically (Fig. 28.11). A recent systematic review and meta-analysis of laparoscopic repair of duodenal atresia found it as safe and effective (i.e., no difference in complications, time to feeding, or length of stay) as laparotomy but with longer operative time.[72] Other intestinal atresias are generally repaired by a standard end-to-end anastomosis. The size disparity between the dilated proximal loop and the decompressed distal loop may require that the proximal bowel be tapered or partially resected, or the distal

bowel may be cut obliquely to allow anastomosis (Fig. 28.12). If these methods are not possible because of size discrepancy, the segments just proximal and distal to the atresia may be brought out as stomas and intestinal anastomosis delayed to allow reduction in size of the dilated proximal segment and growth of the distal segment. When the caliber of the bowel becomes more comparable in size, anastomosis is performed.

POSTOPERATIVE CARE

Postoperatively, an orogastric tube remains in place to decompress the stomach until bowel function begins. Stomas must be protected from desiccation by covering with petrolatum gauze or a stoma appliance. **Ostomies of the proximal intestine have high output because of a lack of absorptive capacity and therefore require replacement of both fluid and electrolyte losses.** The proximal output may be re-fed into a distal mucous fistula, if present, but this technique may be challenging because of problems intubating the distal stoma and securing the feeding catheter to permit infusion. **All infants endure a significant period of bowel dysfunction after surgery, and therefore temporary central venous access should be established to permit nutritional support.** Furthermore, infants with intestinal atresia should undergo screening for cystic fibrosis, which may contribute to both the development of the anomaly and ongoing bowel dysfunction.

Complications and Prognosis

The overall prognosis for these patients is excellent, unless severe associated anomalies are present.[89] **Postoperative complications are also associated with prematurity, sepsis, wound infection, and hypothermia.**[55,89,98] **Prolonged bowel dysfunction is the primary complication after surgical correction of intestinal atresia.** In selected cases, tapering of dilated bowel segments is attempted to enhance the recovery of bowel function.[102] **Some infants fail to recover sufficient bowel function and require long-term parenteral nutritional support,** because of either dysmotility or inadequate bowel length resulting from long segment atresia. Fortunately, **the majority of patients have no long-term problems after postoperative recovery and return of bowel function.**

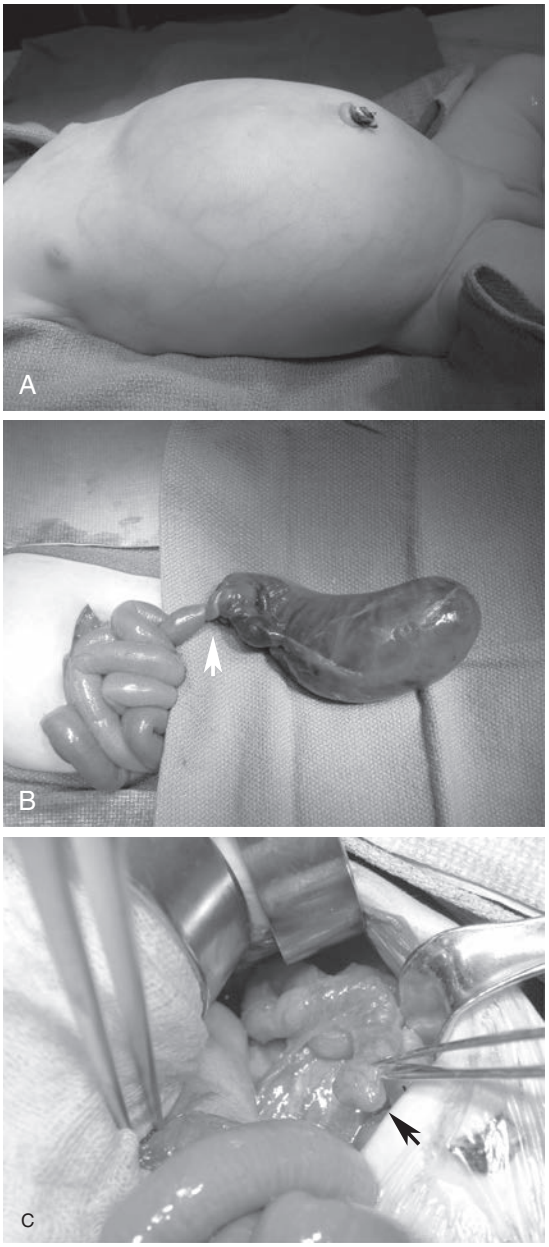

FIGURE 28.12 Newborn with colon atresia. **A,** Markedly distended abdomen. **B,** Atretic colon that has volvulized. *Arrow* shows twist, and note ischemic nature of volvulized colon. **C,** Distal microcolon elevated by forcep *(arrow)*.

NECROTIZING ENTEROCOLITIS

Physiology and Etiology

Necrotizing enterocolitis (NEC) is an inflammatory condition of the bowel of uncertain cause and occurs at a rate of 1 in 1000 live births and in 5% of infants born weighing less than 1500 g (very low birth weight [VLBW]). **NEC is fatal in 17% of all cases, in 20% of VLBW infants who develop the disease, and as high as 40% to 50% in those infants with a birth weight less than 1000 g. NEC is primarily a disease of premature infants, although approximately 5% of cases occur in term babies.** Despite intensive study, major advances in newborn intensive care, and improved survival of the preterm infant in the last two decades, the incidence of and mortality associated with NEC has changed little. **In fact, the increase in survival of preterm infants has increased the size of the population at risk. Perinatal stressors, an immature intestinal barrier, intestinal ischemia, bacterial colonization of the gut, alteration of the intestinal microbiome (intestinal dysbiosis),**[82] **and nutritional substrate in the gut lumen have all been implicated as contributing factors at play in infants who develop NEC.** Other **conditions that result in mucosal injury also have been linked to NEC: hypoxia, polycythemia, hyperosmolar feedings, gastrointestinal infection (bacterial or viral), and severe cardiopulmonary disease.** Current research using animal models implicates upregulation of multiple inflammatory mediators in the injured intestinal epithelia affected by NEC, and the presence of certain anti-inflammatory mediators may be cytoprotective.[48,88]

Inflammation and ischemia initially involve the innermost intestinal mucosa, but as the disease progresses, the muscular and subserosal layers of the bowel become involved. The intestinal wall becomes hemorrhagic and attenuated, with evidence of intramural gas (pneumatosis). Histologically after surgical resection, the intestine shows features of acute and chronic inflammation, with areas of coagulative necrosis. The ileocecal region is most commonly involved (50%), followed by disease limited to the colon (25%) or both large and small intestines (25%). Up to 15% of infants will develop pan-intestinal necrosis, or NEC totalis, which is a nonsurvivable insult. In NEC totalis, gastric pneumatosis, though rare, may be seen on x-ray (Fig. 28.13). Further, **NEC is a significant risk factor for developing short bowel syndrome chronically, if less than 40 cm of small bowel remains in the absence of the ileocecal valve, or in its presence, if less than 20 cm of bowel remains.**

There have been significant efforts to prevent the onset of NEC by modifying the feeding regimens in premature infants. One simple measure to decrease the incidence of NEC is feeding with breast milk instead of formula. In a review of several randomized clinical trials, **breastfed infants had a lower incidence of NEC compared to formula-fed infants.**[22,67,68,87,117] Furthermore, an exclusive human milk diet including fortification with human milk fortifier significantly reduces the incidence of NEC.[4,107] **When compared to preterm formula, donor human milk results in a lower incidence of NEC** (see Table 18.6). In addition to breast milk, **the addition of probiotics (*Lactobacillus acidophilus* and *Bifidobacterium infantis*) to the feeding regimen decreases the incidence of NEC.**[6,19,25,60,108]

Data Collection

HISTORY AND SIGNS AND SYMPTOMS

The **onset of NEC is heralded by the development of feeding intolerance, abdominal distention, and bloody stools in a premature infant receiving enteral feedings.** A history of perinatal hypoxia, respiratory distress, congenital heart disease, or indomethacin administration for PDA closure often is elicited. As **the disease progresses, the infant develops signs and symptoms of septic shock (lethargy, respiratory distress, temperature instability, hypotension, and oliguria). Examination reveals a distended and tender abdomen that may demonstrate erythema, induration, and pitting edema in severe cases** (Box 28.4).

LABORATORY DATA

Complete blood count and serum electrolyte evaluations typically reveal thrombocytopenia, leukocytosis or leukopenia, and metabolic acidosis, respectively. C-reactive protein (CRP) levels are increasingly obtained and appear to be a good marker of onset, persistence, and subsequent resolution of NEC. Stool tests may be positive for occult blood and reducing substances

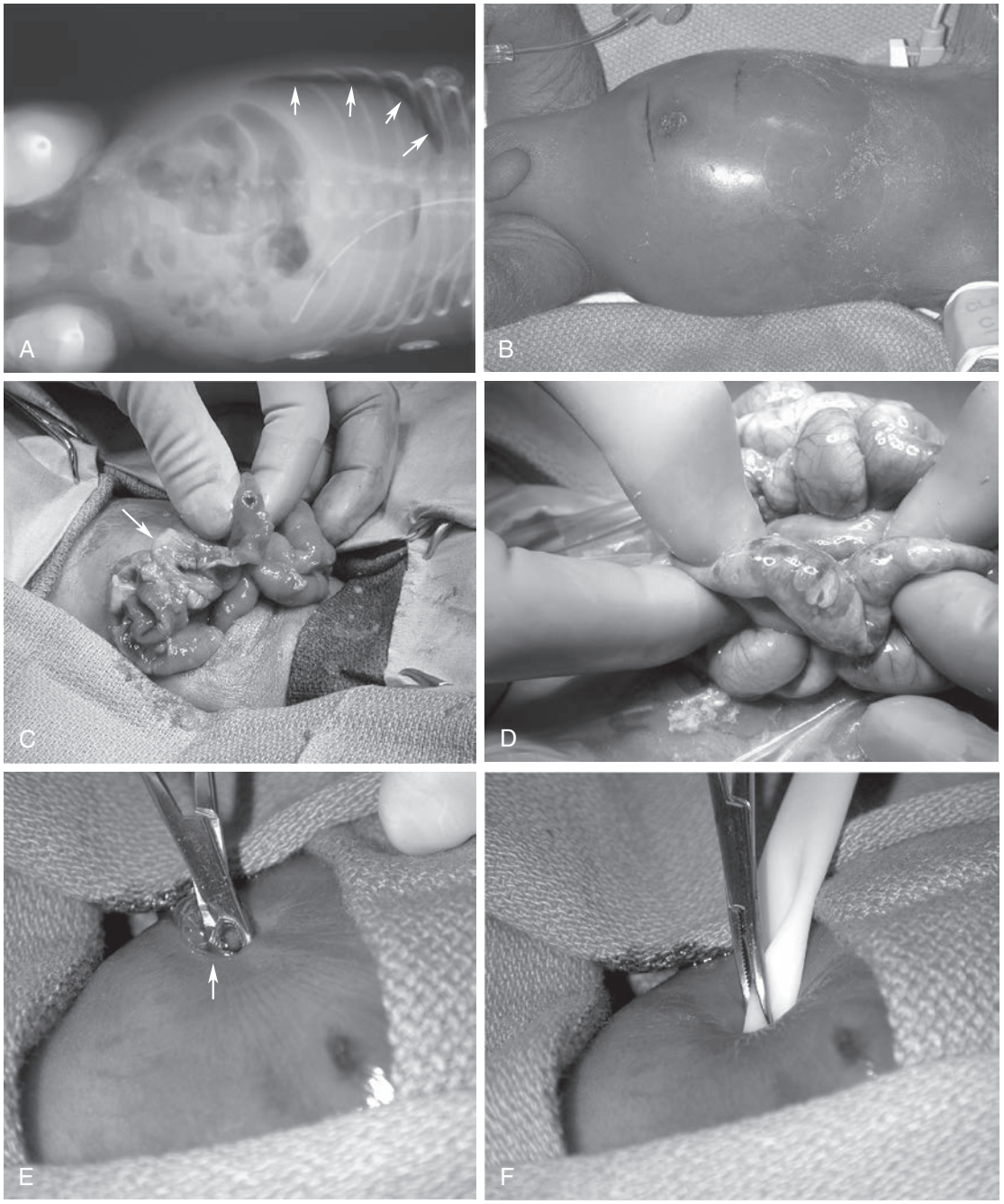

FIGURE 28.13 Several different examples of necrotizing enterocolitis (NEC) in ELBW infants. **A, B,** Pneumoperitoneum on abdominal radiograph (*arrows* in **A**); **B,** Same baby. Note abdominal distention and discoloration. **C,** Findings of NEC at laparotomy: perforation is shown between surgeon's fingers. *Arrow* shows segment of gangrenous bowel. Bowel toward surgeon's middle finger is normal. **D,** Example of pneumatosis intestinalis; this baby had pan-intestinal necrosis. **E, F,** Placement of peritoneal drain in the neonatal intensive care unit (NICU). *Arrow* shows release of pneumoperitoneum (bubbles).

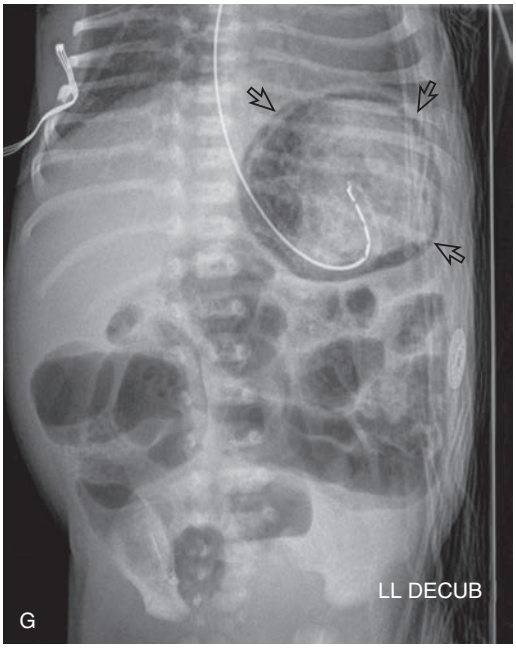

FIGURE 28.13, cont'd. **G**, Gastric pneumatosis instestinalis is a rare finding for NEC, but when present, it indicates a grave prognosis. A lateral decubitus radiograph demonstrates air outlining the stomach *(arrows)* and not collecting in the nondependent portion, confirming intramural, not intraluminal, air.

BOX 28.4 CRITICAL FINDINGS
NECROTIZING ENTEROCOLITIS

Critical assessment findings for necrotizing enterocolitis are:
- Feeding intolerance
- Abdominal distention
- Bloody or hemoccult-positive stools
- Thrombocytopenia, leukocytosis, leukopenia, and metabolic acidosis
- Pneumatosis intestinalis on abdominal radiograph
- Free air on abdominal radiograph in the presence of perforated viscus

in more than 50% of cases. The diagnostic test of choice is the three-way abdominal x-ray series (i.e., flat, left lateral decubitus, and in some instances, cross-table views). Plain radiographs are carefully reviewed for the characteristic finding of pneumatosis intestinalis, or intramural bowel gas. The radiograph should be assessed for free air (pneumoperitoneum), which would suggest intestinal perforation. Other findings may include dilated bowel, portal venous gas, ascites, or a fixed bowel loop that does not change on repeated studies.

A recent systematic review and meta-analysis of the use of bowel ultrasound (US) examination for NEC found usefulness in early identification of high-risk infants with NEC who might benefit from more aggressive treatment, including surgery.[24] More research is needed to establish whether bowel US improves outcomes. Abdominal ultrasonographic evidence of complex fluid collection is predictive of severe NEC requiring surgery.[81]

Treatment

PREOPERATIVE CARE

The only absolute and immediate indication for surgical intervention is intestinal perforation, which may be detected radiographically by the finding of pneumoperitoneum. In a clinically stable infant without findings of perforation, medical management consisting of bowel rest, fluid resuscitation, broad-spectrum antibiotic therapy, and total parenteral nutrition (TPN) is indicated.[90] The infant is monitored carefully (serial abdominal examinations and radiographs every 8 hours) for signs of intestinal gangrene. More than half of infants respond to medical management, but up to 30% of infants treated medically may develop an intestinal stricture requiring surgical management.

A subset of infants continues to deteriorate clinically despite maximal medical therapy, suggesting intestinal gangrene without intestinal perforation. Presence of intestinal gangrene should be considered in infants having persistent metabolic acidosis, thrombocytopenia, leukopenia, refractory shock, erythema of the abdominal wall, or a fixed, dilated intestinal loop on plain x-ray of the abdomen.[69,116]

OPERATIVE INTERVENTION

The principle of surgical management is to resect all necrotic bowel while preserving as much of the intestinal length as possible. In cases of extensive bowel involvement, only necrotic segments of intestine are removed and rarely reoperation at 12 to 24 hours may be planned (a second look). After bowel resection, proximal and distal ostomies are created, and the abdomen is thoroughly irrigated to reduce bacterial and fecal contamination. In severely

premature infants weighing less than 1000 g, primary peritoneal drainage (PPD) to decompress the abdomen after intestinal perforation may be performed in the NICU as an alternative to laparotomy. PPD and laparotomy may have comparable survival rates, but interestingly, infants treated with PPD have substantial improvement in residual bowel length, which may be in part because up to one third of these patients do not require further operative therapy.[26] **Infants with extremely low birth weight (<1000 g) who received PPD had higher survival rates when compared to laparotomy.**[110] A more recent study comparing PPD versus laparotomy for the initial surgery for NEC in infants weighing less than 1000 g at birth found that laparotomy increased the risks of short bowel syndrome without a shorter length of stay or in-hospital survival advantage.[125] Nevertheless, **laparotomy provides more definitive therapy and further aids in establishing the extent of diseased bowel,** which, if NEC totalis is discovered, may reduce futile care. In most cases, **PPD should be considered a temporizing means, or "bridge to laparotomy," to allow complete resuscitation before definitive surgery** (see Fig. 28.13).

POSTOPERATIVE CARE

After laparotomy, **supportive care (i.e., resuscitative fluids, TPN, antibiotics) and bowel rest are continued for 10 to 14 days. At 2 weeks postoperatively, low-osmolar elemental feedings or breast milk may be started once intestinal motility has returned and advanced as tolerated.** A stoma closure procedure is planned for as early as 6 to 8 weeks after the initial surgery. All infants should undergo a preoperative contrast enema before ostomy closure to make certain the intestine and colon distal to the ostomy have not strictured.

Complications and Prognosis

Stomal prolapse or retraction, wound infection, intraabdominal abscess, and intestinal obstruction are early complications. Recurrent NEC is uncommon, but may occur in approximately 5% of infants treated medically or surgically. The **most significant late complication is that of inadequate intestinal length (short bowel syndrome) and the need for long-term parenteral nutrition.** Preservation of the ileocecal valve is critically important to slowing intestinal transit and thereby limiting sequelae of short bowel syndrome. **Babies at highest risk for short bowel syndrome have the ileocecal valve but less than 20 cm of small intestine or have no ileocecal valve and less than 40 cm of small bowel.** For infants treated medically, nearly one third will develop a distal intestinal stricture, most commonly in the colon, that requires operative intervention to resect and to restore intestinal continuity and function. **Survival in infants weighing more than 1000 g has improved from 50% to 80% over the last two decades. Severely premature infants weighing less than 1000 g still have a mortality rate in excess of 51%.**[8,93]

MECONIUM ILEUS

Physiology and Etiology

Meconium ileus is an intestinal obstruction caused by hyperviscous secretions from the intestinal glands coupled with an insufficient excretion of pancreatic enzymes necessary to help digest intestinal contents. The result is tenacious, viscous meconium that creates a sticky plug obstructing the lumen of bowel. The obstruction generally occurs within the terminal ileum, mimicking ileal atresia. **More than 90% of infants with meconium ileus have cystic fibrosis,** a three base pair deletion on chromosome 7.[83] This autosomal recessive gene defect results in alteration of the chloride channel transporter, and therefore fluid flows across the apical surface of epithelial cells. **Meconium ileus occurs in 10% to 25% of patients with cystic fibrosis83,95; prenatally, 20% of mothers develop polyhydramnios. A family history of cystic fibrosis is present in 10% to 30% of cases.**

This ileus of retained meconium is in contrast to **meconium plug syndrome, which manifests as a failure to pass stool with obstruction in the colon and is not specific to cystic fibrosis. Meconium plug syndrome is generally recognized as immaturity of the ganglion cells and generally is benign.**[52] **Rectal dilation and/or contrast enema usually result in passage of the meconium plug(s),** and recurrence is uncommon; however, significant obstruction can develop with rare incidences of perforation. **Meconium plug syndrome, again in contrast to meconium ileus, is associated with Hirschsprung disease in 13% of cases.**[52] A more recent single-center study of meconium plug syndrome found no link with Hirschsprung disease or magnesium tocolysis.[23]

BOX 28.5 CRITICAL FINDINGS
MECONIUM ILEUS

Critical assessment findings for meconium ileus are:
- Abdominal distention
- Bilious emesis
- "Soap bubble" appearance of the bowel on abdominal radiograph
- Microcolon on barium enema

Data Collection

SIGNS AND SYMPTOMS

Meconium ileus is classified as simple (obstruction and obturation) or complicated (volvulus, intestinal atresia, perforation, meconium peritonitis). Uncomplicated meconium ileus presents as distal ileal obstruction caused by inspissated meconium (pellets) and proximal intestinal dilation. The onset of symptoms associated with simple meconium ileus begins 24 to 48 hours after birth. Bilious emesis, progressive abdominal distention, and the failure to pass meconium suggest intestinal obstruction.[83] The differential diagnosis in addition to meconium ileus includes ileal atresia, meconium plug, and Hirschsprung disease.

Physical examination shows a patent anus that may express a small amount of gray meconium. Examination of the abdomen reveals moderate distention with a characteristic doughlike sensation on palpation because of the thickened meconium contained in the dilated bowel. Complicated meconium ileus often manifests more abruptly and progresses more quickly. Symptoms include abdominal distention within 24 hours of birth, respiratory distress (especially if a postnatal perforation has occurred), and an edematous, erythematous abdomen[83] (Box 28.5).

LABORATORY DATA

Abdominal radiograph demonstrates a "soap bubble" appearance of the bowel caused by trapped gas within the meconium and also shows large dilated (with air) loops of bowel with few air-fluid levels because of the viscous nature of the meconium. A contrast enema shows a microcolon and pellets of inspissated meconium at the site of distal obstruction. If in utero perforation has occurred, microcalcifications also may be present on plain abdominal radiographs.

Treatment

PREOPERATIVE CARE

If meconium ileus is suspected, orogastric decompression, IV hydration, and electrolyte replacement are instituted; once appropriately hydrated, a diluted diatrizoate (Gastrografin) or iothalamate meglumine (Cysto-Conray) enema should be attempted.[83] Note that the infant should be adequately hydrated before the enema because of the hyperosmolarity of Gastrografin and Cysto-Conray. Intracolonic instillation of these water-soluble agents draws fluid into the bowel lumen, diluting the viscous meconium and facilitating passage, and may be therapeutic to relive the obstruction. **If the Gastrografin enema results in incomplete evacuation, it may be repeated over the next several days.** However, if the **Gastrografin enema fails to result in passage of meconium, complicated meconium ileus or ileal atresia may be present and operative intervention is indicated.**[83]

OPERATIVE INTERVENTION

The goal of operative treatment is to relieve intestinal obstruction. For uncomplicated meconium ileus, several operative approaches are described to eliminate the obstructing inspissated meconium. Techniques include (1) enterotomy with extraction of the tenacious meconium and irrigation of the bowel with saline solution or 2% N-acetylcysteine (Mucomyst), (2) resection of the affected segment with anastomosis, and (3) formation of chimney ostomies just proximal to the obstruction (Bishop-Koop procedure: bowel is divided to create an ostomy of the distal ileum for continued irrigations; an internal anastomosis of the proximal to distal ileum is fashioned to maintain intestinal continuity). More commonly now, a T-tube enterostomy may be created, in which a soft and small caliber tube is securely placed within the bowel lumen and delivered through a separate wound in the abdominal wall (Fig. 28.14). This tube, like the chimney ostomy, allows continued postoperative irrigations with normal saline or diluted Mucomyst to complete or maintain passage of intestinal contents. In uncomplicated meconium ileus, T-tube enterostomy is as safe and effective as the Bishop-Koop

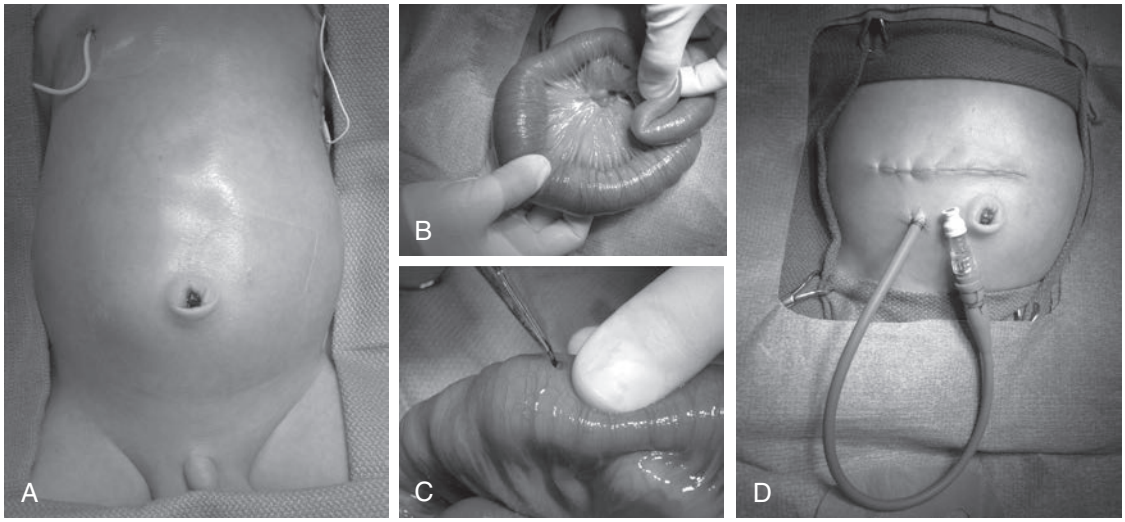

FIGURE 28.14 Newborn with meconium ileus as presenting feature of cystic fibrosis. **A,** Abdominal distention and visible intestinal loops on physical examination. **B,** Equal pressure is being applied to the bowel by both hands of the surgeon. Note how noncompressible the bowel in the right hand is secondary to the inspissated meconium. **C,** Note viscosity of meconium being teased out of the bowel lumen. **D,** After irrigation with Mucomyst and evacuation of the meconium, a tube enterostomy is placed for continued irrigation in the weeks following surgery. Once the baby's bowel is completely cleared of meconium and a full diet is tolerated, the tube may be removed.

procedure.[44] If complicated meconium ileus is identified, the obstructed segment is resected and ostomies are performed to permit postoperative irrigation. **Ostomy closure usually is performed 4 to 6 weeks later.**

POSTOPERATIVE CARE

Postoperatively, nasogastric tube decompression, nutritional support, and irrigation of the rectum or ostomies with saline solution or N-acetylcysteine (Mucomyst) are instituted. Once gastrointestinal function returns, feedings using breast milk (see Chapter 18), predigested or elemental formula, and pancreatic enzyme supplements are started. The diagnosis of cystic fibrosis is confirmed with genetic analysis or sweat chloride testing.

Complications and Prognosis

One-year survival for infants with simple or complicated meconium ileus is favorable (greater than 90%), but long-term survival is limited primarily because of the pulmonary complications of cystic fibrosis.[77] Late gastrointestinal complications of cystic fibrosis include distal intestinal obstruction syndrome (meconium ileus equivalent), appendicitis, intussusception, rectal prolapse, intestinal stricture, pancreatitis, and cholestatic liver disease.[83] A history of meconium ileus is associated with decrease in bone density and fat mass when compared to children and adolescents without meconium ileus.[27]

HIRSCHSPRUNG DISEASE

Physiology and Etiology

Hirschsprung disease is a congenital intestinal disorder caused by a lack of ganglion cells in the bowel wall, principally the colon, which disrupts and abrogates effective peristalsis. A genetic variant is associated with the development of Hirschsprung disease in early fetal life.[42,109,123] During development, neural crest cells (the progenitor or stem cells of the enteric nervous system) migrate along the intestinal tube to populate the entire gut in a craniocaudal fashion, with the distal colon, rectum, and sphincter being the last to be colonized. These progenitor cells divide, differentiate, and proliferate to form the enteric nervous system, of which the ganglion cells are a critical component. Arrest of migration, proliferation, and differentiation

results in the aganglionosis found in Hirschsprung disease, which is a relatively common cause of distal intestinal obstruction in the newborn. **At the site of arrest, a transition from normal to abnormal innervation is present, and all intestine distal to this site will be aganglionic and therefore dysfunctional. The result is a functional obstruction that mimics mechanical intestinal obstruction. In brief, the pathophysiologic consequence of the absence of ganglion cells is failure of the involved rectum and colon to relax, and therefore the fecal stream cannot be passed effectively through the aganglionic region and beyond. Rectosigmoid aganglionosis is most common (85%), with the remainder of patients developing variable lengths of more proximal colonic and, rarely, small intestine disease. Total colonic aganglionosis occurs in roughly 10% of cases.**

Hirschsprung disease occurs in 1 of 5000 live births, having a 4:1 male-to-female predominance. The majority of cases are sporadic (80% to 90%), but familial occurrences are well-recognized and multiple genetic alterations have been identified in affected pedigrees. Associated anomalies are rare in sporadic cases but may be seen in as many as 25% of the familial cases. **Babies born with Down syndrome also carry a higher incidence of Hirschsprung disease than the population at large (2%), and between 5% and 10% of Hirschsprung patients will have Down syndrome.**

Approximately 15% of Hirschsprung neonates will present with meconium plug syndrome (MPS), an obstruction of the colon by inspissated meconium. However, in general, MPS is associated with immature ganglion development and is not indicative of the more serious Hirschsprung disease.

Data Collection

SIGNS AND SYMPTOMS

Ninety-eight percent of normal infants pass meconium in the first 24 to 48 hours of life. Failure to pass meconium early, feeding intolerance, and abdominal distention suggest a diagnosis of Hirschsprung disease. In some babies having a short segment of aganglionic bowel, spontaneous evacuation of stool may be noted, and the infant may appear otherwise healthy. **If vomiting, abdominal distention, and constipation (or paradoxic diarrhea resulting from watery stool escaping around the obstipated stool) continues, further investigation is indicated.** Hirschsprung disease may rarely escape detection during the newborn period, and in older children a history of refractory and chronic obstipation may be the only symptom. **Approximately 5% to 10% of affected infants will present with a picture of enterocolitis (toxic megacolon), characterized by fever, vomiting, abdominal distention/tenderness, foul-smelling diarrhea, and septic shock.** The infant may rapidly deteriorate, with a 50% risk of death if the colon is not rapidly decompressed, either by transanal soft rubber tube irrigations or emergency colostomy. Fortunately, in most cases of Hirschsprung disease, the infant is only mildly ill, allowing time for definitive diagnostic studies before surgical correction is undertaken (Box 28.6).

BOX 28.6 CRITICAL FINDINGS
HIRSCHSPRUNG DISEASE

Critical assessment findings for Hirschsprung disease are:
- Failure to pass meconium within 48 hours of birth
- Feeding intolerance
- Abdominal distention
- Enterocolitis (fever, abdominal distention, foul-smelling diarrhea, sepsis)
- Transition zone on barium enema
- Absent ganglion cells and nerve hypertrophy on rectal biopsy

LABORATORY DATA

The diagnostic evaluation begins with a contrast enema.[10,65] Surgical dogma states that when entertaining the diagnosis of Hirschsprung the first enema should be a contrast enema. This study typically shows a contracted or spastic rectosigmoid colon, with contrast material entering the proximal dilated bowel. The area between the contracted and dilated bowel is called the transition zone.[17] **If the contrast enema is equivocal, an abdominal x-ray film should be obtained on the next day to evaluate extent of retained contrast material. Significant contrast material retained within the distal colon and rectum suggests the presence of Hirschsprung disease. Definitive diagnosis is made by performing a bedside suction rectal biopsy, a well-tolerated procedure in neonates that does not require any analgesics or sedatives. On histology, a biopsy diagnostic of Hirschsprung shows an absence of ganglion**

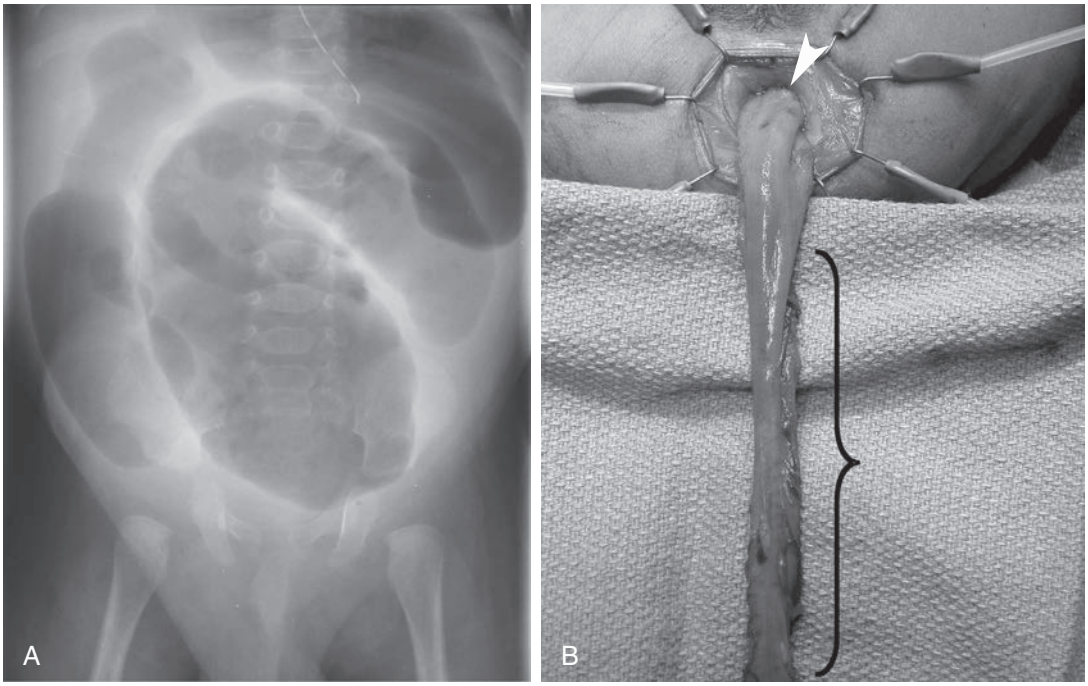

FIGURE 28.15 Newborn with Hirschsprung disease. **A**, Plain abdominal radiograph shows distal intestinal obstruction 2 days after birth in a neonate who has failed to pass meconium. Note absence of gas in rectum/pelvis. **B**, After laparoscopic mobilization and transanal mucosectomy, the diseased bowel may be delivered through the anus. The *bracket* denotes the contracted, aganglionic bowel. *Arrowhead* shows biopsy performed laparoscopically that confirms region of ganglionated bowel. Coloanal anastomosis was performed at this level.

cells and the presence of hypertrophic nerve trunks within the submucosal and intermyenteric plexus. Special immunohistochemical staining is commonly performed by the pathologist to corroborate the diagnosis. Conversely, if ganglion cells are observed on histologic examination, a diagnosis of Hirschsprung disease is excluded.

Treatment

PREOPERATIVE CARE

In infants having Hirschsprung-associated enterocolitis, orogastric tube decompression, IV fluid resuscitation, broad-spectrum antibiotics, and correction of acid-base deficits and electrolyte abnormalities are promptly initiated. Infants who are less ill with symptoms of obstruction are placed on NPO (nothing by mouth) status, and IV antibiotic therapy and orogastric decompression are instituted, permitting time to complete the diagnostic evaluation. Once the diagnostic evaluation is completed, transanal rectal irrigations, not enemas, are performed twice daily until surgery. Babies should have return to normal bowel function with these irrigations and may be fed enterally (so long as rectal irrigations continue) until definitive surgery.

OPERATIVE INTERVENTION

In the presence of profound enterocolitis, an emergency colostomy may be indicated. If necessary, a colostomy is performed at a site of normal bowel (ganglion cells present), as confirmed by a frozen section histologic examination. In selected cases, the neonate will be too ill, so operative time is minimized by the creation of a right-sided colostomy, because most affected babies have more distal colonic involvement. If the neonate presents with milder symptoms, one of several surgical options may be selected: (1) primary laparoscopically assisted endorectal pull-through (Fig. 28.15), (2) primary transanal pull-through, or (3) staged reconstruction (temporary colostomy at the most distal site

of ganglion cells, followed by a pull-through in 3 to 6 months).[97] **In all cases, multiple intestinal seromuscular biopsies are created at the time of operation until the normally innervated bowel is identified. A coloanal anastomosis or colostomy is performed at the site of histologically proven normal bowel. If the anastomosis or colostomy site is missing ganglion cells, the neonate will remain symptomatic—the bowel will not function normally because of aganglionosis.**

Several factors influence the decision to perform a primary pull-through procedure in neonates.[97] The neonate should be of sufficient gestational age and size (generally more than 2 kg), have rectosigmoid disease as demonstrated by contrast enema, not have significant proximal bowel distention, and not have evidence of advanced enterocolitis. Neonates who do not meet these criteria should be treated in a staged manner, with an immediate colostomy and a pull-through procedure (with or without laparoscopy assist) delayed until later in infancy.*

POSTOPERATIVE CARE

The recovery period is generally straightforward, and supportive care is provided until the return of bowel function. **For babies treated initially with colostomy, postoperative care includes teaching the parents about stoma maintenance and hygiene** (Box 28.7). The pull-through procedure entails resecting abnormal aganglionic bowel and bringing ganglionic bowel to the anus. Several variations of the pull-through operation have been described; each has unique advantages and disadvantages, but in general the results are similar regarding long-term stooling patterns. **For neonates having a primary laparoscopically assisted endorectal pull-through, first stool is usually passed within 24 to 48 hours of the procedure, at which time breast milk or Pedialyte may be introduced. Feeds may be advanced to goal (according to tolerance) over the next 24 to 48 hours. Perianal skin care with various barriers is critical in the early postoperative period to prevent excoriation, because defecation is frequent and poorly controlled at this stage of convalescence.** Moreover, **no transanal manipulation (i.e., temperature probes or suppositories) should be performed until after 4 weeks from the date of surgery.**

*References 84, 124,125, 141.

BOX 28.7 INSTRUCTIONS FOR OSTOMY CARE

Supplies

Skin-prep (United)*
Stoma-adhesive paste (ConvaTec)*
Ostomy setup (skin wafer and bag)
Pattern for stoma

Application Instructions

1. Measure the diameter of the stoma, using the measuring guide circle enclosed in the wafer box.
2. Trace the appropriate circle onto the white paper backing of the wafer and cut out the hole. Gently bend and slightly stretch the opening with your finger. The goal is to have the hole 1/16 to 1/8 inch larger than the stoma. A snug but not constricting fit is needed to prevent stool leaking onto the skin.
3. Clean and dry the skin around the stoma.
4. Apply a generous coat of Skin Prep (United) on the skin around the stoma.
5. Apply a thin border of stoma-adhesive paste (ConvaTec) around the stoma.
6. Press wafer firmly to skin.
7. If using a two-piece appliance, snap on the bag and close the end of the bag with a clip or rubber band if it is open-ended. If using a one-piece appliance, the appliance may be applied directly to the skin or to a skin barrier such as stoma-adhesive (ConvaTec).*

Helpful Hints

1. Change the appliance as soon as there is any evidence of leaking!
2. Rinsing the bags with some type of scented soap (peppermint or spice) will help cut down on the bag odor.
3. Precut several wafers ahead of time.
4. When traveling, always have an extra set of clothes and a complete set of supplies, as well as a new setup with stoma holes already cut.

*Other products may be used in place of the brand names upon recommendation of medical supplier, physician, or nurse.
Courtesy Kris Altzenbeck, R.N., The Children's Hospital, Denver, Colo.

Complications and Prognosis

In a recent population-based study spanning an 18-year period, the mortality rate for Hirschsprung disease was less than 2% during the first year of life.[3] Early complications of the pull-through operation include inadequate blood supply to the coloanal anastomosis, anastomotic stricture, anastomotic dehiscence, and cuff abscess. **Later complications include Hirschsprung-associated enterocolitis,**[40]

obstruction,[57] perianal skin excoriation, and recurrent constipation. The infant usually thrives postoperatively and grows normally. It is not uncommon for the infant to have frequent stools during the immediate postoperative period, which gradually normalize in frequency. However, some children, despite a technically satisfactory operation, will experience recurrent constipation requiring some form of bowel management program with or without placement of a colostomy tube (i.e., Chait button) for antegrade enemas.[122]

ANORECTAL MALFORMATIONS

Physiology and Etiology

Anorectal malformations (ARM) encompass a broad spectrum of hindgut anomalies, from isolated imperforate anus in boys and girls, which may include fistulous communications between the urogenital tract and rectum, to the complex persistent cloaca in females. Although the development of the cloaca and its subsequent septation into urogenital and anorectal tracts is not well understood, each organ system is recognizable as a separate entity by the seventh week of gestation. Therefore, persistent cloaca in females arises from an arrest in development of the gut and its complete separation from urogenital tract between the fourth and sixth weeks of gestation. Cloacal exstrophy arises if disruption of the cloacal membrane occurs before the urorectal septum has separated the urinary bladder from the hindgut. Disruption of the cloacal membrane after septation results in exstrophy of the bladder only. Any insult occurring at this critical period of organogenesis places a number of organ systems at risk and accounts for the fact that 60% of infants with cloaca will have concomitant anomalies.[46,61] A genetic predisposition may also exist.[61]

Imperforate anus is the most common ARM, occurring in 1 in 5000 live births, and predominantly affects males (58%) more than females (42%).[61] Imperforate anus is characterized as low, intermediate, or high, and termination of the rectal fistula varies according to gender. The higher the defect, the more likely the presence of other associated malformations. A high imperforate anus is defined as the end of the rectum terminating above the levator ani muscles. Conversely, in low imperforate anus, the rectum descends below the levator complex. A fistulous connection to the perineum or urogenital tract is almost always present. In high lesions, the rectal fistula enters the membranous urethra in the male or rarely the vagina in the female.[61] In low lesions the rectal fistula empties on the perineum of both boys and girls or the posterior fourchette of the introitus, the most common site in girls.[61,84] Congenital VACTERL anomalies and trisomy 21 are common and require further evaluation. Moreover, a high incidence of spinal dysraphism is observed with anorectal malformation; imaging of the spine is indicated.[61]

Data Collection

SIGNS AND SYMPTOMS

Most anorectal malformations are apparent on physical examination of the newborn but may be missed if a careful inspection of the buttocks and anus is not performed. Once the diagnosis is made, a fistula should be sought. In low lesions there may be a thin membrane over the anal orifice, or there may be a fistula along the perineum and scrotal raphe of boys. In girls, the fistula most commonly terminates in the vestibule or fourchette of the introitus. If meconium passes in the urine of boys or, rarely, from the vagina, a high lesion is present. If the condition remains unrecognized, the infant develops signs and symptoms of distal intestinal obstruction. Down syndrome babies having an ARM usually (95%) have a high type variant of rectal atresia without genitourinary tract communication (Box 28.8).

LABORATORY DATA

A plain abdominal radiograph may show features of distal intestinal obstruction without rectal gas, but it will not reliably show termination of the rectum. Perineal ultrasonography, a colostography,[10,61] may be used to establish the termination of the rectum and its distance from the skin, data that may help operative planning. In boys having imperforate anus without a perineal fistula, a contrast study of the urethra should delineate a rectourethral fistula, if present. In girls without a perineal or vestibular fistula, a contrasted genitogram may help define the anatomic relationships of a persistent cloaca. A perineal fistula visible on physical examination does not usually

BOX 28.8 CRITICAL FINDINGS
IMPERFORATE ANUS

Critical assessment findings for imperforate anus are:
- Absence of anus or presence of anteriorly displaced perineal fistula.
- Signs and symptoms of obstruction if diagnosis not made.
- Perineal ultrasound study will identify the level of defect in the absence of a perineal fistula.

warrant imaging of ARM. However, because of the possibility for VACTERL association, echocardiography and abdominal sonography of the genitourinary tract are indicated, as is a plain radiograph of the spine and limbs.

Treatment

PREOPERATIVE CARE

The infant should be kept NPO while evaluation of ARM is underway, and an orogastric tube should be placed to exclude EA and decompress the stomach. If a fistula is present on the perineum or at the fourchette, an early anoplasty may be performed, assuming the baby has no associated cardiac anomaly and is otherwise deemed to be a suitable candidate for a general anesthetic. If early repair is contraindicated, then a perineal fistula tract may be dilated twice daily to promote elimination of fecal contents and until the baby is a more suitable candidate for surgery. If no fistula is visualized and a high lesion or cloaca is present, a divided colostomy is performed and staged reconstruction is planned for later in infancy.

OPERATIVE INTERVENTION

For low imperforate anus, early reconstruction is performed either in the newborn period or in the first months of life, if the infant can produce stools adequately through the fistulous tract with dilations. After colostomy for high imperforate anus, a formal repair is undertaken when the child is 3 to 6 months of age. Approached most commonly through a posterior sagittal incision (buttock), the fistula is separated from the urethra in boys or vagina in girls, and the rectum is mobilized to lie within the center of the sphincter mechanism. The levator muscles and sphincter are closed anteriorly and posteriorly around the rectum, which is then anastomosed to the perineal skin in a procedure known as a posterior sagittal anorectoplasty (PSARP, or Pena procedure).[85] Alternatively, to minimize wound complications and postoperative pain, a laparoscopic-assisted anorectoplasty may be performed (Fig. 28.16). A Foley catheter always should be placed in boys at time of the definitive repair to assist in separation of the rectum from the urethra and to facilitate bladder drainage in the postoperative period; this catheter will be in place typically for 7 to 14 days after PSARP.

POSTOPERATIVE CARE

After anorectoplasty, simple skin care is all that is necessary, and a program of anal dilation is instituted 14 days postoperatively, which will continue for 4 to 6 months. After a colostomy, stoma care and teaching are begun with the parents. Colostomy closure will be performed within 6 to 8 weeks of PSARP, assuming the neoanus is of adequate size and not strictured.

Complications and Prognosis

Mechanical complications of the stoma (prolapse, stenosis, and skin breakdown) may arise but generally do not require revision and should be temporized until stomal closure. Urinary tract infection (UTI) or hyperchloremic metabolic acidosis may result from the fistulous connection of the rectum to the urinary tract. Antibiotic prophylaxis is instituted, and selected infants may require bicarbonate supplement until the fistula is divided.

Constipation is the primary long-term problem after correction of low imperforate anus.[61] Stricture of the anoplasty should always be considered and may be treated with anal dilation or rarely revision anoplasty.

High imperforate anus is most often complicated by incontinence (or pseudoincontinence) and frequent soiling. Long-term results are influenced by the degree of sphincter muscle development and innervation. Approximately 75% have voluntary bowel movements, 50% have soiling episodes, 40% have voluntary bowel movements and no soiling, and 25% have fecal incontinence.[61] Bowel programs and strategies have been developed to permit some degree of social continence so that permanent colostomy can be avoided.[61]

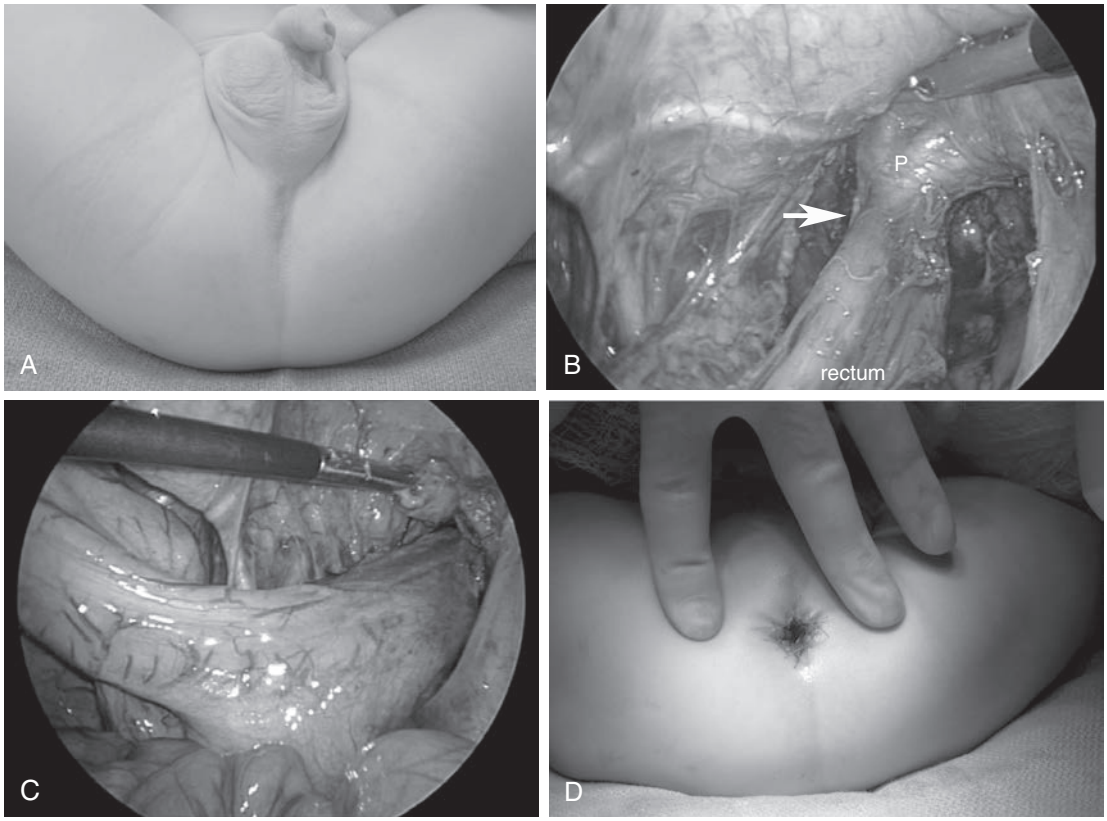

FIGURE 28.16 Male neonate with an anorectal malformation and rectourethral fistula. **A,** Flat perineum without cutaneous fistula. **B,** Laparoscopic view of pelvic structures after dissection. *Arrow* shows rectourethral fistula at level of prostate *(P)*. **C,** Fistula has been divided and ligated (held by 5-mm grasper), and rectum has been delivered through the center of the sphincter complex for colocutaneous anastomosis. **D,** Neoanus.

OMPHALOCELE AND GASTROSCHISIS

Physiology and Etiology

Omphalocele and gastroschisis are distinct defects of the abdominal wall at or near the umbilicus. **Omphalocele is characterized by the persistent herniation of the abdominal viscera through the umbilical ring, and the herniated contents are covered by the normal components of the umbilical cord: the peritoneum, Wharton jelly, and amnion.** Omphalocele, also known as exomphalos, is a defect in abdominal wall development that may result from failure of embryonic enfolding as early as 4th to 7th weeks of gestation or from failure of closure of the exocelomic space, which is usually completed by the 12th week of gestation. **Fifty percent of neonates presenting with omphalocele will have an underlying chromosomal abnormality, most often trisomies 12 and 18 but also trisomy 21.**[16] **Congenital heart lesions, including pulmonary hypertension, are seen in as many as 50% of these affected infants.** Congenital syndromes involving an omphalocele are potentially lethal, usually as a result of the associated abnormalities. Cloacal exstrophy, occurring in 1 in 200,000 pregnancies and the constellation of defects known as the *pentalogy of Cantrell* likely represent the earliest of embryonic failure in the development of this spectrum of anomalies, including omphalocele.

Gastroschisis is a full-thickness defect of the abdominal wall that occurs most commonly

to the right of the umbilicus and exposes the extruded bowel to the amniotic fluid without a natural covering as seen with omphalocele. It has been hypothesized that this defect results from a weakening of the anterior abdominal wall because of a vascular accident involving the right omphalomesenteric artery, which takes over perfusion of the anterior abdominal wall during the seventh week of gestation. Gastroschisis occurs three to four times more frequently than omphalocele, and its incidence is rising in developed countries for unknown reasons.[99] This increasing incidence seems to be occurring in younger mothers, most frequently in those younger than 20 years, although no clear epidemiology has been correlated with this finding. Gastroschisis typically is not associated with major congenital anomalies or syndromes, although 5% to 10% of affected infants have a concomitant intestinal atresia.[16] This atresia is likely secondary to either the initial vascular accident thought to initiate the defect or compromise of the affected bowel segment arising from a constricting fascial defect.

Nonrotation of the intestine, by definition, is uniformly present in all incidences of these two conditions.

HISTORY

Abdominal wall defects are readily diagnosed by antenatal ultrasonography, which is helpful in planning future delivery and therapy. Spontaneous or induced vaginal delivery should be considered in most cases of gastroschisis, because minimal risk of bowel injury during delivery exists.[33,53,35] Babies having an omphalocele may be delivered vaginally, but liver herniation or associated anomalies may dictate cesarean section.

In cases of gastroschisis, severe serositis resulting from exposure of the bowel to amniotic fluid makes closure more difficult and delays the return of bowel function. Early delivery may be recommended for certain fetuses with gastroschisis, if sonographic evidence reveals progressive bowel distention and thickening, suggesting intestinal obstruction or severe serositis.

In cases of omphalocele, prenatal sonography should thoroughly evaluate the fetus for other potential anomalies and may be supplemented by fetal MRI.

BOX 28.9 CRITICAL FINDINGS
OMPHALOCELE AND GASTROSCHISIS

Critical assessment findings for omphalocele and gastroschisis are:
- Typically detected on antenatal ultrasound examination.
- Eviscerated bowel without peritoneal covering in gastroschisis.
- Eviscerated bowel with peritoneal covering in omphalocele.
- Diagnosis of omphalocele necessitates search for other associated anomalies.

SIGNS AND SYMPTOMS

Both anomalies present as a mass of abdominal contents extruding through an anterior abdominal wall defect. Eviscerated bowel without a peritoneal covering characterizes gastroschisis, whereas an omphalocele is defined by a peritoneal covering of herniated bowel and often a segment of liver. Gastroschisis defects are most commonly to the right of the midline and are found adjacent to the umbilical stalk, whereas omphalocele occurs through a central defect at the base of the umbilical cord.

In contradistinction to gastroschisis, omphalocele importantly carries a high incidence of associated anomalies, and cardiac and/or urinary tract malformations are most prevalent. Omphalocele also is a feature of several recognizable syndromes, including Beckwith-Wiedemann, prune belly, cloacal exstrophy, and pentalogy of Cantrell. Chromosomal defects are identified with greater frequency in cases of omphalocele than gastroschisis and include trisomies 13, 18, and 21. Most babies having an omphalocele will deliver at term.

Gastroschisis in contrast is associated with few anomalies outside of the gastrointestinal tract. Malrotation is understood to exist with gastroschisis, and so the most common associated anomaly is intestinal stenosis or atresia (10% to 15%), a rare finding in omphalocele. Babies having gastroschisis are more commonly preterm and small for gestational age (Box 28.9).

LABORATORY DATA

In a neonate having omphalocele, a careful search for associated anomalies is performed before closure is attempted. Echocardiography

and an x-ray examination of the chest and spine are performed to rule out cardiac, chest wall, diaphragmatic, and spinal anomalies. **Abdominal sonography** is obtained to evaluate integrity of the urinary tract. **Gastroschisis newborns do not require routine radiographic evaluations unless otherwise indicated.**

Treatment

PREOPERATIVE CARE

Initial management of gastroschisis includes preservation of body heat and fluid, orogastric decompression, protection of the intestine, and prophylaxis against infection. Covering the exposed viscera minimizes heat and fluid loss. Placing the infant's torso into an impermeable, clear plastic bowel bag is the preferred method to prevent fluid loss. Historically wrapping the bowel in saline-soaked gauze has been advocated. However, if not done properly this method can result in constriction in the blood supply and ischemia to the intestine. **Positioning the infant on his or her side prevents "kinking" of the mesentery at the fascial level and prevents intestinal ischemia.**

IV fluids and broad-spectrum antibiotics should be instituted early. Administration of adequate isotonic IV fluids is essential to the perioperative care of infants with gastroschisis. Given the insensible fluid losses, these infants may require a minimum of 150 mL/kg/day of total fluids. A Foley catheter to measure accurate urine output in the first 24 to 48 hours of life may be useful to modify the fluid requirements of the infant. To prevent bowel distention, an orogastric tube is placed to low continuous suction. In omphalocele, because the abdominal contents are covered naturally, less evaporative and heat losses are encountered.

OPERATIVE INTERVENTION

Rarely, an infant with omphalocele may be too ill (i.e., from pulmonary hypertension or a congenital heart anomaly) to undergo early abdominal closure or may have other lethal malformations or may have a "giant omphalocele," defined as the sac containing a significant portion of the liver (Fig. 28.17). **Under these circumstances precluding early closure, the newborn is given palliative care with a daily application of a dessicant or 1% silver sulfadiazine to the abdominal sac.** The result is eschar formation and subsequent epithelialization in 10 to 20 weeks. After epithelialization has occurred, **gentle compression can be placed on the omphalocele to reduce the contents back into the abdomen. This compression can be accomplished with an elastic wrap or a specially made brace,** which further protects the omphalocele. The brace works to compress the omphalocele to skin level at a safe rate (Fig. 28.18). A large ventral hernia will remain, and the repair may be performed later in infancy. If the infant is allowed to grow without compression, risk arises for progressive "mushrooming" of the sac and loss of abdominal domain, which make subsequent definitive fascial closure highly complex.

Cases of omphalocele not having liver herniation or significant associated anomalies may have the sac removed and primary fascial closure accomplished shortly after birth, or, at a minimum, simple skin closure may be performed, with ventral hernia repair scheduled for later in infancy once abdominal domain has been restored. Some cases of omphalocele will require biosynthetic fascial substitutes to accomplish visceral coverage.

For babies born with gastroschisis, primary surgical repair entails reduction of the herniated abdominal contents into the peritoneal cavity without increasing abdominal pressure to a point that ventilation, venous return, and intestinal blood supply are compromised. If the amount of eviscerated abdominal contents is small or moderate, primary repair is simple and safe. Before closure of gastroschisis, the surgeon searches carefully for associated atresia but may or may not attempt to restore intestinal continuity during the initial operation. If atresia is identified but inflammation and matting of the intestine will not permit safe anastomosis, the atretic bowel may be placed within a silo or returned to the abdomen primarily, and re-exploration may be planned for 4 to 6 weeks later to allow the thickened, edematous bowel wall to normalize, facilitating anastomosis or enterostomy. If atresia is found, but the bowel is not inflamed or matted, intestinal continuity may be restored at the initial operation or an ostomy created, with plans for delayed reconstitution 4 to 6 weeks later.

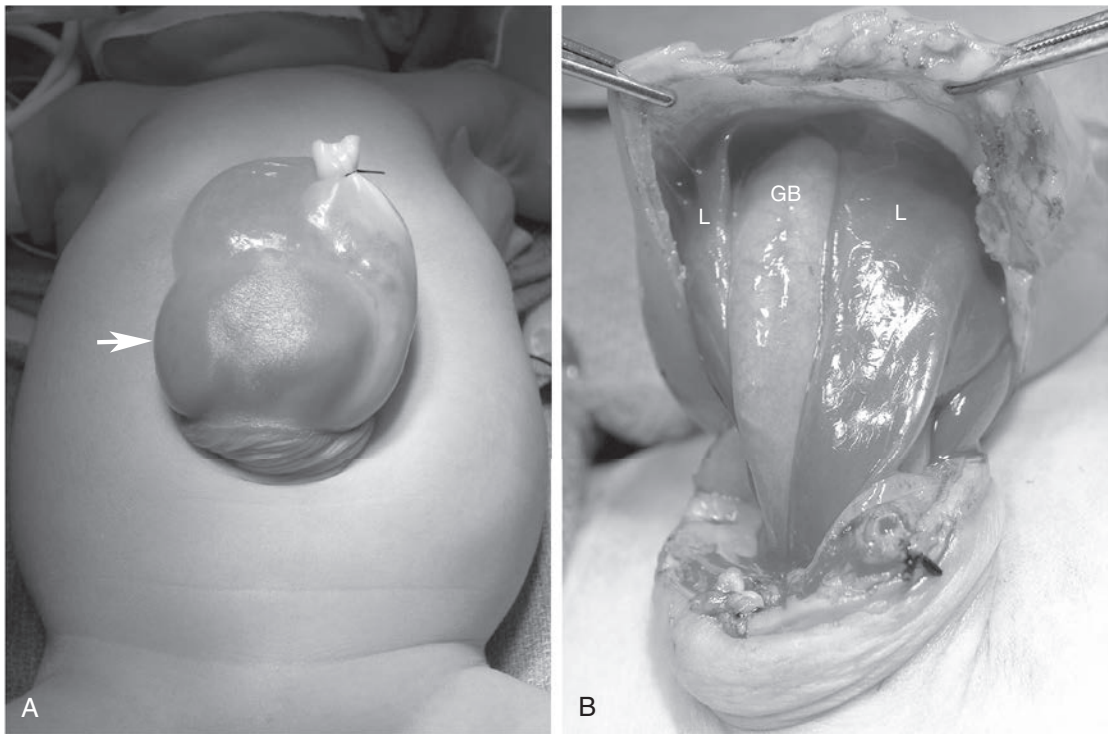

FIGURE 28.17 Neonate with omphalocele. **A,** *Arrow* shows liver contained within omphalocele sac. **B,** Dissection of sac contents. Liver is adherent to lining of sac. Fascial defect was closed primarily. *GB,* Gallbladder; *L,* liver.

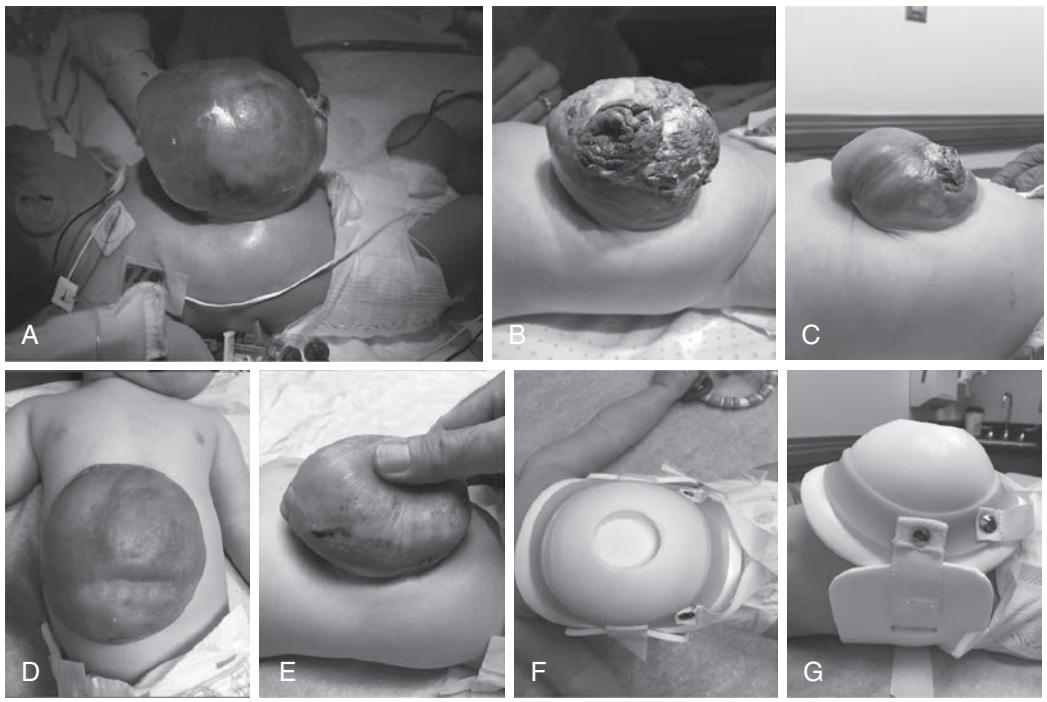

FIGURE 28.18 **A–J,** Neonate born at 31 weeks of gestation with a giant omphalocele. **B–E,** Baby had application of 1% silver sulfadiazine until epithelialization was complete. **F, G,** A protective brace was fitted after complete epithelialization, allowing for safe compression of hernia contents to skin level over time.

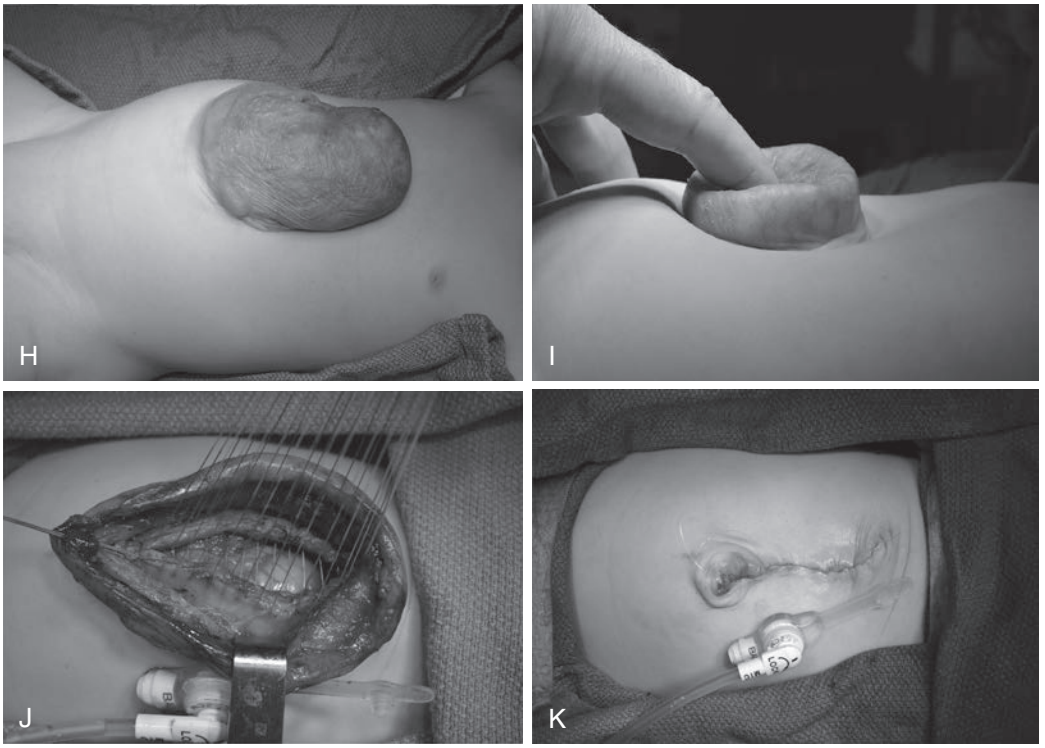

FIGURE 28.18, cont'd. **H, I,** Contents completely reducible to skin level preceding surgical closure. **J, K,** Operative closure that included gastrostomy placement.

In selected cases, the fascial defect may have to be enlarged to allow replacement of the herniated organs into the abdomen because of the small size of the fascial ring, loss of abdominal domain, and the amount of intestinal herniation. The inability to perform primary closure necessitates placement of a **Silastic silo or patch to permit staged reduction** (Fig. 28.19). **Over the ensuing 2 to 7 days, the herniated viscera are gradually returned to the abdomen on a daily basis by gravity (baby remains supine) and by applying gentle and constant pressure to the silo at the bedside (umbilical tape is tied sequentially along the silo until the intestine has reached the fascial level). Once all of the silo contents have been successfully reduced, the infant is returned to the operating room for removal of the silo and closure of the fascia.**[96] **While a silo is in place and for a short period after definitive fascial closure, most neonates will remain on antibiotics.**

Complications and Prognosis

Bowel injury, respiratory compromise, and diminished venous return caused by abdominal hypertension may complicate recovery after primary fascial closure of abdominal wall defects. In this setting the infant is returned to the operating room for placement of a silo. Rarely, a silo may become infected or separate from the fascia, complicating closure by this method.

Recovery of bowel function is uniformly delayed, especially in gastroschisis caused by exposure of the bowel to amniotic fluid. A central venous catheter should be placed at the time of initial surgery for long-term TPN support.[119] Intestinal stricture, incisional hernia, and adhesive bowel obstruction are possible short- and long-term complications.[91] **The principle long-term morbidity associated with gastroschisis is short bowel syndrome.** Morbidity for omphalocele is principally secondary to any associated

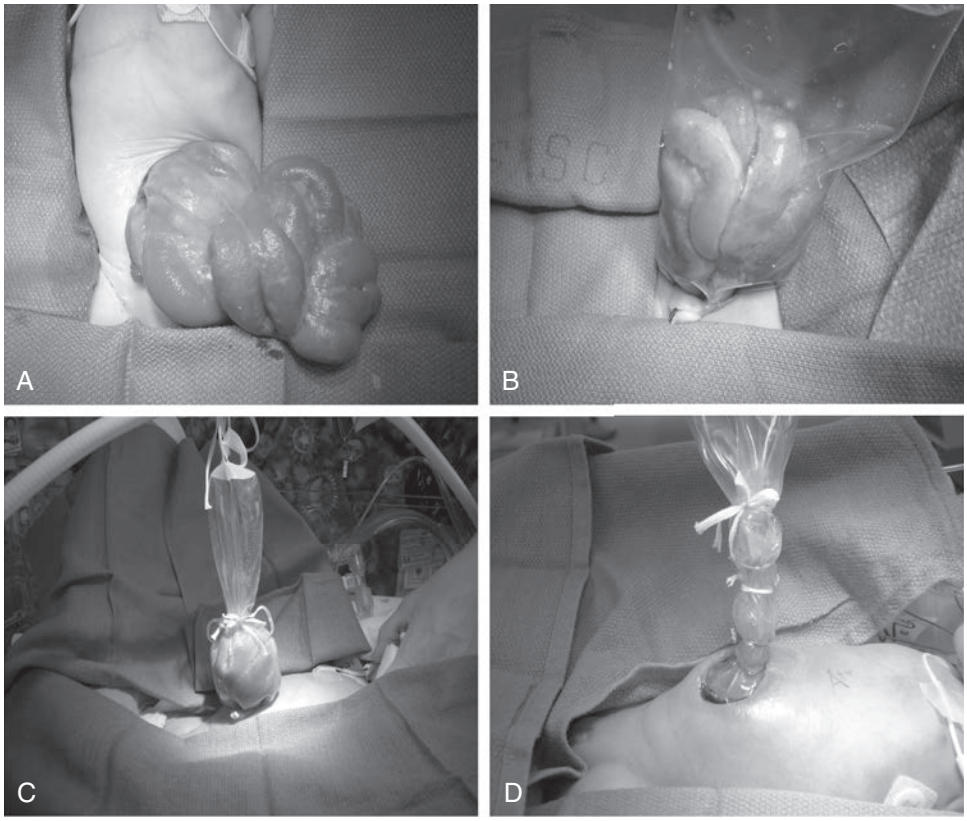

FIGURE 28.19 Neonate with gastroschisis. **A, B,** Note edema and thickening and matting of bowel. Also, note scaphoid appearance of abdomen (loss of domain). As a result, bowel was placed in a Silastic silo. **C,** Postoperative day 1 after placement of silo. Note how the edema has largely drained from the bowel wall (gravity) and how much of the silo contents has reduced spontaneously. The first umbilical tape is placed to prevent bowel from rising in the silo. **D,** Postoperative day 5 (an umbilical tape is applied each day in the nursery), and the bowel has fully returned to the abdomen. The fascia is now ready for closure.

anomalies and the challenges of abdominal closure. **Otherwise, prognosis for both types of abdominal wall defects should be good, unless, again, severe associated malformations are present.**

NEONATAL TUMORS

Neonatal tumors are discovered in every 12,500 to 25,000 live births and account for 2% of all childhood malignancies.[74] The majority of affected neonates present with a mass at birth or within the first month of life, which may or may not have been identified on prenatal screening. **The two most frequently encountered neonatal tumors are teratoma (principally sacrococcygeal [Fig. 28.20] but also cervical [Fig. 28.21]) and neuroblastoma.** Soft tissue sarcomas, infantile myofibromatosis (benign mesoblastic nephroma and malignant Wilms tumor),[7] hepatoblastoma, and CNS tumors follow in frequency. **Malignant tumors rarely arise in the newborn, yet some benign tumors encountered at birth may acquire malignant features later in infancy.** Nevertheless, although a neonatal tumor may be histologically benign, these **tumors may be life-threatening because of size, location, arteriovenous shunts, or rupture with hemorrhage.** Some tumors show invasive or infiltrative characteristics, yet these may not have metastatic potential. Furthermore, screening programs have identified potentially malignant tumors earlier in development, such as for neuroblastoma in Japan,

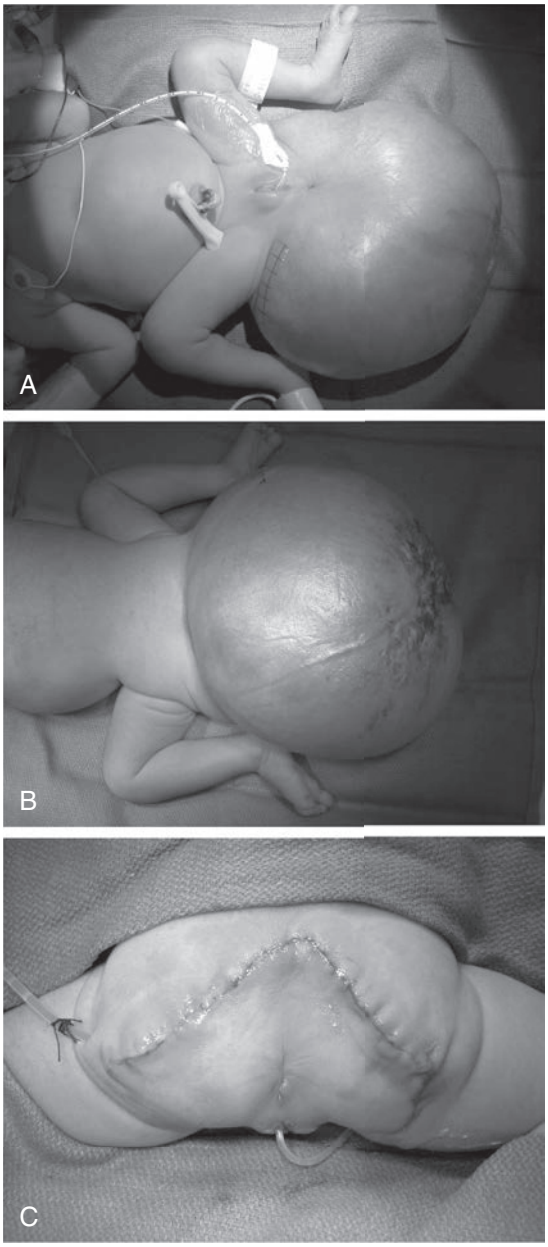

FIGURE 28.20 Female neonate with a huge sacrococcygeal teratoma. **A,** Anterior view. Note anal opening in anterior and just caudal to introitus. **B,** Posterior view. **C,** Immediately after resection. Incision will soften over time.

but have as yet failed to improve overall survival. Some neonatal tumors even show the potential for spontaneous regression. Taken together, neonatal tumors represent a protean mix of diseases that have a low malignancy potential yet the biologic and pathophysiologic behavior may not be entirely predictable.

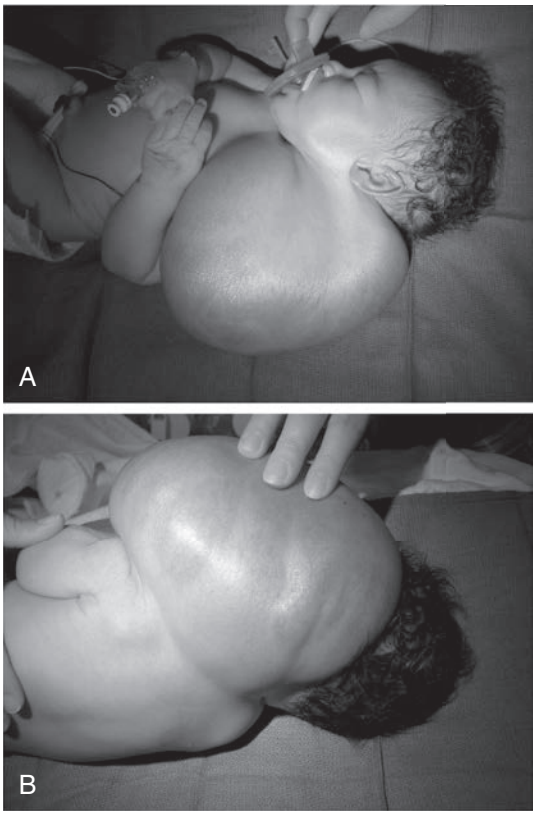

FIGURE 28.21 Huge cervical cystic hygroma. Teratomas show a similar appearance but tend to be more midline than hygromas. Anterior **(A)** and posterior **(B)** views.

The etiology of solid malignancies in infants and children is an area of great interest.[15] Many of these **"congenital" tumors are classified as embryonal tumors because of retained features of embryonic development within the organ in which each tumor arises. Carcinomas, typical of adulthood, are virtually nonexistent in neonates.** Under the microscope, many of these embryonal tumors show a recapitulation of cell types found in early embryonic development of the particular organ, but terminal differentiation of the progenitor cells has not been completed, and so no functional tissue architecture is appreciated. **Associated anomalies may be found in 15% of neonates having congenital tumors, and genetic defects are also relatively prevalent in babies with neonatal tumors.**

Routine prenatal ultrasonography has contributed to an increasing diagnosis of fetal and neonatal tumors. Interestingly, **several fetal tumors, particularly neuroblastoma, have a unique property to undergo spontaneous regression and involution by 12 months of age.** A recent study by the Children's Oncology Group in infants younger than 6 months with small adrenal masses showed that the majority of these lesions will resolve spontaneously without the need for operative intervention.[80]

Commonly, fetuses harboring an embryonal or germ cell tumor will be identified on antenatal US screening.[18,78] Some **tumors, in particular sacrococcygeal teratomas, may be so large as to cause dystocia or may present a significant risk for rupture during delivery, and either scenario could be disastrous.** Further, **a cervical teratoma or cystic hygroma may cause airway obstruction at birth.** Fetuses with these occasionally **huge cervical tumors should be delivered by cesarean section, undergo bronchoscopy, and be intubated before clamping of the umbilical cord, referred to as an EXIT procedure (EX-utero Intrapartum Therapy).**[86] The tumor then may be resected electively once a full evaluation of the disease extent and the presence of any associated anomalies has been completed.

Most neonatal tumors are benign or of low malignancy potential and tend to behave more favorably than the same type of tumor in older children. Neuroblastoma, for example, generally presents as stage I disease in 90% of infants under 1 year of age and is amenable to observation,[80] if small, or complete resection. Hepatoblastomas presenting in the newborn period also tend to behave more favorably than when presenting later in infancy. Despite a collective rarity, presentation of malignant tumors in the newborn period occurs, and much work remains to identify determinants of tumorigenesis and pathogenesis.

MINIMALLY INVASIVE SURGERY

Laparoscopic or minimally invasive techniques are beginning to supplant many surgical procedures previously performed by laparotomy or thoracotomy. Laparoscopic and thoracoscopic procedures have been associated with decreased postoperative pain, earlier return to gastrointestinal function, shorter hospital stays, less wound complications, and improved cosmetic results, when compared with the corresponding open procedures. **Laparoscopic techniques have been applied to many of the neonatal procedures described in this chapter.** Indeed, **laparoscopic Nissen fundoplication for gastroesophageal reflux disease**[58,100] **and laparoscopic-assisted pull-through procedures for Hirschsprung disease**[113,128] **are being performed routinely in the neonate and show shorter time to postoperative feeding, decreased hospital stay, and superior cosmesis.**

Thoracoscopic repair of EA with TEF is beginning to be advocated as an equally effective approach,[124] **and supporters claim improved pain management and skeletomuscular benefits. Additional benefits of the laparoscopic approach include earlier extubation and first oral feeding and shorter length of stay.**[121,124] Laparoscopic repair of duodenal atresia is being performed with good results.[72] Both thoracoscopic and laparoscopic techniques are being increasingly used to repair Bochdalek and Morgagni diaphragmatic hernias with good outcomes in neonates who do not require ECLS.[39,120] Laparoscopy-assisted endorectal pull-through for Hirschsprung disease and for anorectoplasty to correct ARM are becoming increasingly more a part of the neonatal surgeon's armamentarium.[97,113,128] However, pathophysiologic effects of pneumoperitoneum or iatrogenic pneumothorax are only recently being analyzed. Such adverse consequences include reduced intraoperative arterial saturation, increased carbon dioxide retention (CO_2 is used for abdominal insufflation and diaphragmatic excursion may be compromised because of increased abdominal pressure), oliguria or even anuria for up to 6 hours postoperatively, hypothermia, and need for extended postoperative intubation, if procedures exceed 100 minutes, which they often may.[50] As experience increases and technical refinements are seen with improved optical systems and smaller instruments, a broader application of laparoscopy inevitably will occur in the neonatal patient population.

PARENT TEACHING

Preoperative

The advent of ever-increasing mechanisms of prenatal diagnosis allows parents to begin adjusting to the presence of certain malformations,

some minor and others potentially lethal, before birth.[1] Research shows that parents experience various stages of grief, including shock, denial, anger, and sadness when faced with such news. Although the intensity of the negative emotions associated with the initial diagnosis may lessen by the time of delivery, resolution of these emotions should not be expected. Expressions of fear, anxiety, and guilt are likely.

Because parents' fears and fantasies about their infant's surgical diagnosis are frequently worse than reality, they should see their infant as soon as possible after birth and before surgery. Pictures of the infant should be taken before surgery and should include views with and without the defect if possible. **Whenever time and patient condition allow, parents should hold their infant and have pictures made of the family with their newborn.** In the event of a neonate's death, these pictures may be very valuable to the family. In the event neonatal transport from the birth hospital to a referral center is required, **the transport team should do everything possible to ensure that the mother, who may be in the early recovery phase from her delivery, sees her infant before departure.**[20,76]

Not only is breast milk almost always best for the surgical neonate, but this feeding modality also gives the mother a concrete way of helping her ill newborn (see Chapter 18). The new mother should be encouraged to begin pumping breast milk within the first hour after delivery. The key to successful breast milk establishment is to start early, in the labor and delivery suite, and to express milk often, at least 8 times per day with no more than a 5-hour period at night without pumping. The more frequently an infant nurses, the higher is the mother's milk production, so expression of breast milk is the mother's way of "placing an order in advance" for her infant when he or she is able to eat (http://newborns.stanford.edu/Breastfeeding/PMGs.html#sickbaby). Mothers should be taught hand expression and be provided with a pump. **Lactation support should be made available to the mother throughout her infant's hospitalization.**

The planned operative procedure and its expected results, as well as risks and alternatives, are discussed with the parents, ensuring that all questions and concerns are addressed. An informed consent for surgery is signed by the treating surgeon and witnessed by the bedside nurse. The **bedside nurse should be present when the physician meets with the family to discuss the operation, because the nurse is often the most consistent individual hearing explanations from the neonatologist, surgeon, and anesthesiologist, and must answer questions, interpret information, and reassure an anxious family when these teams leave.**

The nurse has a further important role to reassure parents about postoperative analgesia and sedation for their infant. Preoperative teaching can involve educating parents to recognize pain cues in their baby, and they should be encouraged to discuss their concerns if they perceive their baby is experiencing discomfort. Care providers' sensitivity to the neonate's pain and advocating for pain relief are comforting for parents. Toward this end it is the **nurse's responsibility to recognize pain cues in the neonate, including those present in the patient who is therapeutically paralyzed; know the expected duration of severe, moderate, and mild pain associated with various surgical procedures; practice nonpharmacologic intervention; and encourage parents to also provide comfort care where appropriate** (see Chapter 12). Although pain control is essential, side effects can interfere with patient care such as delaying return of bowel function or obscuring an accurate neurologic examination; therefore their judicious use is imperative. **Knowing the effects of narcotic and nonnarcotic pain medications, as well as the potential interactions these medications have with others the patient is receiving, is imperative.**

Parents often fear what the infant will look like on return from surgery. **Providing written material with simple drawings of the defects and operative procedure may help to prevent postoperative surprises. Seeing another patient who has had a similar procedure and has the postoperative equipment that has been described (e.g., colostomy, orogastric tube, chest tube) may be helpful to the family as well. The nursing staff must be careful, however, to protect the privacy of other patients and should get parental consent before using another infant for this purpose.**

INTRAOPERATIVE

Accompanying the infant to the preoperative area and seeing the infant as soon as possible

after surgery are comforting to the parents. Progress reports during the surgery, if possible, are helpful for the anxious family members. After the operation, the pediatric surgeon should immediately see the parents to explain the procedure and any unexpected findings or problems that occurred during the operation. It should be clear to both the family and the surgeon where this important communication will take place, and privacy should be protected during the interchange.

POSTOPERATIVE

After surgery, the nurse should help parents focus on their infant rather than the surrounding intensive care environment. Although the nursing staff should identify the monitors and equipment in the baby's room, and should explain the purpose of each to the family, **encouraging parents in ways to comfort their baby will be of greatest benefit to their postoperative child (and to them). Early involvement in caregiving helps the parents feel as though they are essential to their child's recovery.** Even in the immediate postoperative period, parents can quietly sit and hold their infant's hand or take an axillary temperature.

Mothers should be encouraged to provide breast milk for use as soon as feedings begin. In the majority of cases it will be the feeding that is best tolerated by the convalescing neonate. The nurse acts as a liaison for consultation with a lactation specialist for coaching and instruction if needed. **She should be certain that the mother has access to a pump and supplies and is encouraged to pump every 2 to 4 hours around the clock.** Quiet, private accommodations for breast pumping should be available in or adjacent to the patient care area, and policies should be in place to ensure expressed breast milk is properly identified and stored at all times. **If possible, the mother should also be encouraged to breastfeed her infant, as the infant's improvement allows.**

If an infant is to be discharged home with an ostomy, parents begin to participate in stoma care as early as possible. Consultation with an enterostomal therapy nurse is of further benefit. **Parents begin by learning to cleanse the skin around the ostomy or to prepare the appliance and peristomal salves. Gradually, parents will learn to increase their responsibilities of caregiving as their infant improves. Frequent practice improves proficiency and empowers parents for taking their infant home.** Delay until a few days before discharge does not give parents adequate time for practice and familiarity for home care and does not serve the infant or family well. **The same is true for infants who are discharged with other types of complicated care, such as home TPN or feedings through a gastrostomy tube and/or on a continuous feeding pump.**

Parent teaching includes the possibility of late postoperative complications and recognition of problems that may develop and a plan of action for dealing with them.

The importance of follow-up care is emphasized to the parents. It may be helpful for parents to talk with a "graduate" parent who had an infant with similar problems. Contact information about available resources, such as visiting nurses, graduate parents, and parent support groups are provided to parents before discharge. **A concise history of hospitalization and the discharge plan is made available to all posthospitalization health care providers and a copy provided to parents at the time of discharge.** Encouraging parents to keep a copy of this discharge summary in their diaper bag increases the chances they will have it available should they be required to take their medically complex and vulnerable infant emergently to the hospital.

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29 FAMILIES IN CRISIS: THEORETICAL AND PRACTICAL CONSIDERATIONS

SANDRA L. GARDNER AND KRISTIN VOOS

Technical advances in the care of critically ill and premature infants have resulted in decreased morbidity and mortality of the high-risk infant. These developments have been accompanied by a heightened awareness of the psychological strain and emotional stresses encountered by the family of the sick neonate and the profound effect on family functioning.[5,25,158,174] Realization of the need for a family-centered approach to perinatal care has emerged out of an enhanced understanding of individual and family functioning and the challenges in coping and adapting to stress.[7,100,110] It is essential for perinatal health care teams to be cognizant of the overall psychological needs of families who are experiencing the painful crisis of the birth of a sick newborn.[158] This chapter discusses the complex psychosocial needs of families during this stressful period and offers concrete suggestions for intervention.

NORMAL ATTACHMENT

Emotional connection to an infant begins not at birth but during pregnancy. The terms *attachment* and *bonding*[129] are used to describe this process of relating between parents and their infant. Attachment is characterized by the same qualities used to describe love: care, responsibility, and knowledge. Parental love and romantic love activate the same areas of the human brain, result in brain processing of infant cues, and elevate the "bonding" hormone, oxytocin. Attachment is an individualized process and does not happen automatically.[25,187]

The neonate is totally dependent, both physically and emotionally, on the caregivers, whereas caregivers are not dependent on the infant. Recognition of this unique relationship is evidenced cross-culturally by immediate and prolonged contact with no evidence of separation.[116,187] In most animal species, the mother engages in species-specific behaviors[129] that enable her to become acquainted with and claim the newborn. If there is disruption during this critical period, it can result in rejection by the animal mother and death of the young. Recent studies have shown a relationship between stressful environments, the health of the fetus, and caregiving ability (see Chapter 13). Parental attachment and appropriate caregiving behaviors are crucial for the infant's physical, psychological, and emotional health and survival. Ultimately, this influence can affect the infant's well-being as an adult and potential parenting ability.

Critical and Sensitive Period

In the period immediately after birth, healthy mothers and infants are physiologically and

BLUE type highlights content that is particularly applicable to clinical settings.

psychologically ready for reciprocal interaction.[120] Even though labor and birth are tiring, most mothers feel "high" and have an incredible surge of energy after birth. Psychologically, the family is ready to meet and interact with the long-awaited newcomer. The first hour of life can be a time of alertness for the newborn. Before the sleep phase, the newborn is alert, makes eye-to-eye contact, fixes and follows, begins to search unassisted for the maternal nipple, and begins to feed. At birth, all five senses are operational, and the infant is ready to cue and shape the environment (see Chapters 5 and 13).

The period of mutual readiness between parents and their infant(s) has been compared with the critical period in animals. This human "maternal sensitive period"[129] immediately after birth is an optimal time for attachment to develop. Positive effects of early and extended contact, rather than initial separation, have shown significant differences in caregiving behaviors that persist over time.

Sustained and early contact between parents and their infant gives the family the opportunity for interaction. The presence of the infant enables the parents to understand the reality and individuality of their infant. Early parent-infant contact facilitates parent-infant attachment and contributes to the regulation of the newborn's physiology and behavior.[25,31,158,187] Early skin-to-skin contact between mothers and their infants results in significant benefits: (1) better breastfeeding, (2) maintenance of infant body temperature, (3) higher blood glucose, (4) lower respiratory rate, (5) better heart rate stability, (6) more affectionate maternal behavior, (7) lower salivary cortisol levels, and (8) less infant crying.[31,180] Unnecessary "routines" and procedures that interfere with initial contact and bonding should be deferred, if possible, until the family has time for this important interaction (see Chapter 5).

Although the delay of immediate contact for medically necessary interventions does not promote attachment, neither does it undermine the entire process of attachment.[51] Fortunately, human mothers do not automatically reject their infant if they cannot interact immediately. During medically necessary interventions, it is important to give parents as much interaction (or at least visual contact) with their infant as is possible.

Crisis Event: Pregnancy and Parenthood

Pregnancy, birth, and parenthood are almost universally defined as a life transition and crisis.[77,116,187] Becoming a parent requires a major adjustment of the roles, lifestyle, and relationships. Because previous ideas and coping strategies may not be helpful, life crisis situations challenge the individual with the potential for growth as new responses and solutions are used for problem solving. Periods of upheaval, change, and vulnerability can provide a time of openness, receptiveness, and readiness for help and support from significant others (including professionals).

Influences on Parenting

Opportunities to experience parenting and to observe others in that role are essential learning experiences in developing one's own parenting behaviors and style. The ability to parent is influenced by a multitude of factors that occur before, during, and after the birth of the infant. Previous life events, including degree of life stress/patterns of coping,[152,260] genetic endowment, being parented,[87,92,187] previous pregnancies,[121] anxiety and distress about the parental role,[55,70,92,111,187] and interpersonal relationships[87,187] affect the experience of pregnancy and parenthood. The events of the current pregnancy,★ their significance to the parent, and the availability of support and assistance influence parenting ability.[111,158,187]

After birth, infant characteristics (e.g., responsiveness/vulnerability/severity of illness),[58,92,111] appearance,[25,38] parental feelings of loyalty and hope, the behavior of health care professionals,† separation from the infant,‡ an inability to protect their newborn from pain,[117,192] and hospital practices§ may positively or negatively influence parents. Not only the occurrence of these events but also their meaning to the individual and the type of support received influence parenting abilities.

Two recent Australian studies of maternal-infant bonding during pregnancy and after birth examined

★References 55, 70, 92, 111, 178, 187.
†References 55, 70, 91, 120, 142, 174, 178, 261.
‡References 51, 135, 158, 178, 187, 192.
§References 25, 51, 55, 90, 92, 105, 111, 130, 142, 158, 174, 187.

the influence of antenatal bonding on postnatal bonding and the sociodemographic and psychosocial predictors of attachment.[221,222] The researchers found that the quality and intensity of maternal bonding significantly increased through pregnancy. Both studies found that a strong maternal antenatal bond to the fetus was predictive of a stronger postnatal maternal bond. Poorer maternal-infant bonding at 8 weeks postpartum was predicted by (1) depressive symptoms in the second/third trimesters, (2) older maternal age, (3) mothers born in non–English-speaking countries (4) mothers not employed full-time, (5) breastfeeding problems, and (6) infant crying.[221,222]

Cultural practices influence maternal and paternal attachment behaviors. ★ Studies indicate that cultural differences influence (1) parental emotional responses and perceptions of their infant's illness and disability, (2) parental usage of services, and (3) parental interaction with health care providers.[28] Research demonstrates that how parents interact with their newborn varies based on their culture[94] (e.g., Japanese mothers look at their babies more than Brazilian mothers do, who touch and interact more with them).[140] A study of Thai mothers in the neonatal intensive care unit (NICU) showed that the most frequent maternal behavior was touching (from the infant's extremities to trunk), followed by inspection (of the infant's appearance and recognition of family traits), verbalization (e.g., to the infant and nurse), and facial expression (e.g., smiling/crying/flat).[247] One must be cautious in viewing parental attachment behavior through one's own cultural filter, because this may result in an incorrect assessment of parent-infant attachment.[247] Differences in parent-infant interaction behaviors reflect cultural differences; therefore health care professionals' observations of these behaviors must be evaluated within the context of the family's culture.†

Steps of Attachment

Klaus and Kennell[129] propose nine steps in the process of attachment.

STEP 1: PLANNING THE PREGNANCY

Planning the pregnancy is the initial step of investment and commitment[187] to parenthood. Pregnancies are planned in one of two ways: consciously or unconsciously. Who planned the pregnancy and why this particular time has been chosen are important indicators of the investment of each individual in the decision and in the pregnancy.

Carrying a pregnancy is not assurance that the baby is wanted. Although it may be a legal option, abortion may not be a cultural, moral, financial, or ethical option for the individual woman. Attachment of the mother (or father) to the infant is not ensured merely by the mother remaining pregnant, giving birth, and keeping the infant.

STEP 2: CONFIRMING THE PREGNANCY

Pregnancy confirmation begins the psychological acceptance of the pregnancy. Delaying confirmation enables the fact of pregnancy to be denied and may influence progression to the acceptance stage.

STEP 3: ACCEPTING THE PREGNANCY

Accepting the pregnancy usually begins early in the pregnancy and is characterized by the emotional changes of primary narcissism, introversion, and passivity. Because the expectant mother is less interested in the outside world and more interested in her own inner world, the mother can become attuned to her own needs. Although she was previously engaged in active, extroverted behaviors, during the pregnancy she may contentedly participate in quieter, more introspective activities.

At this early stage of pregnancy, the fetus is not perceived by the woman as separate from herself but as an extension of her body. The psychological changes of pregnancy have survival significance in that caring for herself ensures caring for the fetus as an integral part of herself.[152,187]

During the early months of pregnancy, the man and woman realize that parenting will require a major adjustment of their pre-pregnancy roles, lifestyle, and relationships. The adaptation of parenthood is characterized by upheaval and change, losses and gains. Bombarded with phenomenal lifelong changes, the future parents experience the normal feeling of ambivalence.

STEP 4: FETAL MOVEMENT

Fetal movement, felt by the mother between 16 and 32 weeks of gestation, is the beginning of accepting

★ References 28, 111, 116, 152,182, 219, 220, 231.
† References 116,182, 219, 220, 231, 248.

the fetus as an individual. Fetal movement is the first concrete evidence to the mother of the existence of another person within her. Hearing the baby's heartbeat, seeing the ultrasound images, or experiencing an amniocentesis also confirms the reality of the fetus.[187] Fetal movement is such a significant event that often a pregnancy that began as unplanned and unwanted becomes wanted.

Perception of the first fetal movement is a happy event. When asked "How did you feel when the baby first moved?" most women respond in a happy tone and with a smile. Use of a negative tone or negative words to describe fetal movement is a concern because the individual (fetus) already may be perceived as an intruder.

STEP 5: ACCEPTING THE FETUS

Accepting the fetus as an individual begins with fetal movement. The fetus shows individuality in controlling the movement; the mother can neither start nor stop these movements. With the realization of the presence of another person, parents begin acceptance of the fetus as a separate individual. Love for the fetus as a separate individual occurs as the parents invest a personality in the fetus and start to establish a relationship. Fantasies about how the baby looks, its sex, and the wish for a perfect, healthy infant are common. Women with a history of perinatal loss have been shown to have disturbances in maternal attachment related to differentiating the self from the fetus in a subsequent pregnancy.[170]

Outwardly, preparations are made for the acceptance of an infant into the home; baby clothes and furniture are purchased, and a room is prepared. The fetus may be referred to by a nickname or a term of endearment. The baby's name may be chosen. Choosing a name is a highly personal and significant event. The meaning of the name and who chooses it illustrate the power holder and decision maker within the family. Prenatal questions such as the following may be asked after the birth to elicit information: "Do you have a nickname for the baby?" "Do you have a name picked out for the baby?" "Who picked it out?"

Whether the newborn meets parental expectations for "the right sex" may be crucially important for the parents to attach to the infant. "Do you have a sex preference for the baby?" may be asked before or after the birth to uncover this information. Often parents with a strong sex preference have chosen no names for a baby of the "wrong" gender. "It doesn't matter as long as it's healthy" is often heard and may indicate no conscious gender preference. However, unconsciously, the parents may have a strong gender preference as evidenced by a predominance of dreams about one gender. If dreams are equally divided between male and female children, there may indeed be no gender preference at the unconscious level.

Most parents are fearful of producing a defective child. This fear is experienced as dreams about dead, deformed, or damaged fetuses and babies or dreams with a central theme of destruction. These unconscious contents often are experienced as frightening nightmares that may be imbued with magical ideas such as "If I think (or talk about) it, it will come true." Both before and after birth, it is reassuring for parents to know that this is a common and scary phenomenon, that they are not "crazy," and that the fears are not magical.

Parental expectations of the newborn are established before birth in the personification and relationship with the unseen, unheard fetus. Research shows that a close, high-quality prenatal attachment to the fetus is associated with fewer depressive symptoms in the last trimester and postpartally.[84] Compared with adult women, pregnant adolescents are slower in developing an antenatal emotional attachment to their fetus.[224] After birth, parents often experience the developmental process of working out the potential discrepancy between the wished-for and the actual infant.[241] Before attachment to the actual infant can proceed, the fantasized child must be mourned.

STEP 6: LABOR AND BIRTH

Labor is a physiologic, maturational, and psychological crisis for the family. Birth is the culmination of pregnancy and the reward for the work of labor. Parents' attitudes about the labor and birth experiences may affect their reactions to the infant.[51] Research shows that continuous physical and emotional support during labor significantly improves birth outcomes for the mother (e.g., shortens labor duration, reduces the need for pain medication and operative vaginal and cesarean delivery) and the newborn (e.g., better Apgar scores, better/longer breastfeeding, fewer NICU admissions, fewer complications of obstetric [OB] interventions because fewer OB interventions used). In addition to better physiologic outcomes, improved psychological outcomes include (1) increase in maternal-infant

attachment behaviors, (2) better confidence and ability to cope with labor, (3) better maternal satisfaction and personal control during labor, (4) enhanced maternal self-esteem, (5) positive attitudes toward mothering and family relationships, and (6) easier mothering (i.e., sees baby as less fussy).[226]

Paternal participation in labor and birth is an important issue. Many years ago, health care professionals saw no benefit to the presence of the father and even wished to exclude him because of imagined "horribles" such as increased infection rate, malpractice suits, and disruption of routines. Birth is a powerfully emotional experience; those who attend birth are more attached to the infant than those who do not attend.[129,158] Benefits attributed to a father's participation at labor and birth include use of less analgesia, a more supportive environment, and a deepened relationship[9] between parents and between parents and their infant.[129] Inclusion of the father in perinatal events may engage him for inclusion in parenting activities.[55,158] Rather than just a financial provider, fathering may be perceived as a psychological necessity for both fathers and children.

Parental behaviors at birth such as the following indicate involvement and investment in the infant[103]:

- How does the mother or father look? At the sound of the infant's cry, parents smile and breathe a sigh of relief at this first breath of life. Support, joy, and happiness are positive feelings shared by couples at birth.
- What does the mother or father say? By speaking in a positive tone with words of affection and endearment, the parents relate to each other and to the new infant.
- What does the mother or father do? When offered the infant, both parents will reach out to take the infant. Spontaneously, parents engage in eye-to-eye contact and touch and explore the infant. Affectionate behaviors such as kissing, fondling, cuddling, and claiming characterize positive parental reactions.

A positive, self-affirming birth experience for the mother enhances her feelings of empowerment and self-esteem and thus her self-concept as a woman and mother.[187,226] A birth experience that does not meet parental expectations may have a negative effect on the self-concept of the mother, her perception of her ability to parent, and her relationship with the infant.[51] In fact, "so intricately are mother and infant entwined in a symbiotic relationship, that what is psychically positive for the mother is positive for the infant. What is psychically negative for the mother will affect the infant."[187]

So powerful is the labor and birth experience that women may be unable to proceed with parenting until psychic closure of the experience has occurred. Even women who experience a normal labor and birth process should recount the experience to others. Maternal perception of the events is obvious in tone and content of the recounting. *Missing pieces*[1] is the term used to describe the aspects of labor and birth that are forgotten or unavailable to recall. Long labor, short labor, or medicated labor can cause missing pieces in the mother's memory of the birth. Labor that did not meet expectations because of difficulty, cesarean delivery, use of forceps, or episiotomy could also affect the mother.[1] To proceed with parenting, these women should be encouraged to fill in their knowledge gaps by asking questions or looking at pictures or films of the birth to reconstruct the situation.

STEP 7: SEEING

Seeing and touching are the species-specific ways in which humans attach to their young.[129] Immediate attachment is facilitated by (1) positive maternal feelings toward the infant; (2) the mother's ability to see the infant immediately after birth; and (3) immediate contact between the mother and infant.[25] Delayed attachment may occur when the infant is ill or premature because he or she does not conform to parental expectations of a healthy full-term baby.[25,51,169,247]

Eye contact between parents and their infant in the initial period after birth may be a positive release of parental feelings of warmth, closeness, and caring. As parents see and inspect the newborn, they begin claiming their infant—"He has my eyes" or "She has your nose." Characteristics of each parent and the family are identified in the infant, and the newborn is claimed as a member of the family.[247]

The term *en face position* is used to describe the mother's (father's) eyes and the infant's eyes positioned in the same vertical plane.[129] This positioning enables the parent and the infant to look directly into each other's eyes, to focus, and to regard each other (Fig. 29.1).

The newborn infant is an active participant; he or she cues the mother with eye-to-eye contact. Even minutes-old newborns see and show a preference for the human face (within 7 to 12 inches from

FIGURE 29.1 *En face position.* The infant is held in close contact (the mother's body touching the infant's); the mother is looking at the infant *en face;* the bottle is perpendicular to the mouth; the milk is in the tip of the nipple. (From Klaus MH, Kennel JH. *Parent-Infant Bonding.* 2nd ed. St Louis, MO: Mosby; 1982.)

their face). The newborn can visually follow the parent's face and voice and signal the parent with facial expressions, movement, and vocalization, including a distress cry when separated from body contact with the mother (see Chapter 13).

Deterrents to the infant's full participation in this "getting to know you" phase include removal to the nursery, medication (from analgesia), and eye prophylaxis. Unless medically indicated (necessary for physical survival), newborns should remain with their parents after birth.[158] Because eye prophylaxis irritates and interferes with vision, the "routine" instillation immediately after birth (in the delivery room) can be delayed until after the initial acquaintance process is completed. Maternal depression also has been identified as a risk factor for poor mother-infant interaction.[135]

STEP 8: TOUCHING

In exploring the infant, parents systematically use fingertip contact with the infant's extremities. Gradually, there is progression to palm contact with the infant's trunk (Fig. 29.2). With the healthy term infant, this progression occurs within minutes of the first contact. After gaining confidence and preliminary knowledge, the parent will hold the infant close in a cuddling position.

With the preterm infant, this characteristic progression may take hours, days, or several visits (see Fig. 29.2). Fear of harming the small, fragile preterm infant often prevents parents from feeling at ease in touching him or her.[247] Until the parents feel confident that their actions will not harm the infant, they may be reticent to use palm contact with the trunk. Not only the use of nurturing maternal touch but also the vulnerability of the premature infant affect how touch is perceived by the infant. One study showed that nurturing maternal touch was associated with more secure attachment in robust preterm infants and with less secure attachment in the most vulnerable infants (see Chapter 13).

Holding and cuddling the infant are significantly different from touching and exploring. The amount of holding influences mother-infant interaction with preterm infants.[136] Mothers who have only seen and touched their infant still experience "empty arms." The species-specific behavior of touch is not completely satisfied until the parent can hold the infant. Most mothers have a preference for holding their infants on the left. Explanations for this preference include hand dominance, importance of maternal heartbeat, left breast sensitivity, and advantages in monitoring the infant. A more recent hypothesis proposes that maternal affective signals (both visual and auditory) are given to the infant's free left ear and processed by the more advanced right cerebral hemisphere.[235]

STEP 9: CAREGIVING

The final step of attachment, caregiving, is important for psychic closure of the task of bonding. A meta-synthesis of nine qualitative studies found two simultaneous processes necessary in the transition to motherhood: (1) engagement, a commitment to mothering that involves active attachment to the infant, experiencing the infant's presence, and involvement in caregiving for the infant; and (2) growth and transformation, which characterize the change of a woman into the new "self" of a mother.[187] Men also make the transition to fatherhood in the early postpartal period. A qualitative study of first-time fathers indicates that those who wanted to be highly involved in the care of their baby reported not feeling supported by the health care provider/hospital policies to engage in paternal and parental behaviors that favor involvement with their infant.[55] Fathers experienced more negative (63%) than positive (37%) interactions with nurses

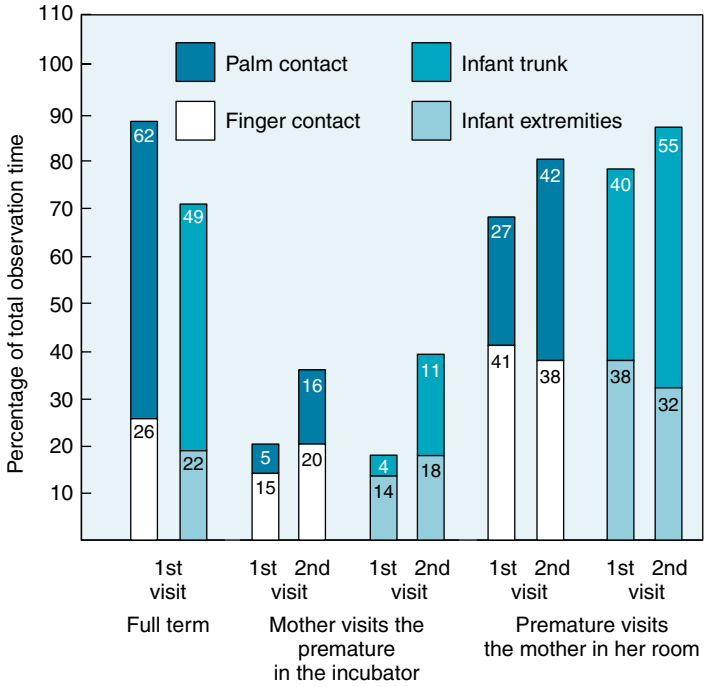

FIGURE 29.2 Fingertip and palm contact on trunk or extremities in three groups of mothers: *(1)* 12 mothers of term infants at their first visit, *(2)* 9 mothers who visited their premature infants in incubators in the NICU, and *(3)* 14 mothers whose premature infants were brought to their maternity rooms and placed in their beds. (From Klaus MH, Kennel JH. *Parent-Infant Bonding*. 2nd ed. St Louis, MO: Mosby; 1982.)

during the postpartum period.[55] Skin-to-skin contact between fathers and their newborns within the first 3 days of life has been shown to enhance father-to-infant attachment when compared with a group of fathers who did not perform skin-to-skin contact with their newborns.[36] In assisting parental transition, nurses and all health care professionals should support, intervene, and use all encounters with both new parents as "teaching moments and opportunities."[55,157] Empowering new parents with knowledge about how to care for their new baby has been shown to have a significant impact on maternal attachment and self-confidence in first-time mothers.[41]

The relationship between the primary caregiver and the infant is reciprocal. In the caregiving relationship, both care provider and infant give to and receive from each other.[91,187] The physical and emotional needs of the helpless infant are satisfied by parental caregiving behaviors such as feeding, soothing, bathing, grooming, and playing. Based on the infant's ability to perceive and receive care, the infant responds to the care provider. Parental expectations of newborn responses include quieting, sucking, clinging and cuddling, looking, smiling, and vocalizing. The parent's capability to soothe and satisfy the infant provides emotional satisfaction and positive feedback about the parent's competency.

Personal needs for comfort, maintenance of homeostasis, and relief from painful experiences are infant expectations of the relationship with the care provider. Care-eliciting behaviors (e.g., crying, visual following, smiling) are neonatal cues used to signal the care provider that attention is needed. Relief from discomfort enables the infant to respond positively to the care provider. The infant experiences the world through the caregiver and quickly learns that the environment is either nurturing and loving or hostile and nonresponsive. Consistent, predictable nurturing and caregiving enable the infant to develop a sense of trust in the caregiver, the world, and the self (see Chapter 13).

Care by parents is the ideal neonatal care situation, because the infant learns and reacts to one set of cues or caregiving behaviors. Cared for by one or two people, the infant can regulate his or her

physiologic behavioral processes (i.e., autonomic, neuroendocrine, behavioral, electrophysiologic) and develop synchrony with the parents.[142,158,187] Single caregiving improves the establishment of biorhythms of the neonate for sleep-wake cycles, feeding, and visual attentiveness. Multiple caregivers confuse the infant, increase distress with feeding, cause irritability, and upset visual attention. Care by parents provides for mutual cuing and acquaintance and a natural setting for observation of parent-infant interaction.[142,158,174]

PSYCHOLOGICAL ADJUSTMENTS TO A SICK NEWBORN

The birth of a child is a major life change. Parents of infants requiring NICU care often experience high levels of stress, and as a consequence their ability to interact optimally with their infant(s) is impaired. For many parents, this may be the first time they have had to cope with a significant challenge in their lives. This may lead to depression, impaired recall, dysfunctional parenting patterns, and poorer developmental outcomes for their child.[69,177,261] The perinatal health care team is presented with a unique opportunity to practice preventive health care. During this stressful time, the families' usual problem-solving mechanisms may not be adequate to cope with the events presented to them.[35] In addition to confronting this situational crisis, the individual or family must master the normal developmental process of parenthood.

Parental behavior and responses are determined not only by preexisting personality factors, social and cultural variables, and interactions with significant others, but also by the immediate situation in which the parents are placed. *The following six major sources of parental stress in the NICU have been identified:

- Preexisting and concurrent personal and family factors
- Prenatal and perinatal experiences
- Infant illness, treatments, and appearance†
- Concerns about the infant's outcome[145]
- Loss of the parental role‡
- Health care providers[5,70,105,111,145,205]

Situational factors can have an important bearing on the family's ability to cope with the crisis and thus affect the overall outcome (Box 29.1). Uncertainty about their infant's future and separation from their infant are sources of parental stress that can dramatically affect the quality of attachment that develops.[5]

Families are psychologically vulnerable after the birth of a sick infant. During this period of crisis, there may be a heightened receptivity to accepting help and being open and responsive to change because the family is struggling for a way to cope with the crisis. Significant potentialities exist for individual and family emotional growth and development.[25,34,70,111] Parental perception of support by nurses has been shown to be significantly associated with maternal depressive symptoms; as the perception of nursing support decreased, there was a corresponding increase in maternal depressive symptoms.[52] The perinatal health team has an opportunity to influence how the individual and family adapt to the crisis.§

BOX 29.1 SITUATIONAL FACTORS AFFECTING PARENTAL COPING*

1. The behaviors and attitudes of the hospital staff (physicians, nurses, and allied health care professionals)
2. The sensitivity used in the process of separation and transfer of the infant to the intensive care unit or, in some cases, the referral hospital
3. The flexibility of hospital policy concerning parental and sibling involvement and visitation in the nursery
4. The instruction of parents in their infant's individual behaviors and characteristics (thus facilitating appropriate parent-child interaction and reciprocity) (see Chapter 13)
5. The staff's comprehension and appreciation of the psychosocial functioning of families and the family's responses and adaptation to stress and crisis
6. The employment of emotionally supportive intervention programs for parents within the nursery setting
7. The development of appropriate discharge planning to provide adequate follow-up care to the infant and family

*References 25, 70, 91, 92, 100, 105, 107, 111, 150, 178, 192, 262.

*References 51, 108, 135, 158, 169, 202.
†References 5, 25, 51, 92, 145, 205.
‡Reference 5, 25, 43, 51, 70, 111, 145, 187, 205, 251.
§References 25, 57, 92, 108, 111, 135, 145, 174, 202, 240.

By providing appropriate supportive interventions coupled with enlightened policies and attitudes that reflect family-centered principles (Box 29.2), the team can have a significant positive influence on the family's ability to cope. Supportive interventions enhance the likelihood for successful adjustment and ultimately a healthy parent-child relationship.*

Family-centered care (FCC) is a philosophy often strived for in the NICU, but current practice and policies often may lag behind philosophy. NICU staff verbalize acceptance of families being involved in care, but their actions do not always reflect their words.[93]

Studies show a discrepancy between nurses' knowledge about the necessity of and their current practice of FCC.[203] Current practice of FCC scored significantly lower than scores representing necessity. Nurses do not consistently practice what they know to be necessary! NICU nurses scored significantly lower on the necessity scale than did pediatric and pediatric intensive care unit (PICU) nurses; nurses with fewer than 10 years of practice scored higher on the necessary and current use of family-centered principles than did nurses with more practice experience.[203] Organizational barriers to implementation include (1) the design of the health care system; (2) lack of emotional support, guidance, and direction for the staff; (3) lack of recognition, confidence, and support for nursing autonomy and skills to perform FCC; and (4) beliefs that dealing with families is stressful, interferes with care of the infant, and is "not part of my job."[70,203]

FCC principles stress that parents are the most important persons in their infant's life, that they have expertise in caring for the infant, and that their values and beliefs should be central during NICU care.[100,110] FCC demands a change from task-oriented, health care provider–centered care to a collaborative, relationship-based model of family advocacy and empowerment.[70,100,142,165] Roles for families in FCC include (1) advocating for their infant, (2) providing peer support to other families, (3) collaborating with and educating clinicians, (4) interacting with other allied health care professionals and therapists, (5) participating in hospital committees, and (6) acting as a change agent in health care settings.[60] Box 29.3 contains key components of FCC desired by families; they are remarkably similar to the Principles of Family-Centered Neonatal Care in Box 29.2. Box 29.4 contains eight principles of patient and family centered care

*References 5, 25, 51, 70, 92, 105, 108, 111, 135, 142, 145, 158, 169, 178, 232, 252.

BOX 29.2 PRINCIPLES OF FAMILY-CENTERED NEONATAL CARE

1. Family-centered neonatal care should be based on open and honest communication between parents and professionals on medical and ethical issues.
2. To work with professionals in making informed treatment choices, parents must have available to them the same facts and interpretation of those facts as the professionals, including medical information presented in meaningful formats, information about uncertainties surrounding treatments, information from parents whose children have been in similar medical situations, and access to the chart and rounds discussions.
3. In medical situations involving very high mortality and morbidity, great suffering, and/or significant medical controversy, fully informed parents should have the right to make decisions about aggressive treatment for their infants.
4. Expectant parents should be offered information about adverse pregnancy outcomes and be given the opportunity to state in advance their treatment preferences if their infant is born extremely prematurely and/or critically ill.
5. Parents and professionals must work together to acknowledge and alleviate the pain of infants in the neonatal intensive care unit (NICU).
6. Parents and professionals must work together to ensure an appropriate environment for infants in the NICU.
7. Parents and professionals must work together to ensure the safety and efficacy of neonatal treatments.
8. Parents and professionals must work together to develop nursery policies and programs that promote parenting skills and encourage maximum involvement of families with their hospitalized infants.
9. Parents and professionals must work together to promote meaningful long-term follow-up for all high-risk NICU survivors.
10. Parents and professionals must acknowledge that critically ill newborns can be harmed by overtreatment, as well as undertreatment, and must insist that laws and treatment policies be based on compassion. Parents and professionals must work together to promote awareness of the needs of NICU survivors with disabilities to ensure adequate support for them and their families. Parents and professionals must work together to decrease disability through universal prenatal care.

Modified from Harrison H. The principles for family-centered neonatal care. *Pediatrics.* 1993;92(5):643.

BOX 29.3 WHAT FAMILIES WANT IN FAMILY-CENTERED CARE[113]

- To be consistently and respectfully involved in decisions about the health care of their family member[73] and their family members to be involved in ways they choose
- Health care providers to listen to the family's observations and incorporate their preferences about treatment into the plan of care
- Useful and understandable information from health care providers; do not "sugar-coat" information[74]
- Personal connection—a relationship with health care providers; need personal connection and to be able to trust those providing care
- Patient comfort and pain control; important to family's (and patient's) perception of the hospital experience
- Information and support for handling transitions in health care

BOX 29.4 EIGHT PRINCIPLES FOR PATIENT- AND FAMILY-CENTERED CARE[223]

- Free parental access 24 hours a day with no limitations resulting from staff shift change or medical rounds (see Chapters 13 and 29)
- Psychological support for parents (see Chapters 29 and 30)
- Pain management (see Chapter 12)
- Supportive environment (see Chapters 13 and 29)
- Postural support (see Chapter 13)
- Skin-to-skin contact (see Chapters 5 and 13)
- Breastfeeding and lactation support (see Chapter 18)
- Sleep protection (see Chapter 13)

proposed by the European Research Network on Early Developmental Care.[223]

A multicenter study was conducted to create an FCC map to enhance the ability of the health care team to work with families to coordinate and deliver care in a holistic manner to meet the developmental, physical, and psychosocial needs of NICU patients and their families. This study led to the development of an innovative Web-based resource to assist individual care providers and family advisors to provide comprehensive FCC to infants and families.[62] The Family-Centered Care Map (available at www.fccmap.org), is based on 63 potentially better practices and is a joint effort of three NICUs (and their families), Vermont Oxford Network's Neonatal Intensive Care Quality Improvement Collaborative, and the Institute for Family-Centered Care. Use of the Family-Centered Care Map results in (1) improved growth for extremely low-birthweight (ELBW) preterm infants, (2) decreased length of stay for ELBW preterm infants by 13 days, and (3) better implementation of FCC principles.[114]

BOX 29.5 POTENTIALLY BETTER PRACTICES FOR FAMILY-INTEGRATED CARE AND/OR NEONATAL INTENSIVE PARENTING UNITS[97]

- Offering antenatal family support
- Providing a warm orientation to the NICU for parents with the first priority reconnection with their baby
- Treating parents as full partners
- Providing staff education on (FIC) principles
- Mentoring parents in developmental care, including skin-to-skin care
- Incrementally increasing parental engagement in all caregiving consistent with the infant's clinical status
- Offering peer and veteran support and a parent support coordinator
- Providing mental health support for parents and staff
- Participating in debriefing sessions after critical events

Family-integrated care (FIC) has evolved from FCC and requires that the family provide all care, except the highest level of technical care, to their newborn. Parents contract to provide 6 to 8 hours of care per day with teaching, counseling, and support from professional caregivers.[194] Parents attend education and medical rounds and are mentored by bedside NICU nurses and "veteran" parents who have had infants in the NICU.[29,160] Specific education for nurses is also necessary for FIC.[76] Potentially better practices for FIC or neonatal intensive parenting units include those listed in Box 29.5.

A pilot program in a Canadian NICU found significantly higher weight gain and incidence of breastfeeding at discharge in infants cared for by their mothers compared with control infants. Parental stress scores in the study group also decreased significantly from admission to discharge from the NICU.[193] Additional advantages of FIC include (1) recognizing the mother's own strengths, (2) increasing parental confidence, (3) developing better problem-solving strategies and attainment of parental roles, (4) developing better emotional preparation for taking the infant home, (5) acquiring the knowledge and tools to parent their infant in the NICU through education, (6) better communication between parents, as well as between parents

and professionals, and (7) the potential to mitigate the trauma and stress of NICU care for both the infant and parents.[29,30,50,161] A clustered randomized controlled trial in Canada, Australia, and New Zealand to measure the primary outcome (weight gain between study and control group preterm infants [<33 weeks' gestational age] at 21 days after enrollment) found higher weight gain in the infants cared for with FIC than in the control group.[195] Secondary outcomes in this multinational study found decreased parental stress and anxiety and higher rates of exclusive breastfeeding at discharge among the families in the FIC system.[195] FIC is currently being studied in clustered randomized controlled trials in 10 Canadian level II NICUs to evaluate clinical infant and maternal outcomes, cost, and length of stay.[23]

Parenting in the NICU is something most families are not prepared for or expect. Finding their parental role in this situation can be difficult and taxing, especially when their infant is critically ill.[70] Such challenges can have long-lasting effects on parental well-being and family functioning.[245] Fenwick et al. reported that mothers perceive their relationship with NICU nurses as either facilitating or inhibiting their ability to mother their preterm infants in the NICU.[70] Actions that facilitate mothering are family-centered. Facilitative nursing actions include fostering the relationship between the mother and infant by (1) assisting mothers to gain intimate knowledge and caregiving opportunities, (2) educating parents about their infant's medical condition, (3) providing ongoing positive feedback to parents, (4) acknowledging the importance of the dyadic mother-infant and father-infant relationship, (5) honoring the mother as the infant's primary caregiver, (6) enhancing mother-infant interaction opportunities, and (7) collaborating with parents and relinquishing control to parents, particularly at the bedside.[70,142]

Family-centered nursing care promotes physical closeness and intimacy with premature infants. Inhibitive nursing action can (1) result in a patriarchal, authoritarian style of care delivery; (2) focus on "protecting" the infant (from the parents); (3) maintain the nurse as the "expert" who retains control by directing and "allowing" parent involvement; and (4) dismiss parental worries, concerns, rights, and skills.[70] In the presence of inhibitive nursing actions, mothers are left with the feeling of "struggling to mother" in the NICU.[70] Mothers who are alienated and disaffected by these encounters feel angry, frustrated, distressed, inadequate, unsure, and anxious.[70] These feelings may result in (1) an inability to resume the relationship with the infant that has been interrupted by the stay in the NICU, (2) a delay in the mothering process, (3) feelings of depression or anxiety, (4) an impact on parenting and caregiving after discharge, and (5) affected perceptions of how they see themselves as mothers.[70] Maternal strategies to deal with highly tense NICU relationships include guarding and speaking out about the situation. Guarding strategies include (1) withholding feelings about inhibitive nursing actions and smoothing over the relationship with the nurse(s), (2) withdrawing from the nursery, and (3) blaming oneself to justify the nurse's actions.[70] Mothers who spoke up did so only after tolerating a number of incidents, and often it was the father who complained. The consequences for speaking out may include (1) earning a reputation with the staff as a "troublemaker," (2) recrimination in the form of sanctions and punitive actions that result in a "struggle to mother," or (3) becoming a disenfranchised mother.[70]

Several qualitative studies examining the "lived experience" of parents of a preterm/sick newborn illustrate parental need for a relationship with care providers in the NICU. A prospective, qualitative study about parental expectations from NICU staff at three NICUs in France studied 30 mothers and fathers of preterm infants younger than 32 weeks of gestation.[95] Fathers in the study described the bond with their preterm baby as more fashioned of words and looks involving distance, whereas mothers experienced the bond more physically. Of prime importance in the ability of these parents to form a bond with their preterm in the NICU was their relationship with NICU nurses. Two aspects of NICU nurses' care were cited by parents: (1) a caring attitude by the nurse toward the baby and parents, coupled with (2) caring communication with the parents about their infant, which decreased parental stress and facilitated interactions. The researchers concluded that the creation of a bond between the parents and their preterm infant is "rooted in their relationship with the caregivers."[95] Another study found that relationships with their baby's caregivers enabled parents to (1) trust that their baby was being cared for well, (2) endure the NICU, (3) feel less isolated and more in control, and (4) have hope.[202] A phenomenologic study of

parents' experiences with kangaroo care in the NICU illustrated the importance of information, communication, consistency, and individualized knowledgeable support and relationship with staff nurses who give parents the "courage" and confidence to hold and attach to their baby.[145] The most recent qualitative study of fathers' needs while their newborn is in the NICU found two prevailing themes: (1) fathers as caregivers and breadwinners and (2) fathers and emotions. Although fathers want to care for their infants and co-parent, they are faced with the dilemma of balancing these desires with the cultural and financial reality of earning an income for the family.[190] Emotions expressed by the fathers included fear of loss, restlessness, a desire to be the stronger parent/partner, a desire for support from other fathers going through the same experience, and a need to be away from the NICU.

Very important in any neonatal illness and subsequent hospitalization is the disruption and stress that is frequently created in the nuclear family system. Just as preterm and sick neonates experience stress in the NICU (see Chapter 13), parents also are stressed when their infant is in the NICU.[43,108,145,174,250] A study of the prevalence of posttraumatic stress disorder (PTSD) in parents with an infant in the NICU found that 35% of mothers and 24% of fathers had acute stress disorder at 3 to 5 days after admission.[144] Thirty days after admission to the NICU, 15% of mothers and 8% of fathers met criteria for PTSD. The severity of parental PTSD was correlated with concurrent stressors and family history of anxiety and depression.[144] More recent studies found an incidence of PTSD in 25% of mothers of high-risk neonates in an NICU, compared with 9% of mothers of healthy infants,[126] and 30% of low-income mothers with very-low-birthweight (VLBW) infants,[79] and it was more common in first-time mothers ofVLBW premature infants in the NICU.[89]

A family's functioning and adaptation to stress have important effects on the family's relationship with the infant and the infant's later development. A premature birth places parents at a higher risk for psychological distress than a full-term birth,[176] and, as a consequence, this can lead to depression, anxiety, and dysfunctional parenting patterns.[69,177,261] A crucial task of the perinatal health care team is to support families and intervene to assist them in adjusting to the unfortunate event of the birth of their sick infant to maximize their own growth, adaptation, and reorganization during this period.*

To assist parents through the difficult experience of having a sick infant, it is helpful to identify the psychological tasks and emotional reactions they experience. This section describes the six psychological issues facing families; it discusses the clinical and behavioral indicators with which parents are struggling and then suggests interventions that the perinatal health care team can employ to help families. It is extremely important to remember that these are generalizations and that each family or person must be approached individually.[187] In addition, in assessing families' reactions, it is critical to look at how they cope over time. Initially, there may be a tremendous amount of upset, disruption, and upheaval within the individual or family system. This can eventually lead to improved functioning and a sense of growth and mastery, "adjustment to the new normal." The key is how the individuals or families reorganize, how able they are to return to a state of equilibrium, the coping strategies they are able to develop, and whether the strategies are adaptive or maladaptive. Attachment and parenthood are complex, interactional developmental processes that must evolve and unfold over time.

Kaplan and Mason[121] describe the following four psychological tasks with which parents of premature infants must deal:

1. Anticipatory grieving and withdrawal from the relationship established during pregnancy
2. Parental acknowledgment of feelings of guilt and failure
3. Resumption of the relationship with the infant that had been previously disrupted
4. Preparation to take the infant home

Two additional tasks also are significant:

5. Crisis events related to labor and delivery
6. Adaptation to the intensive care environment[70]

In general, these six psychological tasks can be applied to any parent's reaction to a sick infant, with additional specific issues arising, depending on whether the infant was premature or born with a congenital anomaly.

Labor and Delivery

The first psychological task involves working through the crisis events surrounding the labor and delivery. Medical problems occurring at any point

*References 25, 51, 70, 92, 105, 108, 135, 158, 169, 192.

during the pregnancy or delivery that threaten the health or survival of the fetus or mother can result in the parents delaying their planning and making an emotional investment in the fetus or infant. Parents may psychologically withdraw from the pregnancy as a way of protecting themselves. The parents of an infant born prematurely often do not have the necessary psychological and physical time to prepare. This deprivation of time may interfere with the parents' ability to complete the final steps of attachment as described earlier.

Parental experiences of giving birth and parenting when the mother is seriously ill have recently been qualitatively studied. Mothers with severe preeclampsia whose premature infants were delivered emergently identified experiences that included (1) conflicting feelings about birth, (2) issues of life and death for them and their infants, (3) longing for the infant despite physical restrictions of access to the NICU, (4) finally becoming a mother by caring for their infants, and (5) being physically exhausted.[254] When both the mother and infant were ill, fathers described the process of becoming a family as a reflection of life and death in a context of separation.[255] These fathers experienced (1) beginning fatherhood grappling with issues of life and death for both the mother and infant, (2) connecting the family, (3) becoming familiar with the infant to establish a relationship, and (4) becoming a father in the public area of the NICU. Facilitating time together for the family to minimize separation, ensuring privacy and individualized care for the father, and providing rest for the mother are key interventions by health care providers.

Parents who have been concentrating on themselves in a healthy, narcissistic way may not yet be ready to transfer their investment to the infant, because they have been prematurely thrust into the role of parents.[111,158] There is an overwhelming sense of losing control of the events of the labor and delivery and their timing.[202]

On the other hand, some parents react in the opposite way. They may wish to be rid of the pregnancy as a way of dealing with their fear of the unknown and the uncertainty facing them. Many mothers of premature infants feel that their infants are alien[25,70,111]; they do not feel that the infant is really theirs, making it easier to have feelings of rejection toward the infant. In addition to feeling insufficient and inadequate about their ability to deliver an infant at term, they feel empty inside, as if something is missing. With a premature birth, there is usually a heightened sense of emergency and concern about the health and survival of the infant and, at times, of the mother, who herself may have suffered complications.

In the case of a full-term infant born with a problem despite a problem-free pregnancy, there is a sense of overwhelming shock and disappointment.[192] Parents immediately sense the problem; as their apprehension mounts, they frequently imagine the worst. Parents of a newborn with a malformation normally experience lowered self-esteem and view this event as an affront to their reproductive capabilities. The mother specifically views it as a failure of her feminine role. Parents often feel that they have failed and that the infant symbolically represents their own defectiveness. Parents not only fear for the infant, they fear for themselves and what this infant may mean to their future. The reaction of the parents is based on the specific psychological, social, and cultural meaning of the defect to the parents and the manner in which it is discussed and handled by the health care team.[129]

The emotional reactions and feelings that parents have at and after the delivery of a sick infant include shock, fright, isolation, panic, anxiety, and helplessness.[158,192,202] Parents may be so overwhelmed by the events that they may initially block any observable emotional response or affect. Staff interventions at this time are extremely important, because they lay the foundation for subsequent interactions between parents and health care professionals. Early comments and influential statements during this critical time can have lasting impressions in the minds of parents. This is also an emotionally difficult time for physicians and nurses, because they too are struggling with their own feelings of inadequacy, failure, and helplessness. Unconsciously, in an attempt to deal with their own feelings, staff may withdraw from parents and not be emotionally available to help. This is a normal response but one that needs to be guarded against, because it only perpetuates a breakdown in relationships and communication with parents that are greatly needed at this time. Many helpful interventions can be employed that are sensitive and supportive and that facilitate the emerging relationship between the parents and their infant.

EARLY COMMUNICATION

In the labor and delivery phase, early communication with both parents is essential. Parents normally are

apprehensive and extremely sensitive to explicit or implicit cues, such as actual statements by the staff, the atmosphere, looks, or a tone of voice that may indicate how things are progressing. Staff behaviors and wording of parent handouts help set the stage for an FCC unit and build family trust.[93] Because of the emphasis on prepared childbirth, parents are extremely sophisticated in their knowledge of labor and delivery practices and immediately sense some deviation from what they expected. Prompt, direct explanations presented in a calm manner are important and reassuring to parents. This explanation of the process of what is or will be happening can be effective because it helps organize the parents at a time when they are extremely vulnerable and feeling out of control. In a review of nursing behaviors identified to assist parents in meeting these needs, emotional support, parent empowerment and education, and a welcoming environment and welcoming parents were all key factors.[43]

Although it is normal for the staff to be guarded, members of the health care team should tell the parents the known facts and what actually is being done for their infant without giving any diagnosis, prognosis, or forecast for the future course of the infant. Avoiding or not talking to parents only accelerates parental anxiety and adds to their growing fantasies or distortions. Parents' fantasies about their infant's problems are usually worse than the reality. Parents often report that when they actually saw their infant, they were relieved because they had imagined that the infant would appear worse.

SUPPORT OF STAFF

It is also important that one of the staff members stays with the parents through labor, delivery, and recovery to offer continuous support and reassure the parents that communication will continue as soon as more information is known. This, again, is an uncomfortable time for the staff, because they may feel helpless and may therefore avoid the parents or revert to performing more technical activities. Some parents may need someone to be with them,[202] not only to talk to them but also, more importantly, to listen. On the other hand, some parents may not be able to talk or verbalize their concerns or fears. Others may wish to be alone with each other or any other significant person in their lives. Because of the varying responses and needs of people, it is extremely important to be sensitive to individual differences in approaching parents.

Parents have expressed their desire to be together when given "bad news."[100,232] As much as possible, talking to both parents at the same time is helpful when discussing the infant's condition. This decreases their distortions and misconceptions, increases the communication and support between parents, and prevents either parent from feeling excluded. The assumption is commonly made that the father is in a better emotional state to hear about the infant; this misconception leads health care professionals to mistakenly exclude or "spare" the mother, which only postpones her ability to begin to cope with the reality of her infant's condition. Sparing the mother may cause the parents to be in different stages of their understanding of the infant's medical condition and in different emotional states. Because emotional support between parents is so critical, the staff should avoid sparing because it can add to the parents' difficulty in being attuned to each other's needs and creates more opportunities for the parents to be out of synchrony with each other. Both mothers and fathers of critically ill newborns generally find each other to be the greatest source of support in the first 2 weeks of NICU hospitalization.[158,260]

SEEING THE INFANT

The question usually arises about the value of the parents seeing their infant, especially if the infant is very small, not likely to survive, or profoundly malformed. Generally, it is assumed that it is psychologically better for parents to have had the opportunity to see their infant, but this must be individualized for each family and newborn. Seeing the infant helps facilitate attachment,[25,158,169,247] decrease exaggerated fantasies, decrease withdrawal from the infant, and enhance the parents' ability to grasp the reality of the situation. Because of the need to respect individual differences in people, the best approach is to give parents the opportunity to decide whether they together or individually want to see and hold the infant.

Contact between mothers and their preterm infants in the first hours after birth is critical for a secure mother-infant attachment. Mothers who saw their VLBW preterm infants within 3 hours after birth showed a higher rate (76%) of secure attachment than mothers with no early contact (41%).[169] These researchers concluded that the 3 hours after birth constitutes a "sensitive period" for mothers of preterm infants to begin a secure attachment.[169] A negative experience for mothers at first sight of

their very preterm baby may result in attachment difficulties at 18 months corrected age.[171] Another study found that only 25% of mothers were enabled by the staff to hold their baby before transport.[68] The opportunity to see and touch the infant in the delivery room or before transport may reduce stressful feelings verbalized by parents who see their infant for the first time in the NICU.

Ultimately this decision should be made by the parents with the support of the health care team. It is not uncommon to find a well-meaning family member, physician, nurse, or social worker advising the parents or making the decision himself or herself and concluding it would be in the parents' best interest not to see the infant. The following arguments are given: "It's better not to get attached." or "It would make them cry or upset them to see the anomaly." or "They could not handle it." or "They would lose control." This decision is for the parents, not the professional, to make.

Some parents may know unequivocally what they want to do; others may be ambivalent or indecisive. It is the role of the professional to give the parents assistance (information and support) in making the decision. The parents may need time to think about it or may have to discuss their fear and ambivalence first, before being able to decide. They may need some factual information and preparation from the professional, such as the appearance of the infant and a description of the equipment. They may need assurance that someone will stay with them. Although time often is a factor and a decision must be made quickly, it is important to move at the parents' pace. The professional should still follow as much as possible the principle of facilitating the parents in seeing the infant. If this is not possible for medical reasons related to the mother's condition, a self-developing or digital picture can be taken, or secure video-conferencing can be used to involve the mother in the NICU admission. If it is medically possible for the parents to touch or hold the infant, the parents should be offered that opportunity. Touching or holding not only facilitates attachment[25,136,158,247] but also can provide parents with an emotional experience that is sustaining and reassuring, helping them proceed through a critical time of separation.

Parents are very sensitive to the staff's attitude toward the infant, as reflected by their comments and the manner in which the staff handle the infant. If the infant is regarded with respect and treated as important, the parent is given the feeling that the infant is seen as valued and worthwhile. This is especially important for parents of an infant with a congenital anomaly; the parents could wonder if their infant is viewed as "damaged goods" by society. In describing the infant to the parent, present a balanced picture of both the normal and abnormal aspects of the infant. In discussing the infant with the parents, staff should refer to the infant by name, if they have named the infant; this helps personalize the infant and establish the infant's unique identity.

CAREGIVING

To reinforce the caregiving needs of parents, discuss with them their plans to feed their infant and provide education to them so that they can make an informed decision. Support should be given whether the parents have decided on breastfeeding or bottle feeding. In most situations, breastfeeding a sick infant is possible and should be encouraged (see Chapter 18). Many mothers can pump their breasts for milk that will eventually be given to the infant. There are many psychological and physiologic reasons why breastfeeding or pumping may be beneficial for mothers and infants alike (see Chapter 18). The breastfeeding or pumping experience helps the mother feel close to her infant and helps her feel that she has some control over what is happening to her infant; she can uniquely contribute to her infant's care in a way that no one else can. Fathers, too, can participate in this activity by their support and interest in the actual breastfeeding or the pumping and milk-collection activities. Many mothers can pump and eventually put the infant to breast, but others cannot because of emotional stresses, the condition of the infant, and the length of time until the infant can feed. Regardless of eventual success, the mother should be encouraged to try if she has an interest; then she can feel that she made an attempt to relate to her infant in this way. If a mother does not plan to breastfeed or pump or if she tries but does not continue, she should not be made to feel guilty or that she failed in her role. She is already vulnerable to these feelings.

After the delivery, when the mother is taken to her room without a healthy infant, she usually experiences a void, as though an amputation has occurred.[92,129] She and those around her are beginning to grieve. The interventions of the staff should be flexible and sensitive to the individual needs of the family. Empathy, responsiveness, and an ability to listen to the parents are important at this time.[158]

Encouraging parents to verbalize and express their feelings and concerns (at their own pace), although difficult to do at times, is useful to the parents. Listening is as important to parents as giving them information.[105] Avoiding their grief gives the mother and father the impression that they are "bad parents" for having feelings of sadness, anger, guilt, or loss; this only increases their level of guilt and isolation. Prescribing tranquilizers also gives the message that is it not permissible to talk about what has happened to them and their infant. Tranquilizers only increase the feelings of unreality that normally are experienced. This stifles the parents' coping mechanisms at a time when the parents should begin to come to terms with what has happened.

Room assignments are a very personal matter, and the mother should be given a choice of where she will stay. Some mothers want to stay in a regular maternity unit; for others, this is too painful and they want to be in a separate area. Flexible visiting guidelines[37,90,158] for the father and other significant persons are essential so they can support one another through a difficult, uncertain period.

In talking to parents, bear in mind that the parents do not remember much of what has been said[202]; it is very difficult for them to assimilate all that has happened, both cognitively and emotionally. Therefore it is important for the staff to move at the parents' own pace. If the infant has been transferred or the chances for survival are limited, the mother should be discharged or given a pass to visit the infant as soon as possible. It is also important to acknowledge to the mother (and father) that they are parents and that they did give birth to a baby. They need the congratulatory cards, gifts, and attention that they would have received normally.

Anticipatory Grieving

After labor and delivery, parents are struggling with the second psychological task of anticipatory grieving and withdrawal from the relationship established during pregnancy. This task requires that parents acknowledge that their infant's life is endangered or that the newborn might die. Events surrounding the labor, delivery, and postpartum period may have indicated to the parents that their infant's chances for survival are diminished. Studies have shown that the decision to transfer an infant to an NICU alone is likely to initiate an anticipatory grief reaction.[51,192]

Parents also may experience feelings of grief and sadness over the loss of the expected, idealized child they had wished for during the pregnancy. For some parents, attaching to a critically ill or malformed infant may be too overwhelming; parents may withdraw from the infant in an attempt to protect themselves from their feelings of hurt, disappointment, and guilt.[25,111] Some parents may feel ambivalent about the infant[111]; they may feel they could not love or cope with an infant who might die or who would have significant physical or mental problems. Feeling uncertain about whether they want the infant to survive can result in feelings of guilt that may cause the parents to withdraw from the infant as a way of avoiding confronting these difficult, painful feelings.

During this period, parents may find themselves in a very stressful position; they are faced with the task of balancing the painful realities of a possible loss against their hopes of survival of their infant.[100] The emotional withdrawal and grieving that parents experience is normal during the critical time that the infant's life is endangered or when parents are faced with the possibility that their infant may have a lifelong problem. This withdrawal becomes pathologic only if it continues beyond the time the infant demonstrates definite signs (to the parents) of improvement and survival. In the case of a newborn with a permanent developmental or physical disability, parents who cannot grieve their idealized infant may maintain this withdrawal, which might lead to attachment difficulties and subsequent cognitive and emotional consequences for the infant.[241]

PARENTAL RESPONSES

Parents exhibit many emotional responses and behaviors that indicate they are struggling with the anticipatory grieving and withdrawal. Some parents are very sad, depressed, and teary, and others may be highly anxious, at times bordering on panic states; others react by having a flat affect, withdrawing, and appearing apathetic. Some parents may exhibit very angry, hostile, confrontational behavior as a way of dealing with their distress. Others may deny the situation by optimistically feeling that "everything will be okay."

Parents who typically are verbal may ask questions reflecting their concerns about their infant's survival; this is especially true after the infant has received medical attention and decisions are being made about treatment, including transfer to the

NICU. The questions they ask physicians and nurses may include "Will he make it?" "What do you think his chances are?" "He'll be okay, won't he?" "Have you seen other babies with this problem?" "Do other babies make it?" and "How long will he be in the hospital?" Parents struggling with their fears may resist seeing, touching, or visiting the infant. If they do visit the infant in the NICU, they may remain distant by having little or no eye contact with the infant, refusing to touch, standing far from the warmer or incubator, and asking few or no questions of the staff. Parents may be reluctant to name the infant; when they do refer to the infant, they say "it," "she," "he," or "the baby." If the infant has been given a special or treasured family name, they may be reluctant to use it.

A common phenomenon occurs when parents, being protective of each other, discourage each other's involvement with the infant. This is especially true at the time of transport, when the transport nurse may suggest to the father or family members that the infant be shown to the mother before leaving. Many fathers are afraid this will increase the emotional attachment to the infant and thus the feelings of disappointment and loss if the infant should die. The father is usually very apprehensive about how to handle the mother's feelings of grief in addition to his own. This type of behavior also is true with regard to medical information; it is not uncommon for one parent to request that all communication go through him or her. The response is "My spouse is too upset or anxious and couldn't handle hearing any bad news." Many times it is actually the parent making the request who is most anxious and who is dealing with this anxiety by projecting it onto the other partner. Work and childcare responsibilities, transportation difficulties, and financial limitations are all legitimate reasons that parents may be unable to have frequent contact with their infant. However, these factors also may serve as unconscious ways to maintain distance from the infant.

Keep in mind that withdrawal and grieving are part of a necessary and natural process.[25] For parents to develop an attachment to and accept the reality of their infant's condition, they must experience their feelings of grief, sadness, anger, guilt, and disappointment over the loss of the expected infant.[231,241] Maternal grief resolution over premature birth, as well as maternal interaction quality, are necessary for secure infant attachment.[231] This grieving serves to free the parents' emotional energy so they can interact with and become attuned to their infant. Grieving enhances the parents' availability to the infant. This availability aids in their feeling competent to handle their infant. The goal, then, of the perinatal health care team's interventions is to help the family realize their feelings are natural and normal and will be accepted.[25] Parents need permission to have their feelings. It is essential to acknowledge to parents that it is normal to be afraid of attaching to an infant who might die or who has a neuromotor impairment. Giving permission diminishes the guilt that the parents may feel about their behavior being abnormal or about being bad parents because they are afraid. Simple statements such as "Many parents tell us they are afraid of getting close to their baby" or "It's scary to attach when you think the baby may die" are helpful.

Sometimes it is useful for parents to verbalize their actual fears. They may fear their infant dying, being cognitively delayed, or being paralyzed. Once their fears are clarified in their minds and either confirmed or refuted by the medical staff, it is usually easier for parents to begin to accept their infant's diagnosis and prognosis and begin relating to the infant. Social workers can provide valuable emotional support to families in helping them deal with their realistic and unrealistic concerns.

COMMUNICATING MEDICAL INFORMATION

Most of the foundational work of FCC rests on effective communication.[209] Health care provider and patient/parent communication behaviors are associated with improved patient health status, recall, treatment adherence, and satisfaction.[122,209] The role of health care professionals in communicating medical information is important. Although the approach should be individualized for each family, some professionals feel a balanced approach is the most beneficial. Parents have stated that information should be accurate, current, and comprehensive but not unduly pessimistic.[105,202] Parents need a realistic assessment of the situation that is honest and direct. Acknowledge the infant's condition and possible problems, but not necessarily every potential problem that can arise.

Parents who hear "brain damage," "retarded," or "the baby will die" are not likely to forget these statements. These statements can linger in the minds of parents and adversely influence how they relate to

their newborn.[107] They may believe that some day "brain damage will show up" or that the infant is susceptible and frail and needs to be treated cautiously for fear of a life-threatening condition. These children may become victims of the *vulnerable child syndrome,*[4,107] a condition in which a child is overprotected by his or her parents and treated as if he or she had a medical problem when it is no longer the case. Parents who are told their newborn may die may have trouble attaching or becoming emotionally invested. When talking to parents, physicians and nurses should be judicious and careful in making statements of a sensitive nature. Definitive statements should be used only when appropriate and necessary. The long-term emotional implications of such statements should be weighed.

There are several other guidelines in communicating medical information to parents. As discussed, parents' perceptions of their infant's condition are extremely important, remain in parents' minds, and can affect their relationship with the infant. Parents easily misperceive information given to them. They may believe that a patent ductus arteriosus (PDA) indicates open-heart surgery and therefore worry that their infant has a heart condition. Or perhaps they think a bilirubin problem means their infant has liver disease. Therefore in beginning any discussion with parents, it is essential to determine and address their perceptions. A staff member might say, "Could you tell me what you understand about your baby's condition?" This will give the physician or nurse the opportunity to correct any misinformation or misconceptions and to hear about the parents' concerns. The perceived morbidity of the baby is a source of stress for both mothers and fathers. Parents' perceptions of the severity of their infant's illness are complex, change over time, and are affected by parental anxiety, infant size, amount and type of equipment and treatments, and amount and type of information received from health care providers.[107] A team member might specifically ask about the parents' concerns or worries: "Could you tell me what concerns you have about your baby?" Asking this can make communication between the perinatal health care team and parents more meaningful and helpful; unless the team deals with the parents' anxiety, discussions become one-sided lectures and benefit only the professional. Discussions should be a dialog between the parent and the professional.

During the course of a discussion and again at the end, it is useful to determine parents' interpretations of what has been said and modify and clarify as needed. The staff should avoid overloading a parent with lengthy explanations that are too technical. It is more productive to move at a pace at which the parent can assimilate the information presented; it is not necessary to describe the entire course of respiratory distress syndrome or bronchopulmonary dysplasia. It is always preferable to use simple language that is understandable. For some parents, the use of statistics is helpful; for others, it is not.[202] Statistics can be confusing, because they do not apply to the individual case and can be misinterpreted easily. When asked about the frequency of brain damage with a grade III intraventricular hemorrhage, a team member might say, "A majority of these babies have some neurologic problem, but some do not." Vivid modifiers such as "This is the worst case of sepsis we have ever had" or "Your baby is the sickest baby in the nursery" are of no real benefit to the parents and only accelerate their anxiety. Finally, if a referring physician and the nursery team are both communicating with the parents, it is essential to coordinate the particular approach. It is very confusing to parents and decreases their trust level for one to be pessimistic and the other optimistic or to receive conflicting information.

CULTURALLY COMPETENT CARE AND COMMUNICATION

Providing culturally sensitive care in a growing multicultural and diverse society is essential and needs to be a constant pursuit in providing perinatal health care to childbearing families and those families who have an infant in the NICU.[102,115] It is important for the health care team to understand the values, beliefs, customs, and behaviors of the particular group(s) they serve. Culture influences beliefs about what causes illness and how that illness should be treated. The perinatal health care team needs to address cultural, linguistic, and spiritual competencies to provide FCC.[83,94,102] The National Perinatal Association has published an extensive resource guide that reviews specific cultural practices and beliefs of several ethnocultural and religious groups.[230] Another excellent resource that discusses health and illness in different populations is the book *Cultural Diversity in Health and Illness.*[242]

In the perinatal setting, some common areas that often emerge center around language, folk practices or traditional beliefs, and nonverbal communication.

Use of Language. If a language or educational barrier is encountered, a qualified interpreter who is

BOX 29.6 GUIDELINES FOR THE EFFECTIVE CHOICE OF INTERPRETERS IN CLINICAL SETTINGS

Interpreter Choice

- Unless thoroughly fluent in patient's language, always use trained interpreter.
- Avoid strangers from waiting room or untrained staff as interpreters because of potential problems with accuracy, confidentiality, and medical terminology.
- Children should be interpreters of last resort because of problems with disruption of social roles, sensitive issues, and accuracy.
- Adult relatives or friends brought specifically to translate are acceptable alternatives when trained interpreters are not available, but there may be problems with accuracy, confidentiality, medical terms, and disrupted social roles.
- Always ask patient whether designated interpreter is acceptable.

Interpreter Use

- Clinician, interpreter, and patient or parent should be positioned in equilateral triangle so important nonverbal cues can be appreciated.
- Speak to and maintain eye contact with patient/parent, not interpreter.
- Ask interpreter to translate as literally as possible.
- If mistranslation or misunderstanding is suspected, return to issue later using different wording.
- Emphasize key instructions and explanations by repetition.
- Use visual aids (charts and diagrams) whenever possible.
- To verify quality and comprehension of translation, have patient/parent repeat information through back translation.

At End of Medical Visit

- Interpreter should write lists of instructions for patient or parent, particularly for prescriptions and other therapeutic interventions.
- Indicate to pharmacists that prescription instructions should be printed in the family's language.
- Interpreter should always accompany patient/parent to schedule follow-up appointments with receptionist.

Reprinted from Flores G. Culture and the patient-physician relationship: achieving cultural competency in health care. *J Pediatr.* 2000;136(1):14–23. Includes information from Perez-Stable, Pachter, and Putsch.

bilingual and bicultural should be used[115] (Box 29.6). This is especially important in obtaining informed consent. A child or children should not be used as interpreters because they may have inadequate language skills and may be embarrassed by the topics being discussed. Interpreters should be familiar with medical information and terminology. A housekeeper or admissions clerk may be bilingual but have no understanding of the medical issues. Often information that is translated, even by a certified translator, is not understood by families if they are not literate. For example, some undocumented immigrants may have only a second-grade education and may be illiterate in their own native language (and embarrassed about disclosing this to the medical team). However, illiteracy does not mean the family is not intelligent. Some very intelligent parents can comprehend complex information if explained in a relevant manner.

Use of pictures augments what is being explained. Providing a list of common medical terms and educational materials in the native language of the parents is a useful tool. At times, despite numerous discussions about the infant's medical condition, the family may appear unable to comprehend what they have been told. Consider that even if the health care provider and family share the same language, the words may have different meanings depending on core cultural beliefs and values and the families' previous experiences.[9] What is considered an abnormality in our Western culture may not be in another culture.

Folk Practices and Traditional Beliefs. Each culture has their own set of beliefs and traditions about health, illness, and treatment. Many cultures believe that there is a balance between hot and cold forces in nature that are essential for health and harmony. These concepts, which are very prevalent in Latin American and Asian cultures, are unrelated to temperature. Pregnancy is seen as "hot," as are vitamins and iron, and should be treated with "cold" products to regulate a proper balance in the system and avoid medical problems. To treat imbalance, one must know what conditions are viewed as hot and cold. There is no general agreement as to what is a hot or cold disease or food. The classification may vary from person to person, so it is imperative to understand the nature of the situation or problem from the perspective of the family.[242] Many of the following beliefs, however, are commonly accepted causes for illness, birth defects, or anomalies:

- *Mal ojo:* A type of magical occurrence caused by a look; the "evil eye" heats up the infant's blood, resulting in fever, crying, diarrhea, vomiting, and aches and pains. This is often treated by a *curandero* (a folk healer), a healing ceremony, or placing an amulet *(azabache)* or leather strap for protection on the infant.

- *Coraje:* Anger or frustration believed to sour breast milk and affect an infant's intrauterine development. It is treated by wearing a good-luck charm in the bra and having a healing ceremony.[83]
- *Mollera caida:* Fallen fontanel is believed to occur when the breast or bottle is removed too quickly. It is believed the soft palate sinks in, causing feeding and swallowing difficulties. Treatment is performed by pushing up the soft palate with the thumb, pulling the hair, and sucking the fontanel.[72]
- *Susto:* A disease or illness resulting from fright. It is treated by relaxation and a cleansing ceremony or other specific actions to counter the *susto.*
- *Lunar or solar eclipse:* A cleft palate, some respiratory ailments, and birthmarks are often associated with an eclipse. It is treated by the pregnant woman wearing a red undergarment or a coin or key over the belly.

Traditional folk healers are multidimensional. In African cultures, they are diviners, herbalists, faith healers, and voodoo practitioners, as well as traditional midwives and birth attendants. Hispanic cultures use a wide range of *curanderos* (*santeros* in the Puerto Rican community), who vary from massage therapists to faith healers and herbalists. Asians rely on medicinal plants or herbology, acupuncture, and moxibustion (heated pulverized wormwood applied to the skin), which restores the proper balance of yin and yang believed to be most helpful during the period of labor and delivery.[242]

In many cultures, decisions are made by a group of elders, removing the responsibility entirely from a new mother and father. Many societies view the whole family as more important than a single individual. Decisions about life and death may be deferred to the elders or the entire family. Ignoring this social structure can result in problems of mistrust and decreased cooperation and communication.

Nonverbal Communication. One must be aware of body language and nonverbal communication and its meaning. Eye contact with the doctor or nurse or authority figures is regarded as disrespectful in some cultures. Loud vocalization may also be considered disrespectful. Rather than openly contradicting a person of authority, a parent will nod as if to communicate agreement but never follow through. Often the parent is viewed as noncompliant. In most societies, touch and space are regulated by rules and social orders. What is acceptable in one group may be forbidden in another; therefore respect personal boundaries and space issues. For example, Southeast Asians typically do not like to be patted on the top of their head or shoulder because this is where the soul resides. In American Indian and Alaskan Native populations, note taking is a taboo. Indian history has been passed down by means of verbal storytelling, and note taking is perceived as insensitive.[242]

Becoming culturally competent health care providers is an ongoing developmental process. One should be aware of the dimensions and complexities in caring for individuals from diverse cultural backgrounds. It is important to understand the family's core cultural dynamics, the meaning of the infant's illness, and the social context within which these life events are occurring. Specific customs, traditions, and taboos of each individual group are available in resource materials.[230,242]

COMMUNICATING MEDICAL INFORMATION: EVIDENCE-BASED PRACTICE

The principles of family-centered neonatal care clearly promote family participation in every aspect of their infant's care. The first four principles concern communication, medical information, fully informed parental decision making, and parental advance directives (see Box 29.2). Researchers have confirmed that information given to parents in the NICU is often communicated in euphemisms, vague statements, and half-truths, and shields parents from the uncertainties and controversies of NICU care.[100] Professional attitudes that may interfere with open, honest communication include (1) assuming that parents are too emotional to assimilate information and make a rational decision, (2) assuming that information about complications and poor outcomes may disrupt attachment to the neonate, (3) assuming that parental guilt and psychological harm will ensue from decision making (despite research to the contrary), and (4) cultural and language differences.[100,101] A multicenter qualitative study of parental values in decision making about delivery room resuscitation for their extremely preterm infants found that (1) all parents wanted to participate in decision making (although few

recalled discussing options for delivery room resuscitation; even fewer recalled being offered "comfort care," even though this was documented in the chart), (2) parents did not report that physician predictions of morbidity and mortality were central to their decision making, and (3) religion, spirituality, and hope were the guiding values for most parents in making their decision.[27,202]

Many parents desire and can handle complete, specific, honest, detailed, unbiased, and meaningful information—the same facts and interpretation of those facts as the staff—delivered in a humane and respectful manner.[74,100,101] Parents have expressed "remarkably uniform and unambiguous requests . . . to receive early, honest, and detailed information in a comprehensible and sympathetic manner and to be together when given bad news."[201] Prenatal consultation has been found to be useful by 80% of mothers in one study.[201] These researchers concluded that "in our population of educated mothers, most mothers prefer to be told exact statistics, rather than generalizations, concerning major neonatal morbidities."[201] Another study of prenatal counseling showed that 90% of mothers reported a positive experience. This study found that even though policy statements recommend a standardized approach to providing parents with child-centered information, and clinicians follow these guidelines, mothers want personalized information focusing on their individual concerns and questions, how NICUs work, and the integration of their family.[81]

A nurse-led intervention with 42 high-risk antepartum women expecting their infant to be in the NICU included an educational video, detailed description of prematurity and care requirements, family participation in the NICU, and a tour.[183] Within 48 to 72 hours after NICU admission, mothers were surveyed and found to be significantly less stressed about the sights and sounds of the NICU and their infant's appearance and behavior over time.[183] Another group of researchers used actuarial data for counseling parents about infants at the limits of viability and for morbidity counseling.[188] More recently, a multidisciplinary group formulated a prognosis-based guideline to assist parents and professionals in shared decision making about infants born at the threshold of viability.[146] Accuracy of prenatal and postnatal counseling of parents is of concern, because information affects practice management and influences parental decision making.[101,133,146,188,202]

Individuals vary in their desire to be informed and involved in decision making. Individuals also vary in the manner in which they assimilate information. Some parents may want extensive information about their situation, whereas others may not. Some parents may not wish to be decision makers and should be able to delegate decision making to a physician of their choice.[100] However, physicians have an ethical and legal obligation to give parents the facts from which to make an informed choice about their neonate's condition, illnesses, outcomes, and the risks and benefits of various interventions.[101] Proactive risk management strategies include effective communication because legal action in the form of civil malpractice suits (60%) and criminal action may result from poor communication between parents and physicians. Because language and cultural barriers in medical settings are increasing, federal and state governments have established a number of laws and standards to ensure that providers and health care organizations provide culturally and linguistically appropriate care.

Poor understanding by parents may be the result of poor communication techniques, contradictory messages, poor parental health, inexperience with medical terminology, denial, language barriers, inability to ask questions, shock over the birth of a preterm or sick newborn, lack of opportunity to review the information, or impaired recall in times of stress.[133,145,202] In one study, parents claimed that a neonatologist had never spoken to them, but, in fact, the conversation did occur and had been recorded.[131] In this study, parents were given a tape recording of their initial conversation with the neonatologist and any subsequent conversations of importance. The recording proved useful; 96% of the mothers and 68% of the fathers listened to the tape again, an average of 2.5 and 1.8 times, respectively. Eighty-five percent of the parents who listened to the recording had forgotten elements of the conversation, and two mothers did not recall that the conversation had ever occurred. Recorded conversations were found helpful by 99% of parents and grandparents, 76% of nurses, and 36% of neonatologists. Of the physicians, 40% were not happy about having their conversations recorded; "legal implications" was the most frequent reason given. As pointed out in the study, the "legal implications" work both ways; recording encourages precise, organized, clear, and humane communication of information while providing an "alibi" if a legal

complication arises. A randomized, single-blind trial found that mothers in the recorded conversation group had enhanced recall about their infant's diagnosis, treatment, and outcome (for up to 4 months) compared with the group without audio recordings (6 of the 98 mothers did not recall the conversation with the neonatologist).[134]

Research has documented that postpartum women have transient deficits in cognitive function, particularly in attention and memory function.[64] Because verbal communication may be poorly remembered, augmentation with written instructions is recommended.[64] In addition to relistening to a recording, if parents are given written information, such as an evidence-based table of likely outcomes of babies at different gestational ages, they can look at it again to review it. Such an evidence-based table for infants from 23 to 28 weeks' gestational age has been presented in the literature for use with parents.[131] This table contains information about mortality statistics, need for assisted ventilation, prolonged use of oxygen, length of stay, use of phototherapy, PDA needing treatment, outcomes of brain scans, and long-term neurodevelopmental outcomes. An NICU staff member can create a table for parents by using their most recent data.[132] With the advent of computerized databases (e.g., the Vermont Oxford Network database) that compare statistics from multiple NICUs and a large cohort of infants, parents can be provided with statistical information from multiple NICUs to compare with the outcomes from the NICU in which their baby is hospitalized. Parents may need assistance in interpreting statistics and making them meaningful to their individual situation. Again, some parents may want and need this type of information, whereas others may not. All communication needs to be culturally and linguistically appropriate.

Ongoing research on the *outcome of gestation table (OGT)* has documented views of parents, nurses, and physicians.[132] The majority of parents and nurses interviewed favored the table; they agreed that the information was frightening but important for parents to know. Parents wanted to keep a copy, and nurses wanted a copy in the medical record. Parents also thought that the information was easy to understand, the table did not contain "too much" information, and although it was frightening, they still would rather have the information. The majority of physicians thought that the table was easy to understand but had "too much" information, and they were ambivalent about using it in their practice. Parents, nurses, and physicians all agreed that the table and its information were not misleading. Of doctors, 21% disagreed about including a copy of the table in the medical record so that other health care providers would know what had been said to the parents. This finding was surprising to the researchers, who thought that inclusion of the table in the medical record would promote consistency in information given to the parents by different members of the perinatal team.

The Neonatal Research Network of the National Institute of Child Health and Human Development (NICHD) has developed a simple Web-based tool (see the Websites for Parents of Premature Infants section at the end of this chapter) to enable clinicians (and parents) to use multiple factors, not just gestational age, in making decisions about intensive care for extremely preterm infants.[143,252] A prospective study of 22 to 25 weeks' gestational age preterm infants ($N = 4446$) in the NICHD cohort found that the likelihood of a favorable outcome of NICU care was best estimated with consideration of gestational age in addition to sex, use of antenatal steroids, single/multiple birth, and birth weight. Calculation of the risk-to-benefit ratio of use of NICU care for the extremely preterm infant provides both care providers and parents with information that is "less arbitrary, more individualized, more transparent and better justified"[252] for informed decision making than use of gestational age alone.[143,252]

The principles of family-centered neonatal care (see Box 29.2) also advocate full and free access to lay and medical literature pertaining to the neonate's condition, proposed treatments, and probable outcomes.[100] Medical literature, articles, books, and videos (in English and Spanish) should be available in the NICU or in the hospital library for the parents' use. A video called *You Are Not Alone* (see the Resource Materials for Parents section at the end of this chapter) is available to help parents understand the impact on the family of long-term handicaps and to support them in making informed decisions. Access to the Internet has proved to be a source of medical information (some accurate; some inaccurate) for families and professionals. A recent survey found that 97% of parents prefer to find their information on the Internet, accessing it daily, and 81% use their smartphone; both of these technologies are preferred over books and brochures for information.[198]

Users report they can receive information, support, and comfort from their online activities and connections.[63] Parents may be more comfortable seeking medical advice from anonymous people in cyberspace rather than consulting their own health care providers. A study of fathers of premature infants and how they use social media found that they used these venues to discuss their concerns and to receive information, companionship, and emotional support.[125] When recommending the Internet as a resource, professionals should be aware of its benefits and its shortcomings.[57]

Acknowledgment of Guilt Feelings

The third psychological task parents are dealing with simultaneously with anticipatory grieving and withdrawal is confronting and recognizing their feelings of inadequacy and guilt in not delivering a healthy infant. Most parents struggling with these feelings are likely to search for answers to the causes of their infant's situation. The mother may focus on concrete things, such as not eating well, the flu, intercourse, birth control pills, or an unwanted pregnancy. The father also may be concerned about his role in not helping his wife enough, placing too many demands on her, an argument he provoked that precipitated labor, or another family member with the same chromosomal abnormality. Parents search for reasons because they need to find a cause for such an event happening to them. It is harder for them to feel out of control and helpless than to feel guilty. Some parents place responsibility on themselves; however, some shift the blame to others in their external world, such as their spouse, extended family, doctor, nurses, or God. Often both parents are concerned with the disappointment that they have caused the other. They may withdraw from each other at a time when they both need acceptance and support.

Realistic answers from the medical team are helpful for some parents in diminishing guilt feelings; in other parents, the guilt may be so deeply integrated in their thinking that it is less easily overcome. For example, some parents may focus on irrational, unrealistic factors, such as "This is my punishment for not being a good wife or daughter" or "This is my punishment for running away from home when I was 15." Often the more irrational the parent's thinking, the harder it is to assuage and resolve the guilt. Many feelings of guilt and failure are normal and expected; the feelings are a problem when the parent does not respond to the infant's progress, because the infant may continue to represent the parent's failure.

PARENTAL RESPONSES

Parents demonstrate many behaviors that indicate they are struggling with guilt and failure. Some parents directly verbalize these feelings and attempt to obtain helpful answers and support from the staff. Less obvious are the parents who are markedly depressed and remain so despite any improvement in the infant. These parents demonstrate the classic signs of depression, such as apathy, loss of interest in appearance and self, withdrawal, and loss of self-esteem. They exhibit an overwhelming sense of helplessness, feeling personally responsible for causing their infant's problem and are helpless to remedy the situation. Other parents struggling with guilt are highly anxious about their ability to handle their infant; they feel they have harmed their infant and are uncomfortable coming to the NICU or participating in their infant's care. Another manifestation of guilt is hostility and anger that is usually directed toward others, such as the spouse, the staff, or God. Instead of focusing their anger on themselves like a depressed parent, they direct it outward, projecting the guilt feelings onto others in their life. They may be angry at the physicians, nurses, or social workers for not making their infant healthy (if the infant is premature) or perfect (if the infant has a congenital defect). Unconsciously, they are trying to make the staff feel as guilty, helpless, and responsible as they do.

FACILITATING ADAPTATION

To intervene with parents, it is useful to assist them in acknowledging that their feelings of failure and guilt are a barrier to healthy coping and adjustment. The staff can provide them with appropriate information to modify and clarify the perceptions that may be the source of some of the parents' guilt feelings. Many parents directly ask about the causes of their infant's problem, and the medical team should counsel them with appropriate, honest information. Other parents are not as direct and verbal; they need to have the subject introduced. A staff member might ask, "Have you wondered why this has happened?" or "Many parents find themselves feeling responsible for their baby's problem, as if they failed. Have you had these feelings?" As parents begin to talk about their feelings, they can often

test reality and discover the irrationality in their thinking. However, some parents continue to feel guilty even though they have been told they are not to blame. Guilt feelings are very complex and may take a long time to resolve; for some, they may never be completely resolved but at least the intensity of the feelings may diminish. If a child recovers from the illness, guilt can be more easily relinquished. If the child has a chronic problem, the parent has a daily reminder of these feelings of responsibility. The more irrational the source of the guilt, the harder it is to dispel. Because this persistent guilt can cause problems in the parents' relationship with each other and with the child, a referral to a perinatal social worker or other mental health professional may be very helpful.

To facilitate support between parents, it is useful to ask whether they have shared their feelings of guilt and failure with each other. Often a spouse may assume that one is angry at or disappointed with the other. Discussing this may bring a tremendous sense of relief and reassurance. However, if the parents are blaming each other and relationship problems develop, a referral to a perinatal social worker or counselor is appropriate.

In some cases, there may be realistic reasons (either intentional or unintentional) why the parent may feel guilty about the infant's problem. Parental drug or alcohol abuse, domestic violence, an accident, or an inherited genetic problem may be a real reason. In these cases, the staff must acknowledge to the parent that there is a causal relationship and then give the parents support by allowing them to talk about their feelings. If causes were not intentional, it is helpful to acknowledge that fact; if they were, it is important to be nonjudgmental. A judging attitude only reinforces the feelings (e.g., guilt, concern, uncertainty) parents are already experiencing and further alienates them from the infant and staff. When this type of psychosocial issue arises, the involvement of a perinatal social worker or other mental health professional is essential.

POSTPARTUM MOOD DISORDERS

The postpartum period is a time of increased risk for development of mood disturbances in women (and men) that affect the entire family.[42,77,108,148,151] The incidence of postpartum mood disorders is estimated to be 15%, with as many as 50% of mothers still depressed at 6 months and 25% still depressed at 1 year after birth.[148] The incidence of paternal depression is estimated at 4% to 12%, and in a more recent study at 27%; paternal depression is underreported, underscreened, underdiagnosed, and undertreated.[184,207] A longitudinal study of paternal mental health during the transition to fatherhood found depressive symptoms scores increased by 68% in the first 5 years of their child's life.[77] The strongest risk factor and predictor of paternal postpartum depression (PPD) is maternal PPD.[184] At a time of individual and family role transition, neither parent receives the support needed from his or her partner when both are depressed.

Symptoms of postpartum mood disorders may be transient and relatively mild (baby blues) or may be associated with significant impairment of functioning (e.g., postpartum depression and psychosis). Women with a history of mood disorders and those who experience depression during pregnancy are at greatest risk.[148] Box 29.7 lists significant predictors of postpartum mood disorders.

Evidence suggests that mothers of premature infants or infants with problems and those with multiple births experience a higher rate of PPD than women who deliver a single full-term infant.[16,94,108,166] A study of 111 mothers whose infants were in the NICU found positive depression screens in 52%, and 30% received an "at-risk for depression" score.[166] Another study found that 20% of mothers of very preterm infants had clinically significant depression, and 43% had moderate to severe anxiety.[220] Although anxiety was common, the researchers did not find identifiable risk factors, but depression was associated with being married, parental role alteration, and prolonged respiratory ventilation for the preterm infants.[220] Maternal anxiety has also been correlated with prolonged length of stay in the NICU.[38] More recent studies of parents with VLBW infants found an incidence of depressive symptoms in 36% of fathers and 40% of mothers[200]; and 42% of low-income mothers in another study.[79] Parental anxiety at birth was 48% for mothers and 47% for fathers of very preterm infants; both parental depression and anxiety had decreased by 6 months.[200] A longitudinal study (from birth to 2 months after discharge) of fathers with preterm infants in the NICU found (1) 12% with high stress levels on admission and 8% at

BOX 29.7 SIGNIFICANT PREDICTORS OF POSTPARTUM MOOD DISORDERS

- History of previous depression (before and during pregnancy; bipolar disorder)[137,150,153]
- Present depression and anxiety disorders (panic, posttraumatic stress and obsessive compulsive disorders; phobias; neurotic personality)[108,109,264]
- Family history of mental illness[264]
- Depression and anxiety associated with previous perinatal loss that continues after the birth of a subsequently healthy infant[26]
- Low quality of prenatal attachment[54,84,199,221,222]
- Antenatal pessimistic outlook about maternity[217]
- Nonworking women with a history of emesis during pregnancy and depression[85]
- Low self-esteem
- Negative, stressful life events[150] (such as childhood physical/sexual abuse[80]; intimate partner violence[127]; prenatal diagnosis of fetal anomaly[44]; mode of delivery that entails maternal lack of control, such as primary or emergency cesarean delivery[84]; preterm birth[94]; multiple birth[86]; infant death[258]; and no anesthesia during delivery[264])
- >BMI (overweight; obese)[264]
- Gestational diabetes[236]
- Giving birth in the summer or fall months[264]
- Marital discord
- Poor social support[94,150]
- Difficult infant temperament
- Childcare stresses
- History of endocrine dysfunction
- Maternity blues
- Single marital status
- Adolescent pregnancy[42,224]
- Unplanned/unwanted pregnancy
- Low socioeconomic status/low household income[150]
- Minority racial and ethnic groups (Native Americans, African Americans, Hispanic; Arab Americans)[40,42,139,153]
- Immigrant women[42,264]

Data from Beck C. Recognizing and screening for postpartum depression in mothers of NICU infants. *Adv Neonatal Care.* 2003;3(1):37; O'Hara M, Gorman L. Can postpartum depression be predicted? *Prim Psychiatry.* 2004;11:42.

discharge, (2) mild depressive symptoms that decreased from 41% to 10%, and (3) major depressive symptoms that decreased from 16% to 2%.[49]

PPDs usually are divided into three categories: (1) postpartum blues, (2) nonpsychotic PPD, and (3) postpartum psychosis, although these disorders do exist along a continuum.[17]

Postpartum Blues

Postpartum blues (baby blues) affects approximately 50% to 80% of new mothers. Symptoms may include mood swings, sleep and appetite disturbances with periods of feeling anxious, irritability, and tearfulness interspersed with times of feeling well. Symptoms often begin within a few days of delivery and persist up to several days. Postpartum blues is time-limited and relatively benign. The symptoms worsen by the 5th or 7th day and tend to resolve by the 12th postpartum day. The occurrence of the "baby blues" does not necessarily indicate psychopathology; however, if the symptoms persist longer than 2 weeks, a further evaluation is needed because approximately 20% of women develop postpartum major depression.[6] A study of delivery mode and PPD found higher Edinburgh Postnatal Depression Scale (EPDS) scores at 48 to 72 hours after birth (but not at 6 to 8 months postnatally) in mothers after primary cesarean delivery compared with spontaneous delivery.[210]

Postpartum Depression

Postpartum depression is relatively common. Several controlled studies reveal that between 12% and 20% of women experience a postpartum depressive episode, and this rate is as high as 26% in adolescent mothers; rates vary by race/ethnic group.[6,153] Most women begin to experience depressive symptoms within the first month after delivery, although some have reported symptoms during the pregnancy. Signs and symptoms include a depressed mood, lack of interest or pleasure in usual activities, guilt, impaired concentration, appetite disturbance, low self-esteem, feelings of hopelessness and worthlessness, and suicidal ideation.[17]

Postpartum Psychosis

Postpartum psychosis is a rare but extremely serious mental illness occurring in 1 to 2 per 1000 deliveries. It generally occurs within the first 2 to 3 weeks after delivery and requires immediate attention. The symptoms are crying, irritability, restlessness, sleep disturbances, delusions, hallucinations, and bizarre, irrational behavior. For example, a woman may view the baby as the devil, claim the

infant is dead, or accuse the hospital staff of switching babies. There are significant risks for infanticide or suicide.

Paternal symptoms of depression occur after the onset of maternal PPD, are worse during the first 3 to 6 months after birth, and have symptoms similar to those of depressed mothers. However, paternal depression manifests with more subtle symptoms that include negative parenting behaviors, withdrawal from social situations, an increase in relationship conflicts, alcohol and drug abuse, and intimate partner violence (IPV).[184]

The causes of postpartum disorders are multifactorial. Pregnancy is a complex biologic process that takes place within a psychological and social context. Some determinants are the psychological makeup of the mother, hormonal changes associated with pregnancy,[66] genetics, socioeconomic issues, stress, the temperament and health of the baby, marital instability, ambivalence toward the pregnancy, culture, and the emotional support system of the new mother.[94,137,148] When the features listed in Box 29.8 occur in mothers with a sick infant, it may be difficult to differentiate a normal reaction to an adverse situation, a grief reaction, from signs of PPD.

In general, postpartum disorders are often overlooked and not appreciated, thereby putting the mother at risk for development of recurrent depression and altered maternal attachment, which are both associated with deleterious effects on the behavioral, cognitive, emotional, and social development of the infant.* A longitudinal study of first-time mothers (with normal pregnancies and healthy babies) found that 22% who were depressed on day 10 postpartum continued with low mood for the first year of the baby's life and had less closeness, warmth, and confidence in parenting their baby in that first year.[151] Given the inherent stresses and emotional impact the birth of a sick infant(s) has on the mother and her family, it is recommended that universal screening for PPD be a part of every family assessment in the NICU.[16,108,220] "Routine assessment will normalize the process, enhance awareness and increase the health care providers' comfort level and competency."[16] An evidence report and systematic review for the U.S. Preventive Services Task Force about primary care screening and treatment for depression in pregnant and postpartum women found that screening these women for depression may actually reduce depressive symptoms in those with depression and reduce the prevalence of depression in a given population.[196]

*References 16, 17, 106, 107, 147–149, 249, 250.

BOX 29.8 CRITICAL FINDINGS
ADDITIONAL FEATURES OF POSTPARTUM MOOD DISORDERS

- Overly concerned for the baby or excessive anxiety over the infant's health
- Guilt, inadequacy, worthlessness, especially feeling like a failure at motherhood
- Fear of losing control or "going crazy"
- Lack of interest in the baby
- Fear of harming the baby
- Obsession

Assessment Tools

Several assessment tools are designed to identify women with a substantial increased risk for PPD. Ideally it is recommended that these assessment tools be administered at each trimester of pregnancy and periodically after delivery to assess a woman's risk status. The literature contains extensive discussion of the various assessment tools and checklists, and their reliability and predictability of PPD.[12,15] Although many tools are available, three seem to be used extensively: (1) the Postpartum Depression Screening Scale (PDSS)[16]; (2) the Postpartum Depression Predictors Inventory–Revised (PDPI-R) (Table 29.1) (these tools are also available in Spanish)[15,20,21] based on a meta-analysis of 84 studies published to identify significant risk factors of PPD[14]; and (3) the Edinburgh Postnatal Depression Scale (EPDS) (Table 29.2).[46,47]

The PDSS and PDPI-R have different uses. The PDSS is a 35-item self-report Likert scale that assesses seven areas: (1) sleeping/eating difficulties, (2) anxiety/insecurity, (3) emotionality, (4) mental confusion, (5) loss of self, (6) shame or guilt, and (7) thoughts of self-harm.[16,19,20] The scale measures depressive symptomatology. The total score ranges from 13 to 175. If a mother's score is 80 or greater, this is a positive screen for PPD, and a referral for mental health follow-up is

TABLE 29.1 POSTPARTUM DEPRESSION PREDICTORS INVENTORY (PDPI)-REVISED AND GUIDE QUESTIONS FOR ITS USE

DURING PREGNANCY	CHECK ONE	
Marital Status		
1. Single	○	
2. Married/cohabiting	○	
3. Separated	○	
4. Divorced	○	
5. Widowed	○	
6. Partnered	○	
Socioeconomic Status		
Low	○	
Middle	○	
High	○	
Self-Esteem	***Yes***	***No***
Do you feel good about yourself as a person?	○	○
Do you feel worthwhile?	○	○
Do you feel you have a number of good qualities as a person?	○	○
Prenatal Depression		
1. Have you felt depressed during your pregnancy? If yes, when and how long have you been feeling this way? If yes, how mild or severe do you consider your depression?	○	○
Prenatal Anxiety		
Have you been feeling anxious during your pregnancy? If yes, how long have you been feeling this way?	○	○
Unplanned/Unwanted Pregnancy		
Was the pregnancy planned?	○	○
Is the pregnancy unwanted?	○	○
History of Previous Depression		
1. Before this pregnancy, have you ever been depressed?	○	○
If yes, when did you experience this depression?		
If yes, have you been under a physician's care for this past depression?	○	○
If yes, did the physician prescribe any medication for your depression?	○	○
Social Support		
1. Do you feel you receive adequate emotional support from your partner?	○	○
2. Do you feel you receive adequate instrumental support from your partner (e.g., help with household chores or baby sitting)?	○	○
3. Do you feel you can rely on your partner when you need help?	○	○
4. Do you feel you can confide in your partner? (Repeat same questions for family and again for friends)	○	○

Continued

TABLE 29.1 POSTPARTUM DEPRESSION PREDICTORS INVENTORY (PDPI)-REVISED AND GUIDE QUESTIONS FOR ITS USE—CONT'D

DURING PREGNANCY	CHECK ONE	
Marital Satisfaction		
1. Are you satisfied with your marriage (or living arrangement)?	○	○
2. Are you currently experiencing any marital problems?	○	○
3. Are things going well between you and your partner?	○	○
Life Stress	○	○
1. Are you currently experiencing any stressful events in your life such as:		
Financial problems	○	○
Marital problems	○	○
Death in the family	○	○
Serious illness in the family	○	○
Moving	○	○
Unemployment	○	○
Job change	○	○
After delivery, add the following items:		
Child Care Stress		
1. Is your infant experiencing any health problems?	○	○
2. Are you having problems with your baby feeding?	○	○
3. Are you having problems with your baby sleeping?	○	○
Infant Temperament		
1. Do you consider your baby irritable or fussy?	○	○
2. Does your baby cry a lot?	○	○
3. Is your baby difficult to console or soothe?	○	○
Maternity Blues		
1. Did you experience a brief period of tearfulness and mood swings during the first week after delivery?	○	○
Comments		
_____		
_____		
_____		
_____		

From Beck C. Revision of the postpartum depression predictors inventory. *J Obstet Gynecol Neonatal Nurs.* 2002;31(4):394.

indicated. The mother completes the PDSS herself, and then it is scored. The tool is used only after delivery. The PPDS has been found to be reliable as a depression screening scale for mothers in the NICU.[166]

The PDPI-R is an inventory that (1) assesses a woman's risk status for developing PPD, (2) can be used during pregnancy and after delivery, and (3) should complement a clinician's professional judgment. It consists of 13 risk factors and is designed

TABLE 29.2 EDINBURGH POSTNATAL DEPRESSION SCALE

HEALTH VISITOR	NUMBER
Today's date _____	Baby's age _____
Baby's date of birth _____	Birth weight _____
Triplets/twins/single _____	Male/female _____

How are you feeling?

As you have recently had a baby, we would like to know how you are feeling now. Please underline the answer that comes closest to how you have felt in the past 7 days, not just how you feel today.

Here is an example already completed:

I have felt happy:
Yes, most of the time
Yes, some of the time
Not very often
No, never
This means: "I have felt happy some of the time" during the past week.
Please complete the other questions in the same way.

In the past 7 days:

1. I have been able to laugh and see the funny side of things:
   As much as I always could
   Not quite so much now
   Definitely not so much now
   Not at all

2. I have looked forward with enjoyment to things:
   As much as I ever did
   Rather less than I used to Definitely less than I used to
   Hardly at all

3. I have blamed myself unnecessarily when things went wrong:
   Yes, most of the time
   Yes, some of the time
   Not very often
   No, never

4. I have felt worried and anxious for no good reason:
   No, not at all
   Hardly ever
   Yes, sometimes
   Yes, very often

5. I have felt scared or panicky for no very good reason:
   Yes, quite a lot
   Yes, sometimes
   No, not much
   No, not at all

In the past 7 days

6. Things have been getting on top of me:
   Yes, most of the time I haven't been able to cope at all
   Yes, sometimes I haven't been coping as well as usual
   No, most of the time I have coped quite well
   No, I have been coping as well as ever

Continued

TABLE 29.2 EDINBURGH POSTNATAL DEPRESSION SCALE—CONT'D

HEALTH VISITOR	NUMBER
7. I have been so unhappy that I have had difficulty sleeping:	
Yes, most of the time	
Yes, some of the time	
Not very often	
No, not at all	
8. I have felt sad or miserable:	
Yes, most of the time	
Yes, some of the time	
Not very often	
No, not at all	
9. I have been so unhappy that I have been crying:	
Yes, most of the time	
Yes, quite often	
Only occasionally	
No, never	
10. The thought of harming myself has occurred to me:	
Yes, quite often	
Sometimes	
Hardly ever	
Never	
Edinburgh Postnatal Depression Scale: Scoring Sheet	
1. I have been able to laugh and see the funny side of things:	
As much as I always could	0
Not quite so much now	1
Definitely not so much now	2
Not at all	3
2. I have looked forward with enjoyment to things:	
As much as I ever did	0
Rather less than I used to	1
Definitely less than I used to	2
Hardly at all	3
3. I have blamed myself unnecessarily when things went wrong:	
Yes, most of the time	3
Yes, some of the time	2
Not very often	1
No, never	0
4. I have felt worried and anxious for no good reason:	
No, not at all	0
Hardly ever	1
Yes, sometimes	2
Yes, very often	3

TABLE 29.2 EDINBURGH POSTNATAL DEPRESSION SCALE—CONT'D

HEALTH VISITOR	NUMBER
5. I have felt scared or panicky for no very good reason:	
Yes, quite a lot	3
Yes, sometimes	2
No, not much	1
No, not at all	0
6. Things have been getting on top of me:	
Yes, most of the time I haven't been able to cope at all	3
Yes, sometimes I haven't been coping as well as usual	2
No, most of the time I have coped quite well	1
No, I have been coping as well as ever	0
7. I have been so unhappy that I have had difficulty sleeping:	
Yes, most of the time	3
Yes, some of the time	2
Not very often	1
No, not at all	0
8. I have felt sad or miserable:	
Yes, most of the time	3
Yes, some of the time	2
Not very often	1
No, not at all	0
9. I have been so unhappy that I have been crying:	
Yes, most of the time	3
Yes, some of the time	2
Not very often	1
No, not at all	0
10. The thought of harming myself has occurred to me:	
Yes, quite often	3
Sometimes	2
Hardly ever	1
Never	0

for the clinician and the woman to discuss each risk factor that might put her at risk for developing PPD. There is no total score; rather, it is a tool that provides detailed information on symptoms.

With some modifications, as reported by a study in Australia, the PDPI-R has been used as a checklist that the woman administers herself. The information from the checklist was then used to initiate discussions by midwives and nurses with women about their postpartum depression.[99]

The EPDS is a 10-item screening questionnaire that (1) is completed by mothers (and fathers)[108] and then scored by clinicians, (2) is useful as an inventory to identify parents at risk to initiate an open discussion about PPD, (3) requires minimal training to administer, and (4) is completed in less than 10 minutes. The EPDS is a reliable and valid measure of depression or anxiety disorders in fathers during the perinatal period[164] and can be used by pediatric health care providers in the outpatient setting to help identify and assist mothers at risk.[65,75] The EPDS can be used at 6 to 8 weeks after delivery and is easy to score. The items are ordered and weighted to reflect severity of symptoms. One study found that the self-administered EPDS and the directed interview EPDS are equal in their ability to screen for PPD, and either technique should be used to screen for PPD.[120] A score of 12+ indicates the likelihood of depression but not its severity, although with this score, further assessment and possible intervention are recommended. If the woman or man scores positive on item 10, thoughts of harming self, immediate intervention is necessary.[12]

Many studies have demonstrated that mothers of sick or premature infants are at greater risk for psychological distress than are mothers of full-term infants. These studies have looked at depressive symptoms in mothers during hospitalization and after discharge. The goal of these studies, by using assessment tools, has been to identify (and ultimately treat) women at risk for depression, thereby decreasing the negative effect on infant development. General themes emerge from these studies.[16,17,44,94,108] Social support was consistently identified as extremely important, both during the hospitalization and after discharge when the mother has full responsibility for the infant(s) for the first time. Increased stress at discharge, the isolation, and being disconnected from the NICU support network contribute to the risk for PPD. Therefore social support is necessary and can serve as a buffer to the effects of depression. Logsdon and Usui's work[155] supported what other studies have found—that closeness to one's partner, social support, and self-esteem are important predictors of PPD regardless of ethnic diversity. Stress and uncertainty surrounding the birth of a sick newborn increase the need for support. Support provided by the health care team to a mother's adaptation to the NICU environment, information communicated about the infant and his or her treatment, facilitating maternal self-confidence, accurate knowledge of infant development (at the time of discharge), and self-care knowledge about symptoms of depression and who to contact for help can influence a mother's risk for PPD.[148,156] All of these factors indicate the need for enhanced FCC in the NICU and after discharge.

Mothers whose infants have chronic complications and who present long-term management challenges are more likely to experience more severe depressive symptoms. In addition, the role of the hospital environment coupled with the appearance of the infant contributes to maternal symptoms. In a study done in Japan, it was found that close emotional support of the father was much more significant than the existence of other modes of peripheral support.[186] This same study concluded that active intervention for PPD is necessary for the mother to be emotionally available to attach to the infant and cope with the infant's hospitalization and subsequent issues related to discharge. More research shows that chronic exposure to maternal depression has long-term negative effects on a child's emotional, psychological, and cognitive development.[108,147,248,249]

Treatment and Intervention

PPD and its symptoms present themselves along a continuum. Interventions should be guided by the severity of symptoms and the degree of impairment of the individual. Because PPD is a complex biologic and psychological phenomenon, a comprehensive approach is needed, including reassurance and support (from a doula or telephone-based peer support), comprehensive professional home visits in which nurses screen and counsel for PPD, problem-solving education,[237] psychoeducation, individual or group psychotherapy, and psychopharmacology.[10,56,82,204]

Fathers identified the need for both professional support and support from family and friends to be

supportive to a depressed partner and to deal with their own depression.[149,150] Parenting classes enable fathers, as well as new mothers, to learn the skills necessary to care for their infant and feel confident, in control, and less frustrated.[186] Education about PPD, its symptoms, and practical coping strategies were also identified by fathers as helpful.[148,149] Depressed fathers are less able to emotionally support the mother and participate in parenting, which negatively affects their relationship, attachment to the infant, and ultimately the emotional, behavioral, and social development of the infant/child.*

Prior studies have demonstrated that when parents experience less stress they are able to form early attachments to their sick infants.[262] Mothers with greater stress have less positive attitudes and interactions with their infants than those with less stress.[48] This lack of parenting confidence has been associated with lower levels of child competence, poorer developmental outcomes, and altered relationships with children into adulthood, and it affects multigenerational familial relationships.[185,239] Conversely, multiple studies have shown that positive attitudes and parental confidence are associated with secure infant attachments that lead to increased competence and better developmental outcomes.[48] Sensitivity training for parents aimed at recognizing signs of infant stress while infants are in the NICU and thereby promoting better mother-infant attachment and improved infant developmental outcomes may be helpful.[62]

In childbirth classes, PPD should be addressed with anticipatory guidance discussing risk factors and early symptoms. Information brochures with resources should be available. Support groups often prepare mothers (and fathers) for the reality of parenthood and provide anticipatory guidance and counseling, skill building, validation, and acknowledgment of the concerns and frustrations of caring for a new infant. There are often support groups specifically for PPD available in local communities and at the statewide level. Referral to national organizations such as Postpartum Support International and Depression After Delivery enables mothers and fathers to access many additional resources (see the Resource Materials for Parents section at the end of this chapter). Other interventions include visiting nurse services, nurse home visitors, parenting classes, referrals to childcare resources, and mutual aid hotlines. NICU-based cognitive behavioral therapy has been shown to significantly decrease maternal depression, but not anxiety symptoms, in mothers of sick babies.[175] A 4-week, five-step individualized intervention program for parents of an infant in the NICU resulted in less anxiety and no depression in 50% of mothers and 80% of fathers at discharge compared with 100% of parents without the individualized program.[33] A meta-analysis found that *any* psychosocial or psychological intervention (compared with routine postpartum care) reduced symptoms of depression and the likelihood of continued PPD within the first year after giving birth.[56]

Many psychotherapy modalities are recommended to mothers. Couples therapy may be part of the treatment plan if there is marital discord; however, even when there are no particular difficulties in the relationship, including the father can be useful in providing information and support for the mother. Suggestions for increased help around the home can be of tremendous value, allowing the mother to obtain adequate rest and care for herself. If the symptoms are very severe, psychiatric day treatment or inpatient hospitalization may be necessary. (In England, there are mother/baby inpatient units.) In cases in which the infant's life is in danger, protective services may have to be involved.

The use of medications (selective serotonin reuptake inhibitors, mood stabilizers, antidepressants, and antipsychotics) may be necessary.[53] In a recent study, the use of antenatal antidepressant medications resulted in fewer postpartum mothers reporting postnatal depressive symptoms when compared with a group of mothers who did not use medication.[159] The use of hormonal manipulation has been investigated. Referral to a clinician who is familiar with PPD is recommended.

Breastfeeding is associated with a reduced risk for PPD that is maintained over the first 4 months of the postpartum period.[98] However, women with postpartum depressive symptoms breastfeed an average of 2.4 weeks less than women without symptoms.[13] The issue of breastfeeding when considering psychotropic medications needs to be addressed.[138] Parents should be provided necessary information about the effects of these medications on the neonate so that the risks and benefits can be considered on an individual basis. All psychotropic medications enter the breast milk, so careful evaluation with the health care team needs to be undertaken (see Table 18.7).

*References 16, 17, 106, 107, 147–149, 184, 249.

ADAPTATION TO THE INTENSIVE CARE ENVIRONMENT

The fourth psychological task involves adaptation to the intensive care environment.[70,92] All of the reactions of guilt, anxiety, fear, anger, and disappointment become heightened when parents attempt to adapt to this unfamiliar and alien environment.[202] They must learn a new language, establish trust in new relationships, and adapt to their role in this setting.[70,165,202] The intense and sometimes chaotic appearance of a high-risk nursery makes it a frightening experience that serves to increase parental feelings of helplessness and anxiety. Parents should gain a sense of security in this environment before initiating a caregiving role with their infant. There may be cultural and linguistic adaptations and geographic obstacles for families who live in small, rural communities and must travel to large, unfamiliar cities and adapt to large hospitals. Locating the hospital and finding accommodations and meals can become overwhelming to parents who have undergone much emotional turmoil. Meeting the infant's care providers, the competent physician and nurse, sometimes can evoke a mixture of positive and negative feelings. Parents may be reassured and grateful for care being given, but their feelings of uselessness, helplessness, and inadequacy can be reinforced.[192] The sophistication of the highly technical care and heroic measures provided to achieve survival for their infant may be met with both awe and uncertainty.[158,202] Family disruption is exaggerated by distance, especially if the infant was transported, and the father must decide whether he is most needed with the infant, the infant's mother, or perhaps other children at home. Decisions must be made about work responsibilities and childcare. The financial concerns related to providing intensive care become an added stress on families and are often compounded by the travel expenditures necessary to visit the infant.

With the development of high-risk perinatal centers, an increasing number of mothers are transported to the maternity division of hospitals with an NICU just before delivery or shortly thereafter. If there is not sufficient time to arrange for her transport before she gives birth, it is strongly recommended that the mother be moved as soon as possible.

In general, having an infant in the NICU has wide-reaching effects on the entire family system (parents, grandparents, siblings, employment, finances,[73] childcare). Table 29.3, written by a mother of a 28-weeks' gestational age neonate 1 year after their NICU experience lists practical ways "to help preemie parents in the NICU." A social worker providing comprehensive services and interventions is imperative to guide the family during this difficult time.

Parental Responses

In comparing the psychosocial adjustments of parents in the NICU, both parents may experience increased levels of emotional distress.[59,202] Mothers have been found to be more anxious, hostile, and depressed than fathers, with poorer adjustments related to work, sexual relations, social environment, and psychological distress.[59] Mothers and fathers experience the NICU stay differently; mothers found the entire NICU experience and its aftermath more stressful than did fathers.[59,111] It is important to include both mothers and fathers in assessments and interventions and to avoid overlooking the father's needs because he may be less accessible.[59,111,158] A systematic review of qualitative studies of the lived experience of fathers of preterm infants in the NICU found paternal ambivalence and five main themes: (1) emotional roller coaster, (2) paternal needs, (3) coping strategies, (4) self-representation, and (5) caregiving engagement at birth of the preterm infant, during the NICU stay, and after discharge home.[206] Another recent study of the lived experience of fathers of preterm infants less than 28 weeks' gestational age found four main themes: (1) looking in, (2) persevering, (3) holding, and (4) finding my way.[154] Fathers described feeling like an outsider in the NICU while learning to trust others, protect mother and baby, and continue working to provide for the family. Fathers need communication, empathy, expectation by health care providers that father will be involved in care and parenting in the NICU, support in establishing a father-infant relationship, and emotional support for the stressful experience of the NICU in a similar fashion as for mothers.[191,202]

A number of nonverbal and verbal signs indicate that parents are struggling to gain a sense of security in the NICU. Some parents appear frightened, overwhelmed, nervous, and withdrawn, asking few questions or being reluctant to call or visit. Others may be highly anxious and unable to focus on their infant and may instead concentrate on other activities or infants in the nursery. Some parents may ask

TABLE 29.3 SEVENTEEN WAYS TO HELP "PREEMIE PARENTS" IN THE NICU

STRATEGY	RATIONALE
"Preemie parents" are different from "termie" parents so don't go on autopilot	"Preemie parents" have a hospitalized child fighting to survive. The scene isn't jubilant yet. We are neither physically nor mentally prepared for the usual frozen meals, cute onesies or requests for pictures. Wait until we start celebrating (likely after discharge).
Curb your curiosity	Please don't pry. Parents may not know why the baby was born early but feel shock and guilt about it. Talking about the baby's health issues and roller coaster of the NICU is too scary and everything is unknown. The same discretion goes for mom's body and health status. If we share, listen. Until then your curiosity must go unsatisfied.
Respect our privacy and let us announce the preemie's birth.	Parents come out of their post-labor stupor to find their intimate, traumatic news spread far and wide. Be discreet. Let "preemie parents" announce our news on our schedule and our way.
Offer to help but don't be too proactive.	Sitting in the NICU inventing errands or shopping lists to make loved ones feel useful is a burden. Let parents focus. My favorite texts were question-free and read, "Thinking of your family. Here to do anything when you want help. No need to reply now." If parents don't respond, be patient. You might be on standby for a few days—or weeks—but we'll probably take you up on the offer.
Keep baby gear out of the house or at least hide it.	After my delivery, with the baby still in the NICU, I came home to a lovely display of new baby clothes on my kitchen counter. But to my husband's shock I collapsed to the floor and sobbed the rest of the night. The clothes reminded me our baby couldn't come home and his survival wasn't guaranteed. Thanks goodness we didn't have a nursery yet. Wait until we say we're ready and then stick to our registry—some preemies need special gear.
If you must send a gift, shop for the parents	Useful items include a nursing apron (or any cover-up for mom while pumping in the NICU), an insulated lunch bag (filled with snacks), a file box with folders (for the mountain of medical paperwork), a notebook and folder (to track conversations and forms), and a chest freezer (for breastmilk). Subscriptions to Netflix and HBO helped us stay awake during kangaroo care. My husband appreciated cash cards to spend on parking and hospital coffee. I enjoyed a home mini fridge for breastmilk and midnight snacks.
Pack high-protein food to eat with one hand.	We were frazzled parents glued to a hospital chair with no oven in sight, so we couldn't heat large frozen casseroles. Luckily some friends assembled lunch packs of little sandwiches, hard boiled eggs, cheese cubes, nuts, apples, breakfast bars, fresh salads, and chocolates. Those packs kept us going without leaving our son's bedside.
Skip preemie clothes	Younger preemies in incubators don't wear clothes. At our NICU, gifts of new outfits for older preemies required separate tracking by the nurses and extra laundry for me. Unless we request outfits with specific features (yay snaps!), wait until baby is home and then go nuts with fashion.
Be calm and cautiously optimistic in front of "preemie parents".	Crying to us on the phone or telling us you're worried sick makes things worse. Be zen. Our parents kept their cool and it reassured us. And please don't tell us our child's birth was traumatic for you, too. Please sort through your emotions with anyone but us.
Tell "preemie parents" you think of them all the time	From Dominican nuns in Brooklyn to a minyan in Denver to co-workers in Seattle, people rooted for us. Their faith pulled us through the toughest weeks.
Recognize that each "preemie parent" has a unique—possibly competing—coping style.	My husband preferred running errands and being distracted. I loved being left alone to hold the baby in silence. Care for each parent accordingly.
Give "preemie parents" time to get their bearings.	In the NICU, parenting can feel untenable. Our home was the only place we could have control or predictability. Coming home to a cleaned house was wonderful. Coming home to a reorganized one was frustrating. Remember baby was born early but isn't coming home early. There's no need to take over. Protect the normalizing things, like nesting or making a registry, for us to enjoy later.
Let "preemie parents" find their own silver linings.	We heard some well-meaning but demoralizing comments like: "At least you get to sleep through the night." No we don't. "Isn't it a relief not to be pregnant?" Stop. "Small babies hurt less to deliver, right?" Ugh. "Welcome to parenthood!" Hmmm…wanna trade places? Yes, they are blessings. Let us discover them—and we will!

Continued

TABLE 29.3 SEVENTEEN WAYS TO HELP "PREEMIE PARENTS" IN THE NICU—CONT'D

STRATEGY	RATIONALE
Skip asking when the baby will come home.	The due date is the target and we're more impatient than you are. We'll share when the NICU staff give the green light.
Wait until you are invited to meet the baby.	We might not be ready for NICU visitors. After discharge, we'll want quiet time to breathe and hold each other without wires and monitors around. We'll invite you when and where the time is right for us.
Respect the quarantine.	Preemies build immunity with time, not exposure. If you're invited to the NICU (or the house after discharge), get vaccinated and follow sanitizing protocol. These precautions are doctor's orders, not overprotective paranoia. We're taking a risk having you over, so please comply. The best guests wear clean clothes without perfumes and wash and gel up without being asked.
Most of all, tell "preemie parents" you believe in them	Friends and family told us we were good parents doing everything right. Your love is powerful medicine and we need it now more than ever.

Modified from Kagan L. 17 ways to help preemie parents in the NICU. *The Huffington Post.* November 21, 2016. Used with permission of Lisa Kagan. Available at: https://www.huffingtonpost.com/entry/17-ways-to-help-preemie-parents-in-the-nicu_us_582f4d65e4b0eaa5f14d441d. Accessed July 8, 2018.

many questions and become very interested in the technical aspects of their infant's treatment, such as respirator settings and laboratory values, in an attempt to understand and cope with their infant's illness.[58,158] Some parents, uneasy with entrusting their infant to strangers, may initially feel a need to remain at his or her side, maintaining a vigil. Some may wish to read the infant's chart or attempt to read material on their infant's particular condition. Others may become angry or upset at minor differences in the infant's care or the nursery policies, such as a respiratory setting being off a point or discrepancies in enforcing visitation guidelines.[70,90]

Research into the mother's needs in the NICU have found that the mother's priority is to safeguard her infant. Mothers perceive that if they advocate for their own needs (e.g., to mother or care for the infant) in the NICU, they will be labeled as "difficult" or "demanding." Maternal needs in the NICU include information and interaction with their infant, emotional safety, and a supportive NICU environment in which to meet their needs (Table 29.4).[167] When these needs are thwarted, mothers feel helpless, powerless, and emotionally vulnerable and are less able to interact with their infant. A major barrier to implementing FCC is the mother's fear about how her needs, feelings, and actions affect the care of her baby. FCC empowers mothers and fathers through collaboration with health care providers.[202]

For families, the relationship with health care providers progresses through three stages: naïve trust, disenchantment, and guarded alliance.[165,167,202] Naïve trust, the belief that the family will be informed and involved in decision making, becomes disenchantment when unmet expectations, distrust, and anger result in the belief that the sick family member needs to be protected. A guarded alliance develops when families become more able to navigate the health care system and are involved, are in control, and participate in the care of their sick member. Helpful interventions include (1) meeting the individual family's needs, (2) providing a welcoming NICU environment, (3) personalizing the infant, (4) teaching parents to interpret their infant's cues and behaviors, (5) fulfilling the continuing need for information, and (6) forming partnerships with families in all aspects of decision making and caregiving,[165,202] including giving them the option to be present during procedures and participate in pain relief for their infant.[117,167]

Facilitating Adaptation

Many interventions can be employed to familiarize and orient families.[92] First, the obstetrician, transport team, or any other professional who has initial contact with parents can give them preparatory information and a description of intensive care. A booklet or video[92] in the native language of the

TABLE 29.4 MATERNAL NEEDS IN THE NEONATAL INTENSIVE CARE UNIT

MATERNAL NEED	RECOMMENDATIONS FOR NICU STAFF
Empowering information	Give information about the maternal situation in the NICU (e.g., feelings, importance of her role as mother of the baby). Give information on how a preterm baby differs from a term baby and how to read/respond to her individual baby's cues/behaviors. Facilitate opportunities for parents to provide direct care for their infant. Understand parental need for modeling and role-modeling on preterm care tasks (e.g., feeding, bathing). Understand parental need for supportive appraisal—give positive feedback and reinforcement of maternal/paternal caregiving (e.g., feeding, diapering) and infant's responses to parental caregiving.
Continuity of care	Understand difficulty or impossibility of mother to negotiate actions with multitudes of caregivers. Use primary nursing for continuity of physical and emotional care for mothers and infants.
Vigilant watching over	Understand maternal observations and actions to safeguard their infant and prevent injury or harm. Understand that mothers fear being seen as "difficult" by the staff, that voicing their concerns would jeopardize their baby's care. Understand mothers' perceptions that the nurse-to-patient ratio/acuity influences her behavior (i.e., mother is hesitant to advocate for her own needs for information, caregiving opportunities, and support). Mothers would shift their priority from interaction with the infant to safeguarding the infant from danger by delaying/rescheduling the activity with the infant. As a result, mothers often become disappointed and frustrated that a meaningful moment with their infant was denied.
Expert knowledge	Understand that, initially, nurses and other health care providers are seen as "experts" in care of the infant. With increasing confidence and caregiving, mothers become "expert" in knowing their own infant and what works best and are truly the "constant" in the multiple caregiving system of the NICU. Understand that mothers receive conflicting messages from health care providers about respect, acknowledgment, and value of growing maternal expertise.
Emotional safety in the NICU	Understand feelings of extreme emotional vulnerability/exposure experienced by mothers in the NICU. Empathy, emotional warmth, and understanding in interactions with nurses and other health care professionals provide mothers with emotional safety. Feelings of emotional vulnerability were engendered when (1) nurses' actions covertly communicated that the mother was a "bother" or an "intruder,"[167] (2) the mother focused energy on controlling her emotions and behaving so the nurse would approve, (3) the mother attempted to negotiate with the staff for access to her own infant, (4) health care providers were not empathetic about maternal worries, concerns, separation, and distress about their infant and need for frequent information,[167] and (5) there were breaches of confidentiality.

Modified from Hurst I. Mothers' strategies to meet their needs in the newborn intensive care nursery. *J Perinat Neonatal Nurs.* 2001;15(2):65; Hurst I. Vigilant watching over: mothers' actions to safeguard their premature babies in the newborn intensive care nursery. *J Perinat Neonatal Nurs.* 2001;15(3):39.

parent that includes basic information and illustrative pictures is extremely useful and should include a discussion of the type of care being provided, normal feelings and reactions parents experience, financial information, a glossary of terms, breastfeeding information, available accommodations and meals, calling and visitation policies, the discharge policy, and a city map. Both at the time of transfer and later in the nursery, a self-developing picture or picture from a digital camera can be taken of the infant for the parents. If the infant is being transported, information should be given as to the general length of time of transport and by whom and when the parents will be contacted after the infant has been admitted and evaluated. Use of video technology such as a webcam can be used to orient parents to the NICU and staff who will be caring for their baby before the baby is transported.[124,228] A personal phone call from the staff or secure video-conferencing can be used to involve the parents in the NICU admission with an introduction, information about the infant and unit, and an inquiry about parental visitation plans. Parents feel less anxious when they have an orientation and a name to whom to relate. The staff can then be prepared to be available when the parents arrive.

Certainly, the first visit to the NICU is overwhelming and stressful.[202] Members of the health care team should welcome the parents and stay with them to explain the equipment and procedures, answer questions, review the infant's course, give emotional support, and generally orient the parents to this new experience. Mothers who have not previously seen their baby report more stress in seeing their baby first in the NICU. Seeing the infant is stressful and may evoke shock, fear, guilt, and helplessness.[178] Be attentive to the mother's physical needs; comfortable chairs and perhaps a wheelchair if the mother has had a cesarean delivery are helpful. The message needs to be conveyed that parents are welcome, that their presence makes a difference, and that they will be partners in the care of their infant.[93,165] Because many parents are uncertain about what questions to ask, it may be necessary at times to help parents construct questions (e.g., "Do you understand why we start IVs in the head?" or "Do you know what blood gases, hood oxygen, and CPAP are?") and repeat explanations using simple, nontechnical language. Relating to the parent's affect or emotional state seems to establish a rapport with the family and helps them feel that the staff is empathetic and understanding. If parents sense the staff's genuine concern and interest in them and their infant, it is easier for them to leave their infant in the staff's care.[167,178,192,202,241] A team member might say, "You look frightened or scared" or "This can be an overwhelming situation" or "You look like you want to cry." Facilitating the parents' relationship with the infant* is essential and can be done by offering the parents the opportunity to touch or stroke their infant, hold the infant if possible, or at least remove eye patches. Pointing out some of the unique personal characteristics of the infant is helpful. A staff member might say, "Your baby is very active," or "He responds well to touch," or "She seems to prefer lying on her side."

Families coming from out of town should be provided with a list of inexpensive housing and restaurants located near the hospital. In many cities, national and local businesses have established nearby homes run by local volunteer organizations for housing parents on a temporary basis. The homes have several sleeping rooms in addition to kitchen and laundry facilities and provide parents with a comfortable, homelike atmosphere at a nominal charge. A natural support system generally emerges among the parents using the home. A list of apartments, hotels, and boarding rooms reasonably priced and rented by the day or week can also be made available. Social workers are often aware of community resources and support available and can secure food, parking, and cab vouchers to give to families to decrease some of the financial stressors.

Parents are usually concerned with the cost of their infant's hospitalization. Some parents feel that if they cannot pay, their child will receive less attention. Parents should be reassured that their infant's care will not depend on their ability to pay. However, they should be referred to the appropriate funding agencies, such as the Handicapped Children's Program or Health Care Programs for Children with Special Needs, Social Security Disability, Title 19 Medicaid, and state child health insurance programs that provide financial assistance.

Because communication is critical, regular conferences between the family and staff (physicians, nurses, and social workers) should be instituted to give consistent medical information and emotional support[73]; this is especially helpful with both extremely critical and long-term infants. Medical interpreters should be made available if parents do not speak English; the same principle applies for deaf parents. Parents should be given the names of the physicians and nurses taking care of their infant and the personnel's specific role in providing both care to the infant and communication to the family. If the physicians and nurses have a rotation system, this also should be explained from the beginning. At the end of a rotation, the transition can be facilitated by the oncoming physician's participation in even a brief conference with the outgoing physician, primary nurse, and parents.[96]

Primary nursing, especially for long-term infants, this can be very helpful in providing for continuity of care.[96] The primary nurse has been identified by parents as the primary source and facilitator of information to parents and between parents and other health care providers and as the link between the parents and infant. In a study of maternal values, mothers associated nurses with the human quality of the NICU, a wealth of knowledge about technology, and valuing the personal characteristics of the infants.[208] In the same study, mothers identified the most desirable attributes of care providers as (1) technical skill/competency, (2) caring about or "really liking" babies, (3) communication abilities, and (4) patience.[208]

*References 158, 167, 202, 242, 261.

Protection of patient privacy and confidentiality is an ethical and legal (state and federal) obligation. Compliance to protect patient privacy, secure private patient information, and protect patient confidentiality is mandatory (in the United States) under the Health Insurance Portability and Accountability Act (HIPAA96). Violations of patient privacy include (1) overheard conversations; (2) failure to identify a telephone caller; (3) failure to obtain written consent to communicate patient information by fax, e-mail, or any other written/electronic format; and (4) leaving patient charts open/accessible to others.[239] HIPAA violations may result in financial penalties ($100 to $250,000) and/or imprisonment. Parental access to the medical record is a legal right (HIPAA96) that cannot be denied by professionals or the hospital. However, institutions may have a specific policy to deal with parent requests for access to the medical record. Many institutions require the presence of a professional to answer questions and interpret medical language for parents as they read the chart. The principles of family-centered neonatal care advocate not only parental access to the complete medical record but also documentation by parents of their own observations in the medical record.[100] All of these activities must be in compliance with the HIPAA regulations.[238]

For out-of-town families, the telephone or secure video-conferencing plays a major role in staff-parent communication. The establishment of a telephone/video calling schedule with families and a toll-free number, if available, can be useful. If the family lives out of town and cannot visit frequently, the local or referring physician can supplement the communication. This physician often knows the family and can talk with them in person. The physician, of course, should communicate regularly with the nursery team to obtain the current medical information and present a consistent approach to the family.

Resumption of the Relationship With the Infant

The fifth psychological task entails the parents reestablishing a relationship with their infant and initiating their caregiving role. Certain medical events may signal to the parents that it is safe to risk a relationship with the infant. These events may be a regular weight gain, changes in feeding patterns or methods, elimination of life support equipment or use of an incubator, the infant crying for the first time or becoming more active and responsive, or the infant's transfer from the NICU to a level II nursery. The parents may begin to read baby books or pamphlets about their infant's condition, buy clothes, set up the baby's room, send out birth announcements, or name the baby. If the infant has a congenital defect, the parents may become involved with genetic counseling and other parents whose infants have similar deficits.

Ideally parents have been involved as partners and caretakers since their infant was admitted to the NICU. If not, parents must begin to shift their level of involvement and activity from that of passive participants to that of active primary caregivers.★ This shift includes the parents gaining confidence in their ability to care for their infant. The family who has been disrupted must reestablish themselves and recover from the crisis in an environment that is sensitive and supportive to this essential task.† The transfer of care from staff to parent is influenced by (1) the stability or lability of the infant's condition, (2) the physical health of the mother, (3) the level of parental support, and (4) staff expectations.[158,192]

Several formalized intervention programs have been developed and tested for efficacy in assisting parents of NICU infants in relating to and parenting these vulnerable infants. An early educational-behavioral intervention program for NICU parents (Creating Opportunities for Parent Empowerment [COPE]) was developed and tested in a randomized controlled trial with 260 families.[173,174] Mothers in the COPE program had significantly less stress in the NICU, more positive interactions with their infants, and less depression and anxiety at 2 months' corrected age compared with the control mothers. Other study outcomes included (1) stronger parental beliefs about their role, (2) parents who were more able to read their preterm infant's cues and behaviors, and (3) shorter length of both NICU and hospital stays (by 4 days and 8 days for VLBW preterm infants) compared with the control group.[174] Another randomized study of an early intervention program found that parents who participated had a reduction in parenting stress after birth of their preterm infant.[119] The March of Dimes initiative to encourage FCC (NICU Family

★References 142, 158, 167, 173, 174, 187, 248.

†References 25, 51, 91, 100, 107, 142, 158, 173, 174, 187, 192, 248, 261

Support [NFS] Program) has been studied at eight NFS sites by interviewing parents, NICU staff, and administrators. Findings include (1) culture change within the NICU resulting in increased family support; (2) enhanced overall quality of NICU care; (3) less stressed, more informed, and confident parents; and (4) increased receptivity of staff to the concept of FCC and its benefits.[45]

Another formalized and researched intervention program is the Mother-Infant Transaction Program (MITP). Sixty-three mothers in Australia were randomized to intervention with the MITP or a control group.[189] Compared with the control group, mothers in the MITP intervention group were found to be more responsive to their infants, were less stressed at 3 months, and had better mutual interaction with their infants at 3 and 6 months.[189] Infants in the MITP intervention group were more attentive, were perceived by their mothers as "easier" with fewer regulatory problems (i.e., colic, sleep, crying), and had better communication skills.[189] A more recent randomized controlled trial of the MITP found a reduction in PPD and longer breastfeeding, but no alteration in maternal stress.[211] A Dutch randomized controlled trial of the Infant Behavioral Assessment and Intervention Program found that intervention mothers had higher feelings of social isolation, but they described their infants as happier and less distractible and hyperactive than control mothers.[172] Other interventions to relieve parental stress have recently been reviewed.[39]

Involvement in caregiving lessens the parents' feelings of helplessness and frustration and facilitates their identification with their role as parents.* Alteration in their parental role is particularly stressful for mothers in the NICU.[21,105,107] Maternal stress and anxiety about their parental role is associated with a longer length of stay in the NICU.[38] The sense of parenthood for both mothers and fathers depends on expectations of the parental role, the infant's state of health, and the environment and professional attitudes in the NICU.[111,158] A study by Jackson et al.[111] found that internalization of the parental role with a premature infant occurs over time and often involves initial feelings of alienation and responsibility that change to more confidence (at 3 to 6 months) and familiarity (at 18 months) with the parental role. For weeks after birth, both parents experience alienation: (1) mothers felt ambivalence about their relationship with the baby and their new role as a parent—a concern for the baby's welfare and a need to participate in and control the infant's care; and (2) fathers shared concern for the baby, felt unprepared for the birth, and were confident in delegating the baby's care to the NICU staff.[111] In this qualitative study, neither parent felt ready for the preterm infant's discharge to home. Taking on total responsibility for the baby's care resulted in both parents feeling insecure, fearful, and worried about the baby and the father taking on more responsibility for infant care. By 6 months of age, both parents had developed more confidence in the care and parenting of their preterm infant; by 18 months, parents had developed a feeling of relationship with their child.[111] For mothers of the smallest and sickest infants, concerns and worries about the infant remained, even at 6 months.[111] Beginning as early as possible in the NICU, health care providers should encourage and facilitate parent participation in their infant's care. † A study of parent participation in five NICUs in Sweden found that earlier gestational age of their infant was the most influential factor for parents in interaction with caregivers and nursing their baby.[199] Another study of fathers' experiences with their preterm babies in the NICU showed that the gestational age of the baby was a significant factor in paternal behavior.[243] This research found two types of paternal behavior: 1) "fathers-of-preterm-infants" who touched their baby as soon as possible, without fear and were struck by the baby's appearance and 2) "preterm fathers" who were reluctant to touch their baby for fear of harming the infant, were struck not only by appearance but also the technology surrounding their infant, and feared that their infant would die. All "fathers-of-preterm-infants" participated in care for their infant, and just over one-half of the "preterm fathers" participated.[243]

Parents can provide skin care for their infant, learn to read and respond to infant cues, help turn the infant even if a respirator is attached, diaper the infant, and possibly feed the infant. If the parents are separated by distance, they can send family pictures that can be posted at the infant's bed; periodic pictures of the infant taken by the staff can be sent back to the family. Parents can send clothing, mobiles, simple toys, and even recordings so that the infant can hear the parents' voices. Some mothers who are

*References 51, 105, 142, 158, 167, 173, 174, 187, 248.

†References 51, 107, 158, 167, 174, 191.

pumping send frozen breast milk (see Chapter 18). All of these reminders help the nursery staff be aware of the real family, who are genuinely interested. These personal attempts made by parents that help them feel they are important to their infant's development should be encouraged. Sometimes foster grandparents or volunteers can hold, feed, and talk to infants whose parents cannot visit frequently.

A prospective cohort study of parental presence and holding in the NICU found significant neurobehavioral benefits for the 81 preterm infants 30 weeks' gestational age or younger.[213] Early parenting (i.e., holding) in the NICU resulted in lower arousal and excitability, better quality of movement, less stress, and less hypertonic muscle tone and thus a developmental advantage.[213] Early sensitivity training for parents in the NICU is associated with improved white matter microstructural development in their preterm infants.[179] Kangaroo care (see Chapter 13), skin-to-skin contact between the mother/father and infant by placing the infant in a vertical position between the mother's/father's breasts, has positive maternal/paternal and neonatal responses. Use of kangaroo care activates the maternal processes of a search for meaning and adjustment to the experience of preterm birth, a recovery of self-esteem, maternal confidence, and enhancement in the parenting of a high-risk neonate.[71,107,128] Successive sessions of kangaroo care ease the pain and emotional suffering as mothers deal with loss and letting go and develop competence and confidence. Paternal attachment is also facilitated by fathers holding their infants and engaging in skin-to-skin contact.[154,158] A study by Sullivan[244] indicates that the earlier fathers hold their babies, the sooner they report feelings of love and warmth. The infant may become a reality to the father when he can hold his infant.[154,158,244] Fathers reported delaying attachment until they were certain of the infant's survival.[244] Paternal involvement with the infants is critical[162] and must be supported, encouraged, and facilitated by the NICU staff.[191]

The use of "graduate parents," parents who have had an infant in the NICU and who have successfully dealt with and resolved the crisis of the birth of their infant, can be extremely valuable.[100,107,158,202] They provide support to parents by sharing common feelings, reactions, and experiences about having a hospitalized infant. Graduate parents can provide support and practical assistance for mothers interested in breastfeeding, parents who take their infant home on oxygen, or parents whose infant requires special medical care such as a shunt, tracheostomy, colostomy, or gavage feedings. Organized graduate parent groups in large tertiary settings have become a very popular means of providing support,[92,107] but locating one parent or couple to talk with parents in a small community can be just as helpful. Parenting classes and Internet resources[107] also can be offered on a variety of topics such as breastfeeding, infant development, premature infant development, sibling and family reactions, discharge, cardiopulmonary resuscitation, coping with the hospitalization, and special medical needs. These classes provide specific, didactic information combined with group discussions that are mutually supportive. Social workers, nurses, and other related health care professionals (e.g., respiratory, occupational, and physical therapists) facilitate the group; graduate parents also participate as a resource.

A third type of support is counseling sessions. The purpose of these sessions is to discuss and deal with common issues among parents arising from the hospitalization of their infant and the effects on their marriage and family life. This type of session also has been helpful for parents whose infant has died. The sessions are usually short term and are conducted by the perinatal social worker and another staff member such as a physician, nurse, or chaplain. The focus of the group is not to give specific medical information but, rather, to provide parents with an opportunity to verbalize their feelings about their infant's hospitalization and receive emotional support.

Recently, telemedicine technologies have been used in the NICU to enhance medical, informational, and emotional support for families during and after hospitalization. Baby CareLink[88] is a telemedicine program that incorporates video-conferencing and Internet technologies to enhance interactions among families, NICU staff, and community health care providers. The link contains information for families about relevant issues during and after hospitalization. The video-conferencing module enables distance learning by the family in their home during the NICU stay and remote monitoring after discharge. A recent survey found that families using this technology were more satisfied with the unit's physical environment and visitation policy, possibly because of the ability to facilitate visitation via teleconferencing when

family members could not be present in the NICU.[88] An integrative review of studies of the use of various technologies (such as videophone, video-conferencing, Skype, FaceTime, HIPPA secure programs such as Polycom and Jagger by Cisco, AngelEye, and NICView Webcams) in the NICU found that both parents and professionals were positive about these forms of communication, but research is limited.[67] One study showed that mothers used the web camera to visit their infant in the NICU more than fathers used the camera.[214] Another study showed that nurses in the NICU spent significant time manipulating the web camera and addressing parental concerns over the phone, which disrupted their workflow and initiated concerns about the quality of care they could give to the infants.[118] Websites for parents of premature infants, children, and adults in the family are available so that parents can support each other, discuss common problems, and share solutions; caution should be used, however, when recommending the Internet (see the Resource Materials for Parents section at the end of this chapter).

Visiting in the Neonatal Intensive Care Unit

VISITING GUIDELINES

Besides their spouse or significant other, parents identify their families and friends as the main source of support through the crisis of having a sick neonate.[167,260] Prohibiting visiting by family and friends or limiting visitors to "two at a time" can isolate parents from a major source of support. NICU visiting policies should be used as guidelines, rather than rules, to facilitate visiting and caregiving by parents and families.★

Care providers should use good judgment and discretion about visitation while understanding and respecting the parents' need to be "in charge" of their infant (e.g., make decisions for their infant).†

Lack of perceived control by parents is associated with increased anxiety, hostility, depression, and poorer adjustment.[70,158,167] A sense of parental control in the NICU is enhanced by parental decision making.‡ Parents should designate their infant's "guest list"—that is, other family and friends who can visit and perform caregiving activities in their absence.[167]

NICU visiting policies vary within the United States[37] and among European countries. Two-thirds of surveyed nurseries "allow" parents to visit during medical rounds, whereas visiting during nurse report was more restricted.[37] When parental visits were restricted, confidentiality was cited as the determinant of the visiting policy.[37] In this same survey, 39% of parents "sometimes" or "often" complained about restricted visitation.[37]

FCC recognizes the family as the constant in the infant's life.[2] Liberal visitation policies are accepted as beneficial for patients and families. The American Academy of Pediatrics (AAP) Policy on Family-Centered Care and the Pediatrician's Role states that creating a 24-hour open- unit policy for families and making a commitment to information sharing are beneficial for families and staff.[7] Specifically, a 24-hour open unit has been shown to decrease length of stay, decrease use of the emergency department, improve parent satisfaction, and decrease parental anxiety.[7] A discrepancy exists between parental requests and visitation practices in many NICUs. Before changing to a 24-hour open-unit policy for parents, NICU nurses in one center had reservations and were skeptical.[256] After implementing the 24-hour visiting policy, most nurses were supportive of the change and reported perceived benefits for families. Parent satisfaction increased regarding time spent with their infant.[256] NICU staff should be open-minded and flexible in determining the policy on visitation during rounds, report, and emergencies.[7,90,100]

Many parents are interested in being included in medical rounds to actively participate in the care, discussion, and decision making about their infant.[7,90,100] A qualitative study of 18 NICU parents included in interdisciplinary teaching rounds in a tertiary children's hospital found that parents (1) had a positive experience and were "comfortable" being included, (2) preferred rounds in which nurses were included and lay terminology was used, and (3) welcomed the ability to communicate, understand the plan, and participate with the team in decision making about their infant's care.[141] Another study reported that family-centered rounds (FCRs) were associated with increased provider satisfaction and collaboration for neonatal nurse practitioners and fellows.[257] In addition, FCRs were associated with enhanced communication between providers and parents. Importantly, there were no negative aspects

★References 2, 90, 107, 158, 167, 181.
†References 70, 105, 158, 167, 202, 208.
‡References 70, 82, 158, 167, 202, 208.

to the introduction of FCRs.[257] If parents and the NICU staff agree to parental participation in rounds, patient confidentiality can be maintained by moving rounds away from the bedside, speaking quietly, and inviting parents to participate in only their infant's care planning/medical rounds[7,90,100] in this or a separate meeting. Another way to include parents in health care team rounds is to use video-conferencing so that parents who are unable to travel to the hospital can participate daily in care of their baby.[263] Their ability to ask questions and participate in care for their infant results in parental belonging, increases their satisfaction, and decreases their stress. Parents may be visitors to the hospital and NICU, but they are not "visitors" to their newborn; parents and family are the constants in the life of a child, whereas health care providers are only temporary "visitors" in the life of the child.[2,142,167,181]

Parents may be more comfortable in the NICU if they are accompanied by a family member or friend.[260] A study showed that black teenage mothers establish a relationship with their infant by visiting regularly and learning how to care for him or her.[178] The research states that when these young women bring a friend or family member with them to the NICU, they are more comfortable parenting and caregiving for their infants. Parental visiting patterns may be categorized by care providers as visiting "too much"[90] or "too little."[91] Financial constraints (e.g., transportation and childcare costs, loss of work time), chaotic social situations, or poor physical and mental maternal health may contribute to fewer visits.[107] Parents may fear that the infant will not survive, may feel helpless, or may not think their visits are important for their sick baby. Parents should be taught by example how important their presence and caregiving are to their baby's survival and recovery. In addition, parents need to be taught to interpret their infant's cues and behaviors (see Chapter 13). Maximizing every parental visit by scheduling care by parents* (e.g., bathing the baby, breastfeeding, providing kangaroo care, nipple feeding) communicates the importance of parental care and enables them "to be an expert on how to care for your baby by the time the baby is ready to go home."

SIBLING RELATIONSHIPS

The inclusion of other children in the events surrounding the birth of a sick newborn is important. From a sibling's viewpoint, the anticipated birth of a new infant is a stressful time of noticeable physical and psychological changes within the family. In preparation for the impending birth, the child is told that the mother will be going to the hospital for a few days and will return with a baby brother or sister. With the birth of a premature or ill infant, the mother may go to the hospital unexpectedly, stay a long time, and not return home with the anticipated playmate. Instead of a celebration of the expected happy event, parents are grieving the loss of the normal newborn and facing the current crisis of their sick infant.

Parents are often unsure about what to tell the other children and whether the children should see the infant. The siblings themselves may feel left out, rejected, or worried that they too may get sick. They may feel they are to blame and that their jealous feelings about their new rival may have caused this tragedy. Confused by their parents' distress, the other children may speculate that it is related to them and their "bad" behaviors. They may be disappointed and angry that they did not get the "playmate" they had wanted. Because parents are unsure about how to manage these issues, it is often helpful for the staff to introduce the topic. Most children's hospitals employ child life specialists who can consult with parents regarding siblings. Child life specialists have extensive knowledge of child development and expertise in talking with children, often using a child's own play in the process of providing support.

Because children will make up an explanation for the infant's illness, it is better to have it based on accurate information. Before explaining the infant's condition to siblings, elicit their ideas and perceptions about "what is the matter." Any fears, fantasies, misconceptions, or accurate information are thus used to begin the explanation of "where the baby is." Explanations must be tailored to the individual child's cognitive and developmental level. The child should be told that the infant is sick but in a way that is different from his or her illnesses, the infant's illness is not "catching," and it is not like any of the illnesses that the child has experienced. To allay the siblings' fears about medical personnel, they should also be told that the nurses and physicians are trying to help the infant "get better." Because children between 2 and 6 years of age are involved in magical thinking, they should be told that they are not to blame and that they did not cause the infant's

*References 70, 142, 167, 174, 208, 261.

problem. If the infant is premature, a team member might say to the child, "The baby came out too early or too soon; he needed more time to grow inside." If the infant has spina bifida, a staff member might say, "The baby's spine did not grow right, so he may have trouble lifting his legs or walking."

A child of 3 years of age or younger usually does not understand much about the coming infant. More important to this age group is the separation from parents who are frequently at the hospital. To ameliorate the separation, childcare arrangements should be structured so that the child is cared for by familiar people in a familiar environment. The best care arrangement is with a familiar person in the child's own home; second best would be with a familiar person in the caregiver's home; and third best would be with an unfamiliar person in the child's own home. The least favorable, of course, is an unfamiliar person in an unfamiliar setting. Many hospitals have a childcare facility run by volunteers or child life specialists that allows the child the opportunity to go to the hospital to "see where Mommy and Daddy are going" yet allows the parents the chance to see their infant without having to care for their older child or children. Parents may also choose to include the young child in all or selected visits.

Children 3 years of age and older have more interest in babies and a better grasp of the physical meaning of life. Sometimes a picture of the baby or a look into the nursery through the windows is helpful to the other children. Many children benefit from visits to the nursery to see their brother or sister. The natural curiosity of the child about "what is going on" in the family is answered when the child actually sees the baby. Behavior problems such as bedwetting, sleeping and eating difficulties, and difficult separations from parents may be prevented or reduced by the reassurance of a visit that decreases the sibling's worry about the baby.[1] Sibling visitation must be individualized for every family.

SIBLING VISITS

The decision to include siblings in the NICU depends to a great extent on the views, beliefs, and attitudes of the hospital staff. Generally, the staff's concerns about and resistance to sibling visitation focus on fear of an increase in nosocomial infection, disruption of unit routine and order, and potential harm to young children from exposure to the NICU environment. Infection control is the responsibility of parents and professionals. Parents must be educated about the dangers of infection and instructed on how to screen their children for symptoms such as fever, cough, or diarrhea. Professional staff must inquire about the health of visiting siblings, including their exposure to communicable diseases. Both parents and children must wash their hands before entering the nursery; small stools allowing children to reach the sink are helpful. Cover gowns are no longer used by parents, siblings, or professionals. With vigilance, no increased bacterial colonization and no increased incidence of infection occur with sibling visits.[240]

Because sibling visitation may be beneficial, each NICU must evaluate the center's situation and consider instituting a sibling visitation policy.[90] The following general principles may be used in developing this policy:

- Communication and coordination between staff and family are necessary to promote successful sibling visitation, including a review of unit policies and guidelines for parents.
- Children must be prepared, according to their age and development, for what they will see, hear, and feel in the NICU. Language should be simple and honest; pictures of the infant or other infants can be helpful. Dialog with parents before the visit regarding how long they believe the sibling visit should realistically be based on their age and development also can be helpful.
- Parents and staff screen the visiting sibling for signs of illness that would exclude the child from visiting.
- Parents and child must scrub their hands thoroughly.
- The initial visit should be held at a relatively quiet time in the nursery when a care provider can stay with the family. If the infant can be moved to a private room or family room area, this is preferable.
- The presence of a qualified child life specialist can be helpful to families for sibling visits.

At the bedside, the child is introduced to the infant and seated on a chair or stool at eye level with the infant. The care provider then again explains the equipment the child sees and any of the infant's "interesting" behaviors such as crying because of hunger, sucking on a pacifier, or eyes open "looking at you." Children may even be included in age-appropriate caregiving tasks. Choosing clothes, handling diapers and blankets, holding the bottle, and

touching and talking to the infant are all ways "to help." The child may bring a present to the infant such as a simple toy, music box, or handmade picture or photograph of the family. After a visit, both parents and staff should be available to talk about the visit or answer any questions. Some children, however, will not discuss the visit or ask questions until some later time. A method for enabling children to express their feelings in a nonverbal way is through play or books. A child who receives a book about physicians and hospitals or a "doctor" or "nurse" doll may "play out" feelings about the brother or sister and the hospital experience.

Creating a comfortable environment in which children feel free to ask questions is essential when siblings visit. Every question deserves an answer, even "I don't know," when appropriate. Children are often quite unrestrained in their remarks and questions. Comments such as "He's sure ugly!" or "Will he die?" or "Why is she tied up (restrained)?" are common. These may be embarrassing to parents who hesitate to make the same remarks or ask the same questions. If the infant is hospitalized for a long time, the other children may lose interest or even wish it were all over. This response may upset parents who themselves may be struggling with the same feelings. The longer the infant is hospitalized, the greater the pressure on time and financial resources. Family routines are disrupted by continuing hospitalization, and the disruption may strain family relationships.

Staff and parent response to sibling visitation has been positive in hospitals in which the policy has been implemented. Such a policy may facilitate family integrity and promotes mutual support during the stressful time of hospitalization. Another advantage of visitation is that the older siblings do not endure repeated separations caused by parental visits to the hospital but are included as important and special family members. The presence of siblings in a nursery can be a rewarding experience for family and staff alike and perhaps is the ideal example of providing safe yet comprehensive FCC.

Although a flexible sibling visitation policy is viewed as the best possible situation, some alternatives such as coloring books and children's books should be considered (see the Resource Materials for Parents section at the end of this chapter). Staff should be sensitive to the needs of the siblings and understand that the parents must deal with both time and financial constraints.

Psychosocial Conferences

Psychosocial conferences for staff members to discuss the dynamics of family functioning and the effect of a seriously ill newborn on the family can be quite useful. These conferences, usually led by perinatal social workers or other mental health professionals, can give staff the opportunity to identify current issues of concern by the family and optimal strategies to support the family moving forward. Another function is to enable staff to discuss and better understand their own feelings and reactions to families, infants, and the many stresses related to working in an NICU. A recent study about secondary traumatic stress in NICU nurses found an incidence of 49% with moderate to severe traumatic stress and 35% with symptoms of PTSD.[18] The qualitative part of this study found five themes related to the NICU nurses' descriptions of their traumatic experiences caring for sick babies and their families in the NICU (Box 29.9).

Disruptive behaviors such as intimidation, rudeness, incivility, and harassment are serious stressors in health care organizations. Recently two studies of rudeness toward NICU teams illustrate deleterious effects on the target, the team, and witnesses.[215,216] Rudeness from colleagues[215] and parents[216] both resulted in adverse effects on individual clinician performance and team performance. Individual clinicians exhibited less accuracy in diagnosis and more errors in orders and carrying out orders, resulting in poorer quality of care. NICU teamwork disruptions

BOX 29.9 THEMES USED BY NICU NURSES TO DESCRIBE THEIR TRAUMATIC EXPERIENCES

- NICU nurses' traumatic experiences intensified by: (1) multiple scenarios, (2) the longer the nurse cared for a baby, the greater the impact on the nurse at the baby's death and (3) being the primary nurse also impacted nurses harder when the baby had complications or died
- Parents insisting on aggressive treatment: so distressing
- Baby torture: performing painful procedures—hurting babies that nurses were trying to help was very distressing
- Questioning their skills: Did I do enough?
- The grief of the family is contagious

From: Beck CT, Cusson RM, Gable RK. Secondary traumatic stress in NICU nurses. *Adv Neonatal Care.* 2017;17(6):478.

included less information sharing and workload assistance among team members. The negative impact on teams and individuals may disrupt the ability of a team to compensate for poorer performance by an individual team member. The researchers opine that negative human interactions, regardless of their source, may be an underlying cause of iatrogenic incidents in health care systems. Cognitive bias modification (CBM), consisting of computerized training modules to alter a subject's threat-oriented biases by promoting a benign or more positive interpretation, was effective when used as a preventive rather than a treatment intervention.[216] Daily CBM was effective in shifting clinicians' attention away from perception of rudeness as a threat, thus enabling working NICU staff to preserve their cognitive resources—the critical thinking and psychomotor skills necessary to care for their patients. In the study, daily CBM "immunized" participating staff members for an entire shift.[216] Further research is necessary to determine if CBM attenuates the effects of rudeness over longer periods and to identify and test alternatives to CBM.[216]

Weekly rounds with the entire multidisciplinary team (physicians, nurses, nutritionists, lactation consultants, pharmacists, home health nurse coordinator, social workers, case managers, and financial counselors) are an effective vehicle to discuss and develop medical discharge and psychosocial care plans about each infant and family. Having an infant in the NICU has wide-reaching effects on the entire family system. Families arrive at the doors with their own unique stories and struggles that must be factored into the care and support provided to the family.

The involvement of perinatal social workers to assess and evaluate the psychosocial functioning of families, provide support and counseling services, and coordinate the discharge planning and follow-up care for the infant and family is essential. Social workers should complete a comprehensive assessment at admission for all families with an infant in the NICU. After assessment and discussion with the team, specific focus and interventions for high-risk cases can be identified (Box 29.10), as well as general support needs for all families. Providing support in complicated medical conditions, including the death of the infant, is also extremely important. Programs should be implemented for staff members to increase their competency and comfort level in identifying and intervening with psychosocial issues.[227]

BOX 29.10 HIGH-RISK FACTORS INDICATING NEED FOR SOCIAL WORK INTERVENTION

1. Teenage pregnancy (11–18 years of age)[25]
2. Single parent
3. Substance abuse[25]
4. Psychiatric history that interferes with appropriate functioning (including postpartum depression), especially as related to parenting abilities
5. Mother or father with a history of being physically or sexually abused or early deprivation by own family, or history of having abused or neglected own children
6. Intimate partner violence/domestic violence[168]
7. Mental disability, borderline intelligence, or significant physical handicaps
8. History of loss with previous pregnancy or loss of child because of stillbirth, birth defect, prematurity, abortion, custody case, or death
9. Rejection of or ambivalence about current pregnancy as manifested by requests for termination of pregnancy, attempted abortion, or relinquishment
10. No prenatal care with previous or current pregnancies
11. Pregnancy exacerbating extreme depression, anxiety, or suicidal thoughts
12. Stressful home or personal situation because of marital or financial problems or lack of support
13. Long-term hospitalization during pregnancy requiring intervention in helping family adjust by arranging for younger children at home or for financial assistance
14. Other children with physical or mental handicaps
15. Attachment difficulties with the infant
16. Prior history with social services
17. Inadequate housing and living arrangements and homelessness
18. Inadequate food and other essentials
19. Incarceration of mother/father
20. Military families
21. Undocumented immigrants

Intimate Partner Violence (Domestic Violence)

IPV is recognized as a serious risk factor for adverse pregnancy outcomes.[8,168,246] A study of IPV in first-time mothers participating in the Nurse Family Partnership found prevalence rates of (1) 8.1% in the year before pregnancy, (2) 4.7% during the current pregnancy, and (3) 12.4% in the year after the pregnancy.[229] A meta-analysis of 92 studies found prevalence rates of 28.4% for emotional abuse, 13.8% for physical abuse, and 8.0% for sexual

abuse.[112] Risk factors for abuse during pregnancy in this meta-analysis included abuse before pregnancy, low education level, unintended pregnancy, low socioeconomic status, and being unmarried.[112]

Injuries resulting from physical abuse increase the risks for low birth weight, preterm birth, intrauterine growth restriction, stillbirth, and neonatal complications.[3,61,104] Emotional abuse is associated with a 1.6-fold increase in preterm birth; the combination of physical and emotional abuse increases the preterm birth rate 4.7-fold.[225] Poorer maternal outcomes include antepartum hemorrhage, depression (2-fold to 3-fold increased risk for major postpartum depression; 1.5-fold to 2-fold increase for elevated depressive symptoms),[24] inadequate prenatal care, poor nutrition, poor weight gain, substance use, high maternal cortisol, hypertension, early cessation of breastfeeding, poorer parenting behavior, poorer mother-infant bonding, antenatal/postnatal depressive symptoms, and perinatal death.[3,127,259] Perinatal violence and stress also are significant risk factors for preterm birth in the teen population, with higher rates of IPV than for older mothers.[22] Pregnant women may be victims, perpetrators, or participants in reciprocal violence.[234] In one study, women participating in reciprocal violence had the highest levels of depression, used substances (alcohol, illicit drugs, and tobacco), and were not happy about their pregnancy.[234] This finding is consistent with numerous other studies showing depression before, during, and after delivery, a greater prevalence of substance abuse, alcohol misuse in partners, poor nutrition, lower rates of contraception use, and higher repeat pregnancy.[3,127,229]

Because IPV is so prevalent and has serious negative effects on the entire family system, protocols and procedures (that are compliant with the policies of the setting [i.e., hospital, outpatient clinic, emergency department] and the reporting laws of the state) should be in place. Legal definitions of IPV vary by state, but IPV is *illegal* in all states. The health care team needs to be educated to recognize the signs and behaviors that may indicate IPV (and child abuse).

Because abuse is so pervasive and too serious to remain unidentified, health care providers should routinely ask all women patients about IPV (although men also can be victims). The AAP and the American College of Obstetricians and Gynecologists have position statements and guidelines for routine screening for IPV in all women.[8,246] Battering beginning during pregnancy is a very common phenomenon. Use of standardized screening tools, an anonymous computer-assisted self-interview,[212] and recurrent screening results in higher identification rates (i.e., one study found higher disclosure after birth than during pregnancy).[123,197] For a discussion about the benefits and risks of routine screening, refer to the U.S. Preventive Services Task Force recommendation statement.[253]

Pregnancy offers a unique opportunity for health care professionals to intervene in IPV.[163,168,170,197] Once a potentially abusive situation has been identified, culturally and ethnically sensitive interventions should be initiated.[163] Interventions vary, depending on the disclosures made by the mother or father (or partner) and the needs identified. Recommendations for interventions include (1) educate the woman about community supports, (2) discuss options with the victim, (3) help identify a safety plan, (4) make appropriate referrals, (5) comply with state statutes about reporting responsibility, (6) document assessments and interventions, and (7) refer for treatment and aftercare (essential). Because of the complexity of issues generated by IPV, a multidisciplinary team approach is recommended.

Transfer Back to the Referring Hospital

Transfer of the infant from a tertiary center back to the referring or local community hospital for convalescent care and discharge is a frequent occurrence. This can help facilitate the relationship between the infant and parents, because the infant will be more accessible. Parents generally view the transfer as positive if the hospital is closer to home and if they feel comfortable with the level of care provided. Transfer is stressful, and there is always an adjustment period and difficulty coping any time a transfer occurs.[73] Parents must adapt to different personalities of medical personnel, different procedures, and different visiting policies. Preparing the parents for the transfer, orienting them to the new hospital, and talking to the staff of the referral hospital about the infant and the parents are important to help ease the transition.

Preparation to Take the Infant Home

The sixth psychological task for parents concerns preparation for taking the infant home. Parents must understand their infant's individual needs and

personality characteristics and must feel a sense of competency in relating to and caring for their infant. Discharge is an anxiety-provoking event and ushers in the "crisis" of homecoming, which parents must face and master.[58,107,111,158] The unsuccessful resolution of the previously discussed five psychological tasks can contribute to maladaptive parenting and a poor outcome for the infant, including the possibilities of attachment difficulties, overprotectiveness, failure to thrive, vulnerable child syndrome,[129] emotional deprivation, and battering.[129,171] To achieve a positive parent-child relationship after the hospitalization and through the transitional period that ensues, provision of appropriate follow-up support through the home adjustment period is crucial.[129,158] A recent study found that fathers of preterm infants experience more stress (i.e., higher cortisol levels) than mothers after discharge of their very preterm infants to home.[78]

Several behaviors demonstrate that parents are trying to understand the infant's care in preparation for discharge. First, parents may ask questions verbalizing a variety of concerns. For a premature infant, they might ask, "Do I need an apnea monitor at home?" or "Can the baby have visitors?" or "Do I have to wash my hands when handling the baby?" For an infant with a congenital anomaly such as spina bifida, the parents might ask, "Can I lay the baby on his back?" or "Can I bathe him?" or "Do I have to pump the shunt?" For an infant with a heart defect, the staff might be asked, "Do I need oxygen?" or "Do I have to handle him differently?" or "What about going to higher altitudes?" or "Is my baby at risk for sudden infant death syndrome (SIDS)?" All of these questions on the part of parents are typical and normal and represent the parents' working through their fears and anxieties.

On the other hand, parents who are highly anxious,[58] extremely overprotective, or very indifferent should be a concern to the health care personnel. The inability to deal with the task of taking the infant home may indicate some unresolved feelings related to the previous psychological tasks. Although most parents whose infants have been in an NICU do admit to initially treating their infant differently until they "got to know their child," a group of parents who are excessively overprotective does exist. This type of behavior often stems from parents who are struggling with intense feelings of guilt and failure. These parents either protect their baby from everything because they feel so responsible for having caused the infant's initial problem, or they demonstrate an indifference or lack of concern for the infant and the infant's welfare. Such parents may have an ambivalent attachment to their infant, who may continue to represent the threat of death or the parents' personal failure. This group of parents should be considered high risk for potential parent-child relationship difficulties and should be evaluated to determine an appropriate intervention.

At discharge, there are infants whose medical conditions are still fragile, and there is a substantial indication that these infants may not be normal and may have long-term problems. These infants may be temperamentally difficult to manage, and parents understandably treat them differently. These parents and infants need additional support and appropriate intervention (see Chapter 31).

The perinatal health care team can employ many interventions to assist parents with discharge and through the transitional period that follows (see Chapter 31). Parents' perceptions of the transitions from hospital to home center around three themes: (1) effective parent-to-staff communications, (2) feeling informed and involved, and (3) being prepared to go home.[11] In the hospital, adequate teaching of caregiving skills that enable the parent to develop a sense of mastery and competence is of paramount importance. Parent education regarding the care and needs of their baby is a learning process that begins at admission and continues throughout the inpatient stay. In addition to tasks of care, parents should participate in planning and providing developmentally appropriate care and be able to read and respond to their infant's cues (see Chapter 13). Maternal concerns about the infant's care center on elimination, feeding/weight gain, the infant's health (breathing, development, or ongoing medical problems),[107] and preparation of medications. If parents do not feel comfortable with their infant, their anxiety can cause adverse interactions with him or her. The parent needs to know the infant's mannerisms and behaviors; otherwise the parent may feel exhausted and resentful and then guilty. Teaching caregiving skills often can be facilitated in an environment that is less intense and crisis-oriented than the NICU. Whenever possible, an infant should be transferred to a setting that is more conducive to the parents' initiation of the primary caregiving role, such as a special care or transitional nursery, a level II unit, or a general pediatric ward. Care by parents before discharge enables

parents to assume full responsibility for their infant's care, tests the reality of caregiving, helps them learn caregiving activities and their infant's behavioral patterns, and confirms their readiness for independent parenting and the infant's readiness for discharge.[107,174,187]

Adequate discharge planning and follow-up arrangements should include general pediatric care; home health care; nurse home visitors; referral for early intervention services, if indicated; and parenting classes, especially for young or psychosocially high-risk parents. Numerous studies document positive effects of home visitation programs. Referrals to county social service departments should be made for single mothers who are eligible for Temporary Assistance to Needy Families; the Women, Infants, and Children (WIC) program; Title 19 Medicaid; and state child health insurance programs. For infants with special problems (e.g., spina bifida, cerebral palsy, Down syndrome), referrals should be made for special programs that provide early intervention services for the infants and support groups for parents. Parents whose infants have special medical needs (e.g., gavage feedings, tracheostomy or colostomy care, oxygen, or ventilators) should be evaluated by the medical and nursing teams to determine helpful community resources (e.g., equipment, supplies, respite, emergency care) and to make appropriate referrals. Home nursing care and homemaker services sometimes are covered by medical insurance and may be necessary to provide actual nursing activities and to relieve parents from the emotional burden inherent in caring for an infant with medical problems. For infants who are developmentally or physically challenged or at risk, participation in developmental intervention programs and other follow-up clinics provided by many hospitals that have NICUs are extremely valuable. These infants are eligible for Part C of the Individuals with Disabilities Education Act (IDEA). Locating babysitters who will care for a child with special problems can be an overwhelming task for parents; cultivating a resource list for parents and suggesting that parents exchange services with each other can also be helpful. Graduate parents, neonatal nurses, or respite care organizations can provide a useful service to parents in this situation. Last, parents should be referred to appropriate funding agencies (e.g., Health Care Programs for Children with Special Needs, Title 19 Medicaid, state child health insurance programs, Social Security Disability) that provide financial assistance.

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The Online PPD Support Group. Available at: www.ppdsupportpage.com.

30 GRIEF AND PERINATAL LOSS

SANDRA L. GARDNER AND BRIAN S. CARTER

As a life passage, pregnancy and birth are associated with hopes, expectations, joy, and happiness for the future. Although pregnancy and birth constitute a developmental crisis and a major life change, expectant parents reasonably believe the gains of a healthy, happy child and family life offset any setbacks. Unfortunately, not all perinatal events have a happy ending. Loss of a healthy infant in the perinatal period when premature delivery occurs also affects the parents' friends, family, and professional care providers.

Perinatal loss may be the first time a young adult has had to cope with the illness or death of a loved one. Perinatal loss is especially significant because (1) it is sudden and unexpected; (2) it is the most difficult loss to resolve[34]; (3) it interrupts the significant developmental stage of pregnancy and the situational crisis of pregnancy[34]; (4) it is the loss of a child who did not have the opportunity to live a full life[63,167]; (5) it prevents progression into the next developmental stage of parenting that has been anticipated and rehearsed (at least mentally) during pregnancy[119]; (6) it is fraught with ambiguity and disenfranchised grief[6,112]; and (7) it represents a narcissistic loss, a loss of self, for the parents.[159,188,189] Perinatal loss also often means interpersonal exclusion from the activities of childbearing friends and siblings.

Unfortunately, loss and grief often are thought of only in relation to death. However, as final and irreversible as death is, it is just one form of separation and loss. Although less obvious, other loss situations may have an equally crucial effect. Loss comes in many forms, and during the perinatal period, loss may occur without necessarily resulting in death. Circumstances of perinatal loss are parallel and, at the same time, different because they all entail grief and mourning, yet each has unique dimensions and characteristics. The process of grief, its stages, and its symptoms are reviewed next as a framework for understanding one's own feelings and those of others experiencing a loss. A desire to help and an idea of what is and is not helpful are essential for effective intervention by professionals.

THE GRIEF PROCESS

Grief, the characteristic reaction to the loss of a valued "object"—a person or thing—is not an intellectual and rational response.[65] Rather, it is personally experienced as the deep emotion of sadness and sorrow. To the individual, grief feels overwhelming, irrational, out of control, "crazy," and all-consuming. Mourning occurs in phases over time. After acknowledgment that the person no longer exists, gradual withdrawal of emotion and feeling occurs, so that eventual psychologic investment in a new relationship is possible.

A literature review of the theoretical perspectives of parental grief from the United States and the United Kingdom reveals a change from a traditional to a "newer" model of grief in the Anglo-American culture.[50] Traditional models of grief emphasize the severing of bonds with the deceased, whereas "newer" understandings of parental grief emphasize parents retaining a relationship with their dead child.[176,194] After reviewing nursing, medical, and social science publications and choosing relevant ones, Davies states: "the concept of continuous bonds challenges the dominant assumption that resolution of grief is achieved through severing bonds with the deceased."[50] Parents wish to know that their child's birth and death have meaning and

BLUE type highlights content that is particularly applicable to clinical settings.

purpose and that their child "mattered" and will be remembered by them and by others who have been "touched" and "changed" by the child.[35] After the death of a child, parents may develop approaches to "making meaning" from their loss in order to maintain a connection to the child, honor and keep the child's memory alive, and help others facing similar circumstances.[55] Parents in one study said that intergenerational acknowledgment of the ongoing relationship with the deceased child by grandparents was very important, especially during a subsequent pregnancy.[142,176]

For grief to occur, the individual must have valued the person who is lost so that the loss is perceived as significant and meaningful. Because, prenatally, there is an investment of love in the fetus or newborn, the neonate is a valued person. To the extent that prenatal attachment has occurred, grief should be expected and felt at the loss of the fetus or newborn. Therefore, loss at birth is a significant loss of a valued (although as yet only imagined) person.

Loss, whether real or imagined, actual or possible, is traumatic. The individual is no longer confident in him- or herself or in his or her surroundings because both have been altered. Mourning and grief are forms of separation reactions. Fear of separation and abandonment is a universal aspect of childhood regardless of age or developmental stage. Perhaps the loss of a significant other awakens these childhood fears and reminds us of the basic "insecurity of all our attachments."[125]

Life changes are stressful for the individual because they threaten to disrupt continuity and a state of equilibrium.[150] Significant changes in the family configuration, such as the accession of a new member, are normally a stressful occasion for family members. Perinatal complication or loss is an even more stressful event for which the family has little or no preparation. The result of this type of crisis may be personal growth, maintaining the status quo, regression, or mental illness.[34,151] Often, the outcome depends on a combination of coping skills and the type of help received during the crisis.[49]

Decreasing the element of surprise through preparation for the situation to be encountered may modulate the effect of the event. Anticipatory grief[116,166] functions to both prepare and protect the individual from the pain of impending loss. Prenatal diagnostic procedures, such as ultrasonography,[80] amniocentesis, and fetoscopy, can detect a variety of severe or lethal birth defects. When there is forewarning that the pregnancy/fetus or the newborn is not healthy, parents may begin a process of and psychologically prepare for the loss of their baby while at the same time hoping for the child's survival.[15,16,185,204]

Parental withdrawal from the relationship established during pregnancy may accompany the intense emotions of anticipatory grief. Detachment protects and defends the parent from further painful feelings associated with the investment of self in a doomed relationship. If anticipatory grief proceeds, the parent may detach to the point of being unable to reattach to the infant if he or she survives. In this situation, the infant survives, but the relationship with the parents may be significantly impaired. Maintaining even a remote hope that the fetus or newborn will survive protects the parents from the full experience of grief and total detachment from the baby. Accordingly, antenatal counseling suggesting "the baby will not survive delivery" or "will live only a few minutes" may be detrimental to adjusting to a fairly fluid situation at the time of birth (i.e., a lengthier survival for which some attachment could be anticipated as valuable).

The degree of parental anticipatory grief is correlated with positive feelings about the pregnancy and the mode of delivery but generally not with the severity of the infant's illness. The greater the parental investment and the higher the expectations for the pregnancy, the more anticipatory grief can be expected should perinatal complication ensue. The relative severity of the medical problem itself, however, is not associated with the degree of anticipatory grief.

PERINATAL SITUATIONS IN WHICH GRIEF IS EXPECTED

Loss is a fact of life, not just of death. Every stage of development requires a loss of the privileges of the preceding stage and movement into the unknown of the next stage. Any life event involving change or loss is accompanied by grief work, including moving, divorce, separation, death of a spouse or family member, injury or illness, retirement, job change, menopause, and even success.[150] The concept of loss is even applicable to the physiologic and psychologic events of normal pregnancy and birth. Certainly, when pregnancy fails to produce a live, healthy infant, a perinatal loss situation exists

BOX 30.1 PERINATAL SITUATIONS IN WHICH GRIEF REACTION IS EXPECTED

1. Pregnancy
2. Birth
   A. Normal
   B. Cesarean delivery
   C. Forceps
   D. Episiotomy
   E. Medicated
   F. Prolonged or short labor
   G. Place of birth
3. Postpartum (see Chapter 29)
   A. "Postpartum blues"
   B. Depression
   C. Psychosis
4. Abortion
   A. Spontaneous
   B. Therapeutic
   C. Elective
   D. Selective
   E. Selective reduction (for multiple gestation)
5. Stillbirth
6. Loss of the perfect child
   A. Premature
   B. Baby with an anomaly
   C. Sick newborn
   D. "Wrong" sex
7. Neonatal death
8. Relinquishment

(Box 30.1). These perinatal losses, including stillbirth, loss of the perfect child, and neonatal death, are discussed in detail in this chapter.

Stillbirth

Stillbirth is the demise of a viable fetus that occurs after fetal movement when the parents have often thought of the fetus as having personality and individuality. For parents, a stillbirth is a life-changing event that may result in psychologic, social, and physical costs and affect interpersonal relationships and subsequently born children.[30,105] From the crisis of a stillbirth, parents may also develop resilience, new life skills, and new capacities. Because stillbirth occurs later in pregnancy than most pregnancy terminations, there are increased parental expectations about the baby and the birth process. Selective pregnancy termination for genetic indications is often performed in the second trimester of pregnancy and involves the death of a wanted child. Although parents understand the validity of the reason for terminating the pregnancy, sadness, guilt, social isolation, and self-blame often accompany the decision to terminate.[122] The anxieties related to termination procedures, which may include labor and birth, and the feelings of helplessness, isolation, and depression should be acknowledged and handled as in a stillbirth.

Fetal demise in utero happens either prenatally or in the intrapartum period. For 50% of stillbirths, death is sudden, is without warning, and results from unexplainable causes. The majority of women who experience the death of a fetus in utero spontaneously begin labor within 2 weeks of fetal demise. Carrying the dead fetus while waiting for spontaneous labor or induction is sad and difficult for the woman and her entire family. Feelings such as helplessness, disbelief, guilt, and powerlessness characterize this period. There often is an almost uncontrollable urge to flee and escape the unpleasant situation.

For the family that experiences intrapartum demise, the joyous expectations of labor and birth suddenly change to fear, anxiety, and dread that the "worst" could have possibly happened to them. The suddenness of fetal demise in labor and birth affects both parents and professionals with feelings of shock, denial, and anxiety. Whether the fetal loss is early or late, the woman and her family maintain hope by believing that the professional has made a mistake and that the fetus is still alive.[164] The onset (or continuation) of labor is approached with both hope and dread: hope that the infant may be born alive and dread that the infant's death will soon be a stark reality.

The discomfort of labor and birth is particularly difficult for the woman whose fetus has died because her work will not be rewarded with a healthy infant. However, overly solicitous use of drugs at birth is not recommended because they relegate the experience to unreality and give it a dreamlike quality.[203] Keeping parents together through this crisis is important for mutual support and sharing of the birth.[163] The deafening silence of a stillbirth forces the reality of the infant's death on both the parents and the professionals present at birth.[163] A recent study of communication and staff

presence at stillbirth deliveries found that bereaved mothers were less likely to have family members and hospital staff present at delivery and that African American mothers were half as likely to have heard about their stillbirth from a midwife or physician.[76.]

In the past, at the birth of a stillborn, the mother was heavily sedated or anesthetized, and the neonate was hidden and whisked away immediately. These women were often left with fears and fantasies: "Was the baby normal?" "What was the baby's sex?" "What did the baby look like?" Seeing, touching, and holding the infant, when culturally appropriate, can promote completion of the attachment cycle, confirm the reality of the stillbirth for both parents, and enable grief to begin.[21,164,203]

Because it can be easier to grieve the reality of a situation than a mystical and dreamlike fantasy, contact with the stillborn enables parents to grieve the infant's reality rather than endure their most frightening fantasies about the baby.

After confirming the reality of the infant's death, a search for the cause, characterized by the universal question "Why did the baby die?" begins. Either or both parents may blame themselves or feel guilty about real or imagined acts of omission or commission. An autopsy may determine the cause of death, but most often the cause is unknown, even after an autopsy. However, an autopsy may be useful in reducing parental guilt and uncertainty about future pregnancies, as well as in aiding the recovery from the loss.[43,130, 203] The "empty tragedy" of stillbirth forces the mother to deal with both the inner loss of the fetus and the outer loss of the expected newborn. Fathers who experience stillbirth as a "waste of life" are especially appreciative of the tokens of remembrance from the baby and need help in expressing their grief.[163]

Loss of the Perfect Child

Although pregnancy ends in the birth of a live newborn, the pregnancy outcome may not be what the parents had anticipated. The birth of an infant who does not meet parental expectations represents the realization of the parents' worst fears: a damaged child. Newborns who are preterm, have an anomaly, are sick, or those with the "wrong" gender or who ultimately die represent the loss of the imagined or hoped-for perfect child.

After the birth of such an infant, parental reactions include grief and mourning for the loss of the loved object (the perfect child) while adapting to the reality and investing love in the baby with an anomaly.[69,71,175] This reaction is analogous to parental mourning at the death of a child.[175] However, unlike the finality of death, the birth of a living baby with an obvious anomaly entails a persistent, constant reminder of the feelings of loss and grief because of parental investment of time, attention, and care for either a short time (preterm or sick newborn) or a lifetime (physically or mentally impaired child).[153,175]

The psychic work involved in coping with the reality of the imperfect child and the inner feelings of loss is slow and emotionally painful.[67,153] The process is gradual and proceeds at an individual pace that cannot be hurried but can be facilitated and supported. Detachment from and mourning the loss of their fantasized child are necessary before parents are able to attach to the actual child.

The birth of an imperfect infant represents multiple losses for parents. A primary narcissistic injury, a threat to the woman's self-concept as a woman and mother, and a threat to the father's self-concept as a man and a father all occur when a less-than-perfect infant is born.[47,48,67,108] Because the child is an extension of both parents, a less-than-perfect (i.e., deformed) child is equated with the perceived less-than-perfect part of the parental self. In the mind of the parent, the imagined inadequate self has failed and caused the birth of the damaged baby.[108]

Prematurity

Every woman expects to deliver a normal, healthy infant at term. Therefore, the onset of premature labor is both physiologically and psychologically unexpected. Premature birth is a crisis and an emergency situation characterized by an increased concern for the survival of the newborn and often the mother. Premature labor and birth are accompanied by feelings of helplessness, isolation, failure, guilt, emptiness, and lack of control.[108,175] The negative and dangerous atmosphere surrounding the premature birth experience may influence the relationship with the premature infant, who also may be perceived as dangerous and negative.

Normal adaptations to pregnancy are abruptly terminated by the birth of a premature infant.[108] Prenatal fantasies about the infant and the new roles of mother and father are interrupted by a premature birth. This forces parents who are "not ready to not

be pregnant" to grieve the loss of a term infant and imposes premature parenting on individuals not yet ready for the experience.

As discussed in Chapter 29, anticipatory grief is one of the normal psychologic tasks accompanying premature birth. Anticipatory grief may be decreased by early contact between parents and neonate and, conversely, increased by separation of parents from preterm newborn.[108] Prolonging anticipatory grief with failure to progress through the other tasks results in altered relationships with the parents if the preterm infant survives.

Infants With a Birth Anomaly or Syndrome

In approximately 2 of every 100 births,[108] an infant is born with a congenital anomaly. Because society values physical beauty, intelligence, and success, the birth of a physically or mentally impaired baby is seen as a catastrophe in our culture.[200]

Antenatal use of ultrasound now makes it possible to identify potential fetal problems in utero. As parents receive the information antenatally, they begin the process of anticipatory grief.[16] They experience feelings of shock, anger, guilt, and hope. At the birth of the baby, there usually is the confirmation of the anomaly, and parents must deal with the reality of the situation. Whether anticipated or not, however, the birth of a baby with a congenital anomaly is accompanied by ambivalent feelings for all concerned (parents, relatives, friends, and professionals). The first reactions to the reality of the situation are feelings of disbelief and shock. Feelings of shame, revulsion, and embarrassment at creating a seemingly damaged and potentially devalued child are common.[171] Guilt, self-blame, and a search for a cause or reasons for the tragedy are intermixed with feelings of anger.

The severity of loss and feelings of disappointment heavily burden the parents, a burden they may believe that no one else has experienced.[108] Their loneliness and isolation may be intensified by their self-imposed withdrawal from others. Unlike the birth of a healthy infant, the birth of a sick baby or one with an anomaly is not celebrated with announcements, visits, and gifts from friends and family. The negative responses of society's representatives (family, friends, acquaintances, and professionals) may increase the parents' negative feelings for an impaired child.[200]

The extent of the infant's anomaly cannot be used as a criterion for the degree of parental grief reaction, although a gross, visible anomaly may elicit more emotional reaction than a hidden or minor one.[108] A seemingly "minor" anomaly as defined by a health care professional may represent a severe impairment to individual parents. The professional, who has had more contact with infants with a wide range of anomalies, views the individual infant's anomaly in a different context than that typical for the parents, who may have limited or no experience with such an affected child or adult. The professional also views the infant's anomaly from a less personal, more objective, and less narcissistic position than the new parents.

When the newborn is sick, the degree of mourning and parental feelings of grief and loss are not equated with the severity of the neonate's illness.[15,173] Even seemingly minor illnesses such as jaundice or respiratory difficulty requiring phototherapy or minimal oxygen supplementation are associated with parental concern for survival and feelings of grief and loss.[140] These feelings often are not acknowledged by the parents or professional care providers because of the nonserious medical nature of the condition. In the mind of the care provider, self-limiting and treatable conditions are compared with more serious and often fatal neonatal illnesses. The care provider feels relieved about the minor nature of the neonate's condition and conveys this to the parents: "This is an easy condition to remedy. You don't have anything to worry about. The baby will go home in a few days."

Thus, only the medical aspects of the newborn's illness are dealt with, whereas parental feelings remain unspoken and unresolved.[31] In an altruistic attempt to reassure and comfort the family about the newborn's complete recovery, the professional unwittingly may discount the parents' real feelings. If the care provider is not concerned, parents may feel that they, too, should not be concerned and thus distrust and discount their own feelings.

Neonatal Deaths

The reactions accompanying neonatal illnesses are similar to the grief reactions experienced by parents whose infant dies.[15,49] Failure to acknowledge (even minor) neonatal illness as a loss situation and to work through the associated grief can prevent parents from detaching from the image of the perfect

child and taking on the sick newborn as a person to love. This may result in an aberrant parent–infant attachment. The liveborn infant who is critically ill or has a severe anomaly will be the focus of a "painful time of waiting"[15] for the family. They must deal with the uncertainty of whether their child will live and be healthy, live and continue to need extensive medical or special care, or die.

More deaths occur in the first 24 hours after birth than in any other period of life. Yet the death of a newborn is not the expected outcome of pregnancy. The majority of neonatal losses are caused by congenital anomalies incompatible with life (20%) and prematurity (17%).[86] Regardless of the cause of death, even infants who live only a short time are mourned by their parents.[101] Prenatal attachment and investment of love in the newborn result in a classic grief reaction at the newborn's death.

Even a short period of life between birth and death gives parents an opportunity to know and take care of their infant. Completion of the attachment process enables parents to psychically begin the next process of detachment. Attachment to the baby's reality encourages detachment from that reality rather than from the parents' most dreaded fears and fantasies about their infant. Parental contact with the child before death enables them to share life for a brief time.

In the case of multiple births, when one or more infants die and the others live, parents simultaneously grieve the loss of the deceased infant or infants while attaching to the survivors.[114,145,146,187] In many situations of multiple births, the surviving infant or infants are in an intensive care nursery. The contradictory feelings of love and attachment and grief and detachment, as well as the anxiety associated with the care and well-being of the surviving infant, are emotionally draining for new parents. The process of grief may slow the parents' ability to become intimately involved with their surviving infant(s).[146,147,187,195] They may have ambivalent feelings toward the infant(s) who survives or toward the infant(s) who dies. With the loss of one infant of a multiple birth, there is less support for the grieving parents because the frequent response is that they should be thankful for the survival of one (or more) of their infants. Research shows that the death of a twin (or higher-order multiple) is as great a loss for a mother as the death of a singleton.[59,145,146,181] Helpful interventions include (1) acknowledging the uniqueness of every baby; (2) viewing, holding, and photographing the babies together—living and dead; (3) allowing for private time with each deceased infant; (4) giving similar mementos and keepsakes from each infant, deceased and living, to the parents; and (5) providing reassurance about the health of their surviving child.[145-147,187] One study found that farewell rituals do not influence the intensity of perinatal grief.[60]

Generally, the death of a newborn occurs despite everything done to prevent it. This provides parents with some measure of comfort in knowing that they did everything possible. Yet when the neonate is so severely ill or deformed that a decision about initiating or continuing life support is necessary, the parents have an extra burden. The situation may involve conflicts between physicians, nurses, and family wishes, causing significant personal anguish. Professionals who convey information sensitively, compassionately, and honestly facilitate care transitions toward comfort/palliative care. Such a situation is tenderly conveyed in the article entitled "Four Wishes for Aubrey."[36] Aubrey's parents are asked what they would like to do with their little boy to make lasting memories. Without hesitation, Aubrey's mother states the following wishes for her 5-month-old terminally ill son:

1. Allowance of more than three visitors in his room at one time
2. The ability to hold Aubrey to her chest and lie down with him; the mother wanted a bed large enough (in his private room) for her and her son to lie down together (Fig. 30.1).
3. The ability to take Aubrey outside so that he can feel the sun and a breeze

All of Aubrey's mother's wishes were made possible by caring, compassionate professionals who actually suggested and accommodated the fourth wish: arranging for special photography of the family with Aubrey, such as *Now I Lay Me Down to Sleep*.[139] Aubrey's family has participated in local and national education for health care providers learning about palliative care and in numerous teaching forums with other parents.[36] The authors enumerate the lessons learned from and with this family: (1) the importance of asking each individual family what is important to them; (2) the caution to never presume that we know what any family needs or wishes; and (3) the cruelty of presuming and minimizing every family's uniqueness, power, and right to their own experience.[36] The article ends with the lesson that fulfilling the family's wishes was profoundly moving

FIGURE 30.1 **Aubrey and his mother.** (From Carter BS, Brown JB, Brown S, Meyer EC. Four wishes for Aubrey. *J Perinatol.* 32[1]:10–14, 2012.)

and gratifying for the health care providers who were creative, engaged, and caring for Aubrey and his family.

As a consequence of the federal Baby Doe regulations, most hospitals now have ethics committees that address a variety of the medical, legal, and ethical controversies (see Chapter 32). The decision-making process may be collaborative, parent initiated, directive, or nondirective.[145] Regardless of who makes this decision, it is primarily the parents who will live with its ramifications, including feelings of grief, an ongoing void in their lives, and a desire to live better lives to honor their infant.[9] When parents are involved in the decision-making process, they wonder if theirs was the right decision regardless of what it was. Whether the baby lives or dies, they wonder how a different decision would have changed their lives.

STAGES OF GRIEF

The experience of grief is a staged process that occurs over time. To detach both externally and internally from the lost loved object, emotional investment is withdrawn so that it may be invested in new love relationships.[116] Each stage of grief represents a psychologic defense mechanism used to help the individual adapt slowly to the crisis. This slow adaptation is purposeful because it prevents the individual psyche from being overwhelmed by the pain and anguish of loss.[144]

Although each stage of grief is recognizable, the process of grief is dynamic and fluid rather than static and rigid. Parents, families, and professionals progress cyclically through the stages of grief rather than in an orderly progression from beginning to end. However, each person experiences the process of grief uniquely and at an individual pace. Knowledge of each stage is necessary to assess where an individual family member, the family as a unit, and the staff are in their grieving process. This information is then used to support individuals when they are in their particular stage of grief. Rather than attempting to maneuver grieving individuals from stage to stage, contributing to their defense, or stripping individuals of their defenses, knowledgeable professionals are prepared to understand and honor the individual's grieving process. Regardless of the type of perinatal loss, the experience of that loss through staged grief work closely parallels the grief stages described by Elisabeth Kübler-Ross.[110]

The feelings of disbelief and rejection of the news are reflected in the responses "No! This couldn't happen to me!" and "It isn't true! They've made a mistake!" This immediate response protects the individual from the shocking reality of loss by postponing the full effect of reality until the psyche can handle it.[164] By holding on to the fantasy of a positive outcome (e.g., the loss of the heartbeat is only temporary, or the dead infant belongs to someone else), facing the awful truth and the grief associated with it is delayed, at least temporarily.[164]

The initial stage of grief is characterized by overwhelming feelings of being stunned and surprised. This often is seen as emotional numbness, flat affect, or immobility.[203] Emotional detachment often is expressed as an inability to cope or respond with activities of daily living, an inability to remember what others have said, and a tendency to repeat the same question.[56,63] For the tragedy to be handled in manageable pieces without overwhelming the individual, the mind may acknowledge the event only intellectually, and there is a corresponding lack of emotional reaction,[203] or the event may be compartmentalized so that only a part of the situation rather than the whole becomes the focal point of attention.

Anger is the result of a gradually developing awareness of the situation's reality. As the significance of their perinatal loss begins to dawn on them, parents (and significant others) experience the diffuse emotions of anxiety and anger.[108] With the

full effect of their loss comes more focused feelings of bitterness, resentment, blame, rage, and envy of those with normal pregnancy outcomes.[110]

Social prohibitions against the expression of anger, especially for women, encourage this powerful emotion to be turned inward toward the self. Anger directed inward results in depression and a deepening sense of guilt. "Why?" and "What did I do wrong or not do right to have caused this to happen?" are the hallmarks of the self-examination and self-blame that accompany perinatal loss.[108,203] Answers often are irrational and have no cause-and-effect relationship with the reality of the circumstances. Irrational, feared causes include sexual intercourse (common worry of both men and women), career (of the mother) outside the home, superstitions, dietary habits, or lifting heavy objects.[203] Ideas of punishment (for past wrongs, for negative or ambivalent feelings, or for an unwanted pregnancy)[17] often are thought to be the reason for the failed outcome. The search for a reason to answer the question "Why me?" requires correct information to dispel unrealistic fantasies of causation. However, the question does not require a literal answer (often no concrete answer exists) but is merely a wish for a change in the situation.[17]

Anger directed outward is usually expressed as overt hostility to those in the immediate environment (family, children, care providers, and infant)[203] or toward God.[144] Fathers exhibit more anger than mothers.[77] Blame and anger may be destructive forces in the relationships among family members and may prevent these relationships from being a source of comfort and support. Venting of angry feelings toward professional care providers protects these family relationships for more positive interactions. Anger moves the grieving process along, but the persistence of anger may prevent grief work from progressing to subsequent stages.

Bargaining may occur concomitantly with denial and shock as an attempt to prevent or at least delay the loss. Bargaining usually occurs with whoever the parents (family or staff) believe the Supreme Being is. The "Yes, but" of this stage is a form of "conditional acceptance" while still attempting to make the reality other than what it is.[17,110] With an infant who has a congenital anomaly, bargaining may take the form of shopping for a physician or searching for the magic cure.[200]

The onset of depression and withdrawal marks the stage of a greater level of acceptance of the tragedy. With the true realization of the effect of the loss, the individual acknowledges that indeed there is a reason to be sad. The predominant feelings of this stage are overwhelming sorrow and sadness,[130] evidenced by tearfulness, crying, and weeping.[164] Feelings of helplessness, worthlessness, and powerlessness contribute to the sense that life is empty and futile. Withdrawal may be evidenced by requests to be left alone, by decreased or complete cessation of visits to the infant, and by silence.[110] The degree of withdrawal may be indicative of the depth of depression and the extent to which there is guilt and self-blame.[164]

Acceptance is the resolution stage of the grief process that is heralded by the resumption of usual daily activities and a noticeable decrease in preoccupation with the image of the lost infant.[116] This stage usually is not witnessed by perinatal professionals. The acceptance stage is characterized by emotional detachment of life's meaning from the lost relationship and reestablishing it independent of the lost object.[110,125] The lost relationship is seen in a new light—as giving meaning to the present.[125] The aggrieved person relinquishes that part of him- or herself that was defined in the lost relationship and establishes a new identity that is emotionally free to attach in another relationship.

For the family of a child with a congenital anomaly or disability, acceptance is not an all-or-nothing proposition but, rather, a daily adaptation and coping with the child and the effects of the anomaly or disability.[169] For the family, periods of frustration and sorrow alternate with periods of delight and enjoyment of the child. Because of the chronic sorrow experienced throughout the life of a child with an anomaly, the final stage of resolution of the family's grief is possible only after the child's death.[141,200]

The acceptance stage represents the ability to remember both the joys and sorrows of the lost relationship without undue discomfort.[65] With gradual integration of the loss, there are progressively fewer attacks of acute, all-consuming pain.[125] When recalling the lost infant, there are fewer feelings of devastation and more feelings of sadness. The ability to "celebrate the loss" also identifies grief resolution. Celebration of the loss does not mean recall without sadness and sorrow but with an ability to find some meaning, some good, and some positive aspects in the situation (e.g., "At least we had our child for a time, even though it was a short time").

SYMPTOMS OF GRIEF

Although each person copes with grief in individual ways, there are expected reactions to loss situations. Knowledge of the differences and commonalities of the grief experience enables care providers to understand their own reactions, as well as to share their thoughts and feelings with the grieving family. The professional care provider must learn to "hear" what the family says about how and where each member is in the process of grief resolution. Often the "message" is not a direct reference to the loss or one's feelings but, rather, nonverbal communication. The professional must learn to recognize that individuals often communicate more by what they do and what they omit than by what they say.

The signs and symptoms of acute grief have been well described and include both somatic and behavioral manifestations of the emotional experience of the loss (Box 30.2).[143] The behavior of the bereaved is characterized as ambivalent.[125] In certain perinatal situations, parents simultaneously hope that the infant will live and wish for the infant to die; they want to love and care for the infant and at the same time wish to reject him or her.[108] These feelings are frightening and socially unacceptable and therefore often remain unspoken.

Often the intensity of grief is greater when the relationship with and feelings about the lost person are ambivalent.[104,125] Even with the most positive of pregnancy outcomes, taking a newborn into the family results in ambivalent feelings for all family members. The degree of disruption that a perinatal loss brings to the family is equated with the severity of grief, especially because reproduction and a healthy perinatal outcome are highly valued in our society.[125]

MALE–FEMALE DIFFERENCES

Although members of both genders have the same grief reactions, women express more symptoms (crying, sadness, anger, guilt, and use of medications)[61,127,156] than men. This difference in symptomatology does not represent a different experience of grief but merely a different expression of it. Understanding these differences and the reasons for them is crucial for care providers working with parents at the time of perinatal loss. Explaining these differences to parents is also crucial so that diverse grief responses do not become divisive in the relationship.[61,156,176]

The father's degree of investment in the pregnancy, impending parenthood, and the circumstances of birth all affect his feelings of loss. Because the father's body does not directly experience the changes of pregnancy, the pregnancy initially may be less of a reality to him than to the pregnant woman. This lag in the physiologic reality contributes to a lag in the psychologic investment of the father in the baby. The father's lag in psychologic investment often contributes to incongruent grieving, a difference in mother's and father's grief reactions. Fathers often comment that the infant became real when he felt the fetus move in the mother or at the first sight of the new infant. Fathers who form an early attachment to the child feel sadness, disappointment, and often anger at being denied the expected son or daughter.[77,99,127,128,163] Conversely, fathers who have been normally ambivalent or overtly negative about the pregnancy may feel guilt and responsibility for the failed outcome.

Participation of the father in the events of labor and birth also influences his attachment and, ultimately, his feelings of loss. Exclusion decreases his involvement in these life-crisis events, whereas inclusion has many advantages for the mother, infant, and self (see Chapter 29). If the infant is ill, the father may initially have more and closer contact than the mother.[15] In the birth place, the father may see, touch, or hold the infant before the mother does. The father observes the initial resuscitation and stabilization and may accompany the infant to the nursery and on transport to a regional center. Often the father receives the first information and support about the infant's condition and returns to the hospitalized mother with the news. This early, prolonged contact coupled with the father's increased responsibility often contributes to the development of a closer and earlier bond between father and infant than between mother and infant. The initial lag in prenatal investment may be offset after birth by concentrated contact between the father and the baby, thus making the loss highly significant to the father.

Societal expectations about masculinity and femininity markedly influence the expression of grief. Society's message to men starts early in life: "Big boys don't cry" and "Don't cry, you'll be a sissy" (i.e., girl). The preferred male image

BOX 30.2 CRITICAL FINDINGS
Signs and Symptoms of Grief

1. Somatic (physiologic)
   a. Gastrointestinal system
      Anorexia and weight loss
      Overeating
      Nausea or vomiting
      Abdominal pains or feelings of emptiness
      Diarrhea or constipation
   b. Respiratory system
      Sighing respirations
      Choking or coughing
      Shortness of breath
      Hyperventilation
   c. Cardiovascular system
      Cardiac palpitations or "fluttering" in chest
      "Heavy" feeling in chest
   d. Neuromuscular system
      Headaches
      Vertigo
      Syncope
      Brissaud disease (tics)
      Muscular weakness or loss of strength
2. Behavioral (psychologic)
   a. Feelings of:
      Guilt
      Sadness
      Anger and hostility
      Emptiness and apathy
      Helplessness
      Pain, desperation, and pessimism
      Shame
      Loneliness
   b. Preoccupation with image of the lost infant
      Daydreams and fantasies
      Nightmares
      Longing
   c. Disturbed interpersonal relationships
      Increased irritability and restlessness
      Decreased sexual interest and drive
      Withdrawal
   d. Crying
   e. Inability to return to normal activities
      Fatigue and exhaustion or aimless overactivity
      Insomnia or oversleeping
      Short attention span
      Slow speech, movement, and thought process
      Loss of concentration and motivation

Data from Colgrove M. *How to Survive the Loss of a Love.* New York: Lion Publishing; 1976, Lindemann E. Symptomatology and management of acute grief. *Am J Psychiatry.* 1944;101:144; Marris P. *Loss and Change.* New York: Pantheon Books; 1974.

in our society is the autonomous, independent achiever who is always strong and in control, even in the face of disaster.[77,78] In keeping with this image, the father may feel that he must make all the decisions and have all information filtered through him to protect the mother. However, this altruistic gesture prevents full disclosure to and involvement of the mother. Assuming the role of a strong protector also involves a heavy price for the father in the suppression of his own feelings and delay of his own grief work.[61,128,156] The role of a "tower of strength" often engenders feelings of resentment from the mother. Although he attempts to live up to his (and society's) expectations of himself, the woman views his apparent lack of feelings and emotions, especially crying, as "He doesn't care." A recent study showed that distress experienced by the mother but not by her partner resulted in longer-term marital dissatisfaction for the mother.

Many men have difficulty dealing with irrational behaviors, as well as with the normal ambiguity and conflict of life. This difficulty makes the emotional response of grief and its accompanying ambivalent feelings and conflicts produce discomfort and anxiety in many men. The expression of appropriate human emotions becomes threatening and makes them feel vulnerable. To decrease the anxiety associated with grief and its expression, men often deal with feelings by denying them, increasing their workload, grieving internally, or withdrawing from the situation and refusing to discuss it.[127,156]

The father's attitude and ability to communicate about the loss may help or impede the mother's grief work.[166] Lack of communication between a couple

may contribute to intense mourning, psychiatric disturbances, and severe family disruption.[101,156,186] Synchrony of grieving between the mother and the father is important in an ultimate healthy resolution for the family.[29,44,156] If the father denies and suppresses his own feelings of loss and grief, he may react to the normal signs and symptoms of grief in his partner as if they were abnormal. Often the father can resolve his grief faster than the mother, and he may become impatient with her continual "dwelling" on the loss. Grief decreases over time: for mothers, the decrease occurs from 3 to 13 months, whereas the decrease for fathers occurs from 3 to 6 months.[202] Sometimes fearing the woman's prolonged grief, the man decides to "spare her" from his feelings and does not discuss them with her. Instead of being comforting as intended, failure to share grief leads to isolation and alienation within the relationship.[108,156]

In some situations, the man may experience intense emotions several months after the death, not unlike those his partner experienced at the time of the crisis. Because these intense emotions occur so long after the crisis, he may not even associate them with the death.[56,108] A recent study found that at 30 months after the death of a baby, fathers were more distressed than the mothers, who were the more distressed initially after the death.[186]

TIMING OF GRIEF RESOLUTION

Parents

Emotional recovery from the pain of perinatal loss occurs with time. There is no complete agreement on the length of time necessary for the individual to resolve grief. Indeed, a specific timetable for mourning may be impossible to establish.[17] However, some general time frames are available for the duration of a normal grief reaction.

Acute grief reactions are the most intense during the first 4 to 6 weeks after the loss,[116,125,144] with some improvement noted 6 to 10 weeks later. Normal or uncomplicated grief reactions may be expected to last from 6 months to 1[14,65,104,108,144,182] or 2 years.[104,125] A recent study found that maternal resolution of grief occurred at 1 month in 38.2% and at 18 months in 62.6 % after the birth of a preterm infant.[199] In this study, unresolved maternal grief at 18 months was associated with mothers who had higher maternal stress at 1 month after preterm birth.[199] Indeed, significant losses of a spouse or child may never be completely resolved[50,159,188]: "I'll never get over it."

One parameter for differentiating normal from pathologic grief has been the length of time for grief to be resolved. Grief work may still be categorized as normal/uncomplicated even if it lasts longer than a year, especially if the person is working through unresolved grief from the past. Grief work is normally energy draining. Dealing with more than one grief or loss situation compounds the intensity of mourning and may prolong the grief reaction. Because perinatal loss represents more than the loss of the newborn (loss of the perfect child, loss of plans for the future, and loss of self-esteem), feelings of sadness and depression may still be evident for a year or longer.[108,127,186,203] A study of white, Hispanic, and black parents (176 mothers and 73 fathers) examined their health and functioning at 1, 3, 6, and 13 months after the death of their infants. At 13 months after the death, one-third of the responding parents had clinical depression and posttraumatic stress disorder (PTSD).[201] At every time period, more Hispanic and black mothers had PTSD symptoms and more moderate/severe depression at 6 months. In the first 13 months, 98 hospitalizations for anxiety, depression, panic attacks, chest pain, and cardiac problems were reported, and 29% were stress-related.[201] A more recent study found that 75% of women had high PTSD scores after perinatal loss.[93] In another study, 9 months after a perinatal loss, bereaved women had a four-fold higher risk for depression and a seven-fold higher risk of PTSD, with a minority receiving any type of psychiatric treatment.[73] The presence of negative thinking about life and the world is associated with persistent depressive and grief symptoms for up to 10 years after perinatal loss.[109] During the first 6 to 13 months after the death of an infant or child, parents have an increase in acute and chronic illnesses, hospitalizations, and medication use.[26,53,201] Two Danish studies have shown that the birth of an infant with a congenital anomaly[39] and a perinatal loss increase maternal mortality, especially from cardiovascular disease.[92] In another study, mothers experiencing perinatal bereavement were 3.5 times more likely to have symptoms of elevated anxiety and 3.6 times more likely to have more depressive symptoms when their very preterm infant was 7 years of age compared to mothers without perinatal bereavement.[181]

Sorrow and grief may even last a lifetime. For families of children with anomalies, "chronic sorrow"[46,56,87,141,153,175] is a natural phenomenon and experienced as long as the child lives. These parents live with the constant reminder of what is not and what the child will never be and can never do. The grief of death is final—parents do the work and go on; chronic sorrow is grieving on a daily basis. Expecting the parents to adjust to or accept their child's defect without any elements of lingering sadness is unrealistic. Although hampered by small sample sizes, research on the gender differences in chronic sorrow show more intense chronic sorrow in mothers than in fathers.[46,87,123] Chronic sorrow is a normal and justifiable reaction to the daily stresses and coping necessary when a child is living with a birth defect or major impairment. The final stage of grief resolution is possible only with the finality of the death of the child.

Even when grief has been resolved, anniversary grief reactions are normal.[191] Feelings of sadness, crying, and normal grieving behaviors may be reactivated at certain times. These anniversary reactions may not be limited to the infant's date of death but also may be felt on the expected date of delivery, on the actual birthday, or on seeing an infant of the same age and gender as the lost infant. Holidays may also reactivate grieving behaviors, especially those that bring together family and friends and recall memories of joy and happiness.

Staff

Those sharing a crisis (complication, illness, or death) often become closely attached, so that the loss is felt not only by the family but also by the professional care providers.* Repeatedly dealing with death and infants with anomalies increases the professional's exposure to personal feelings of grief and loss. This may be perceived either as a threat or a personal opportunity for growth.

The critical variable in the ability to face or assist others in handling loss is the manner in which the care providers have been able to resolve their own personal losses. Unless the care providers can cope with personal feelings of loss and grief, they may not be able to give of the "self" to others. Care given without genuine involvement and responsiveness to the family's feelings does not facilitate and may actually impede the mourning process. Professionals who can deal honestly with their own feelings will be able to help others cope with theirs.[41,146]

Helping parents deal with their grief may be difficult for professionals because of their attitudes and feelings about perinatal loss. For professionals trained to preserve life, loss of the best pregnancy outcome or death itself represents both a personal and professional failure.[108] When success is equated with life, the failure of death (or loss) is associated with feelings of guilt, anger, depression, and hostility.[203] Just when professionals are expected to be supportive and therapeutic, they may be overwhelmed with their own feelings. A recent qualitative study of nurses' reactions to being present at a perinatal loss found recurring themes: (1) getting through the shift, (2) symptoms of pain and loss, (3) frustrations with inadequate care, (4) showing genuine care, (5) recovering from traumatic experience, and (6) never forgetting.[149] Professionally, care providers may feel helpless when all efforts inevitably result in no change in the outcome.

The feelings and stages of grief experienced by the family are the same ones felt by the staff who are attached to the parents and their newborn. Many professionals working in perinatal care are of childbearing age, so identifying with the parents and their plight is relatively easy. Because the sick, anomalied, or even dying or deceased infant could easily be that of the staff member, they share with the parents the special stress of the loss of a child. The care provider often experiences the same fantasies of blame as the parents: "What did I do (or not do) to cause this?"

Repetitive contact with loss situations and death exposes the staff to recurring feelings of frustration, guilt, self-doubt, depression, anger, classic grief reactions, helplessness, sadness, hopelessness, loneliness, PTSD, and covert relief.[57,70,82,129,133] Such uncomfortable feelings often lead to behaviors of avoidance and withdrawal as a means of self-protection; this has been called "compassion fatigue."[41,82,146,159] Adequate medical care may be given, but psychologic care of the family may be neglected.[119] The involved primary care providers may decrease their attachment to both parents and infant when an unfavorable outcome is inevitable. Withdrawing emotional support and involvement may spare the professional but only adds to parental feelings of isolation, inadequacy, and worthlessness. Professionals who have risked family attachment and shared grief work may be more cautious in

*References 41, 57, 146, 149, 154, 156, 159.

future involvements to protect themselves from the pain of loss.

Asynchrony and individual differences in handling grief reactions also may cause problems among the professional staff. Constant exposure to perinatal loss may desensitize some individuals until they are blasé or even callous about the crisis, whereas the grief reactions of others parallel the family's reaction. Some staff members may have reached the stage of acceptance, whereas others who cannot let the infant go persist in the idea of a magical cure, a characteristic of denial. The rationale of prolonging the child's life may in reality be prolonging death, and inevitably one needs to accept death's finality.

Staff members cannot offer support to families experiencing loss unless they receive support in dealing with their own grief reactions.[41,66,70,129,131] Those who receive support learn about their feelings and how to handle them and so have no need to displace their pain to others. The three most effective ways that neonatal intensive care unit (NICU) nurses have identified to manage their stress after a neonate's death are (1) discussing with coworkers, (2) supporting and comforting the grieving family, and (3) talking with their own families.[57] Various formats are available for meeting staff needs, such as mutual support of colleagues or group sessions involving peer counseling on a long- or short-term basis.[41,57,66,108,154] Group meetings provide a vehicle for support and for sharing information and feelings among staff members.[41,57,66,108,154] Facilitated by an objective person with expertise in group process and the concepts of grief, such "debriefing" meetings have the goal of helping the staff members deal with their reactions so that they will be better equipped to help the parents.[54,129] Group sessions also serve to decrease stress, increase job satisfaction, and ultimately help prevent burnout and PTSD.[82,133] A systematic review of 16 qualitative studies on how nurses cope with the death of a patient found that both intrinsic and extrinsic resources, listed in Box 30.3, are used. A national survey of 490 critical care nurses, interviewed after unsuccessful resuscitation, found that the coping behaviors of denial, self-blame, self-distraction, and behavioral disengagement were significant predictors of PTSD symptom severity.[131] In this study, the availability of institutional support affected the severity of post-code and PTSD symptoms. Staff members are encouraged to retain their humanity when an environment is created in which emotions are valued and their healthy expression facilitated, both at the time of loss and in its resolution.[54,97,129,154]

BOX 30.3 COPING RESOURCES USED BY NURSES AFTER THE DEATH OF A PATIENT[205]

- Intrinsic:
  - Setting boundaries
  - Reflection
  - Crying
  - Death beliefs
  - Life and work experience
  - Daily routines and activities
- Extrinsic:
  - Talking and being heard
  - Spiritual practices
  - Education
  - Programs
  - Debriefing

Sharing grief work with a family gives the care provider a chance for personal growth, to review past personal losses, and to evaluate the adequacy of their resolution. Helping others with loss or grief provides the professional with the opportunity to contemplate present and future losses, including one's own mortality. By working with those who have suffered a significant loss or death, a health care provider may gain a deeper perspective about life.[96]

INTERVENTIONS

Those in a crisis feel an openness to help and assistance from others, so that they emerge either stronger or weaker, depending on the help they receive.[32,151] This increased openness also makes those in a crisis more vulnerable to the reactions of others—to their facial expressions, tone of voice, and choice of words. Helpful professional interventions provide psychologic assistance during a highly vulnerable period of personal development. The goals of intervention are to maintain the precrisis level of functioning and to improve coping and problem-solving skills beyond the precrisis level (i.e., to facilitate personal growth). Effective intervention is characterized by helping grief work get started, by supporting those who are grieving adaptively,

and by intervening with individuals who display maladaptive reactions.[44,49,62]

For professionals, understanding parental perspectives of the experience of the death of a newborn should enable the provision of more sensitive and evidence-based care for grieving families. The results of two research studies provide some insight into what is helpful and what is not helpful for grieving families. The first study was a systematic review of 61 studies and more than 6000 parents who suffered a neonatal death.[72] This study found that parents valued emotional support, grief education, and attention to mother/baby. Nonhelpful and distressing behaviors from health care providers included avoidance, thoughtlessness, insensitivity, and poor staff communication.[2,72] Another study conducted semistructured interviews with mothers/fathers (n = 19) a mean of 1.9 years after the death of their infant. This exploratory study found a low level of grief, effective coping, and factors important to parents in end-of-life care for their infant.[28] Review of the data from this study, provided in Table 30.1, instructs health care professionals in helpful and nonhelpful interventions during the stressful experience of a dying infant.[35] Because 76% of the dying infants were in the NICU or pediatric intensive care unit (PICU) and 42% of the families had hospice/palliative care team involvement,[28] perhaps the low level of grief and the positive adaptation displayed by this small group of parents were because of the sensitive, helpful interventions of their health care providers. A more recent French survey of parental experiences (after the death of their newborns) found that half of the parents did not think that their feelings and decisions were respected.[64] Parent responders also felt that parental autonomy (in palliative care situations) was difficult for professional caregivers to respect.[64]

TABLE 30.1 PARENTAL PERCEPTIONS OF GRIEF AND IMPORTANT FACTORS AT THE TIME OF INFANT DEATH: RESEARCH BASIS[28,42,176]

STUDY FINDINGS	COMMENTS
1. Parents scored significantly lower than other parents who had lost a child and other adults with grief experience.	1. Lower levels of grief were measured by the Revised Grief Experience Inventory (RGEI), a 22-item Likert scale.
2. Study investigators viewed parents as positively adapting after loss of their infant.	2. Mean scores were 33.16 (out of a highest possible score of 36) on the Post-Death Adaptation Score, a 10-item scale rated by professionals.
3. Seven important aspects of care:	3. Identified by parents:
A. Honesty	A. Parents expect professionals to be honest in giving information about the infant/condition to them. Parental anger results when (parental) perception is that honest information was not given.
B. Empowered decision making	B. Parents want to be involved in medical decision making, especially about withdrawing life support. Parents who had been involved were glad they had been part of the decision process and felt supported by the medical team. Parents felt anger and abandonment when the decision to withdraw support was not believed to be respected by professionals.
C. Parental care	C. Parents needed care as much as their baby; when staff was insensitive to their needs, parents felt upset.
D. Environment	D. Parents appreciated comforts of sleep/family rooms as well as private, quiet areas where the infant died with family/parents. People present at the death were more important than the place of death. Parents expressed fear when left at home with their dying infant; parents wished they had held the infant longer.

Continued

TABLE 30.1 PARENTAL PERCEPTIONS OF GRIEF AND IMPORTANT FACTORS AT THE TIME OF INFANT DEATH: RESEARCH BASIS[28,42,176] — CONT'D

STUDY FINDINGS	COMMENTS
E. Faith/trust in nursing care	E. Parents had greater trust in nurses than other providers; most had positive experiences with their infant's nurses. Parents appreciated nurses personalizing and respecting the infant (using baby's name) as well as providing for the infant's comfort and opportunities for parental care (such as skin-to-skin care at the end-of-life)[111] for their baby. Negative experiences included mistakes in care and unprofessional behavior.
F. Physicians bearing witness	F. Parents thought it important that the physician be with them throughout the process, including being present at the time of the infant's death. Parents perceived the absence of the physician at the time of the child's death as negative, especially if they had been told that the physician would be there for them. Parents found it meaningful when the physician and other medical staff had contact with them after they had gone home.
G. Support from other hospital care providers	G. Parents appreciated support that they received from chaplains, social workers, and palliative care and child-life workers. Parents also appreciated support and help from these providers in dealing with siblings.
4. Seven coping strategies:	4. Identified by parents:
A. Family support	A. Parents relied on family support to cope with the death, appreciated family presence at the hospital/home when the infant died, and found it helpful to talk to extended family about their infant. When extended family members were not supportive and avoided talking about the infant, parents were distressed.
B. Keeping the memory alive	B. All parents showed researchers mementos of their dead infant and emphasized the importance of bringing things home (e.g., photos; plaster castings of hands/feet; blanket/clothes) from the hospital that had been used/belonged to the infant who died. Parents especially appreciated tangible reminders (e.g., garden/tree) and rituals to remember their infant.
C. Spirituality/faith	C. All families were comforted by their religious beliefs and found meaning and purpose in their infant's life and death. No families reported negative spiritual experiences or abandonment of their religious beliefs.
D. Altruism	D. Many parents wanted to and did "give back" to the hospitals that had cared for them and their dying infants. These altruistic acts took the form of monetary and equipment donations, volunteering, and becoming resource families to other parents with sick children.
E. Refocusing on life	E. The presence of other children in the family assisted parents in continuing to focus on life and the daily requirements of their surviving children. All parents acknowledged that having another child would never replace the infant who died.
F. Validation of decision	F. Parents were comforted by autopsy results that validated that they had made the correct decision for their infant. Parents also appreciated when physicians communicated to them their support of the parents' decision.
G. Bereavement support groups	G. Bereavement support groups resulted in positive experiences for most families, especially in being able to talk freely about their dead infant with others who understood and were not uncomfortable. However, some parents did not feel validated in their grief/loss of an infant by other parents in the group whose children were "older" when they died.
H. Follow-up	Follow-up of the family after perinatal loss is important to parents and health care providers

Nonhelpful Interventions

Caring for pregnant women and their infants is supposed to be a "happy" job. Birthing and caring for infants are supposed to be times of joy and celebration. Because no one expects death or loss to occur in maternity or nursery areas, when it does, both staff and families are shocked. To protect themselves from the reality of the situation or to "spare" the family, professionals may engage in interventions that do not help themselves or their patients. Such interventions may be meant altruistically but do not have the characteristics of effective intervention.

Maintaining the state of denial arrests grief work by preventing or delaying the acceptance of the reality of the loss situation. Progress toward resolution is not begun until the stage of disbelief is relinquished. Using drugs, not talking or crying about the loss, and using distraction all contribute to maladaptive reactions by maintaining the state of denial. The use of tranquilizers, sedatives, and other drugs does not help the recipient but, rather, benefits the giver. Excessive use of these medications prolongs the denial stage by making the feelings and emotions foggy and dreamlike.[101] The energy needed to begin the grief work is dissipated by the effect of the medications. Avoiding the reality of the situation becomes easier when mind-altering drugs make the tragedy even more unbelievable.

Not talking about the loss is a powerful way of denying that the child ever existed.[146,156] The inability of professionals to acknowledge that the loss has occurred and that the family is in pain maintains denial and repression.[31] Not discussing the loss prevents parents from learning the facts and facing their reality. Because a fantasy will be created to substitute for the unknown, the fantasy of what happened and why will be worse than the reality. By receiving truthful, honest communication, parents are not left to spend energy dealing with frightening fantasies.

Professional avoidance and unwillingness to talk with parents after a loss communicate other powerful messages that impede grief work. If the loss is not important enough to discuss, then perhaps it is not important at all. Not talking about the loss serves to reduce it and communicates to the parents, "I don't care; therefore, neither should you." Avoidance of the topic or a hurried, businesslike, or social communication that skirts the issue tells the parent that grief work is dangerous, that grief emotions are dangerous, and that others are afraid of grief and those experiencing it. In essence, not discussing the loss gives a clear nonverbal message to not grieve.

An inability to cry in response to a significant loss is not helpful and impedes grief work. The prohibition against crying may have been learned early in life or may be the result of unresolved grief work. Parents may feel the need to be strong for each other, their family, or the staff and thus do not cry. Sometimes role reversal occurs, and the grieving person feels the need to support others rather than be the recipient of support. Often the significance of parental loss is neither recognized nor acknowledged by the professional for fear that he or she will cry. Rather than talking about the loss as a technique to facilitate tears, no one says anything so that no one will cry, and no one's grief progresses through the grief stages.

Distraction is another way of denying the loss or its significance. Professionals, a spouse, or other family members try to distract parents from the feelings and emotions of acute grief by engaging in light, social conversation or by keeping them busy with work or recreation. Dealing only with the physical care and not the need for psychologic care after birth is a form of distraction used by care providers.[81] Parents are preoccupied with their shattered expectations of the past and the stark reality of the present, and they are not interested in distractions.

After an unfavorable perinatal outcome, the couple is often confused about their status: "Am I a mother or father . . . or not?" This experience has been called the "ambivalent transition into motherhood."[120] Failure to acknowledge the newly acquired role of mother or father (even if the fetus or newborn dies) discounts the parent's psychologic investment in the pregnancy, fetus, and newborn. Quickly removing the infant from the maternity or nursery areas or removing all the baby items from the home negates the infant's existence.[108] This is not helpful for grief resolution and prevents parents from making choices and decisions and thus maintaining control over the reality of the situation.

Isolation of the grieving family prevents the development of dependent relationships with others who might potentially provide support and comfort. Without others, parents cannot share their grief and may thus increase their feelings of guilt, anger, blame, and lack of self-worth at their failed

pregnancy. Those directly experiencing a perinatal loss may be isolated from the rest of society, including their families, who do not view the loss of a pregnancy or neonate as significant.[21,108,112,156] Empathy with the parents' definition of the loss is important and necessary for society to be supportive. The goal of recent research, professional literature, and education has been to sensitize the care provider to the effect of perinatal loss. Only recently have books and Internet sites specifically about perinatal loss become available to inform and assist parents.

To decrease contact with the grieving mother, the staff may neglect her or perform cursory physical care, or there may be overconcern for providing physical care.[128] Assigning a room at the end of the hall, not going into the room, delaying answering requests, and placing the mother on another floor are ways of avoiding families. Use of private rooms and room assignments off the maternity floor may be helpful but may allow staff to remove themselves from the unpleasant and uncomfortable situation. Early discharge to a supportive environment may be helpful but, without plans for follow-up, may merely be a way to remove the constant, painful reminder.

Keeping the childbearing couple together throughout the perinatal events facilitates a shared experience of the reality of the situation. Separation of the mother and father or of the couple from friends, family, and other children is not helpful. Exclusion of family members from the experience also prevents them from providing support for the mother and the couple. Relaxed visiting policies and as much contact as possible between the hospitalized mother and the father (and other family members) are important.[38,146]

Prohibiting contact between the parents and the infant allows fearful fantasies of the truth that are always more frightening than the reality of the situation. Delayed contact prolongs the state of disbelief and denial.[44] Restrictive visiting policies in the nursery, institutionalizing an infant without looking at all alternatives, or any other policy that separates parents from their infant does not facilitate grief. Especially in the case of an anomalied, stillborn, or dead infant, the message of delayed contact, or none at all, is that the infant is too horrible and unacceptable to be seen or touched. Because parental egos are so symbiotically attached to their offspring, an unacceptable child is equated with an unacceptable and unworthy self. The fantasy that the damaged or dead child is representative of the damaged and defective self is borne out in the behavior and separation policies of the care providers.

In an attempt to offer the grieving family comfort, friends, relatives, and even professionals often make comments that are *nonsupportive* and *nonhelpful*:[108,146]

- "Well, you're young. You can have more babies."
- "Just have another baby right away."
- "Well, at least you have others at home."
- "It's better to lose her now when she's a baby than when she's 4 years old."
- "He never would have been totally normal anyway."
- "He was born dead. You didn't get a chance to know or get attached to him anyway."
- "It's God's will."

Clichés and platitudes such as these do not help because of the message they give about the parents and the infant.[164] These comments at best reduce and at worst negate the effect of prenatal attachment to the fetus. The importance of psychologic investment and attachment by the parents to this fetus or newborn is said to be basically unimportant and essentially nonexistent.[108] Because infants are viewed as an extension of the parent's self, "by a not very subtle process of identification, the parents see a part of themselves in the baby, and nobody likes to be told that part of them is better off dead."[164] Also, comforting parents whose infant has died with the information that the child was not perfect and never would have been normal and healthy reinforces their belief that they are as defective and unsatisfactory as their dead child.[108]

Such comments also convey a message about the importance of an individual life. Essentially, they say that one fetus or newborn is fairly interchangeable with another. They negate the importance of and indeed the existence of the infant for the parents, siblings, family, and society. The life of the individual is devalued because "another baby" easily replaces him or her. Comparing one infant's illness or anomaly with another's is not helpful for parents whose own infant's anomaly is certainly more important than any other infant's problem.

The power of words to help during grief is outweighed only by their power to not help. Because parents are increasingly open during a perinatal crisis, they are sensitive not only to what is said and how it is said but also to the nonverbal

message. Giving premature or false reassurance may be more for the relief of the professionals than for the parents.[32] Comments such as "It's okay" and "Everything will be all right" must be genuine and timed appropriately for the parent. Telling parents that they have a child with Down syndrome and then saying "But everything will be all right" is hardly helpful. Giving reassurance that subsequent pregnancies and infants will be all right or unaffected is not helpful before the parents are ready to think about and project into the future. It is important to remember at these times that in the future, these parents may not remember specifically what you said, but they will remember how you made them feel.

The basic terminology accompanying perinatal grief situations may be upsetting to parents. Instead of *dead,* professionals often substitute less frightening and less final words. The use of *loss* when *death* is appropriate may be misinterpreted (especially by children). The terms *lose, loss,* and *lost* connote misplacing, so comments such as "I'm sorry you lost your baby" may be responded to by "I didn't lose (misplace) my baby. My child died." Medical professionals skirt the use of the words *dead, died,* and *die.* Care providers are taught as students to use the word *expired* when referring to a patient who has died. Meant to soften the effect of *dead,* the word *expired* may have its own effect, as a mother whose infant son died wrote in a poem: "The baby expired they said, as if you were a credit card."[180]

Other situations that do not facilitate grief work include dealing with multiple losses or stresses and ambivalence or mental illness.[104,203] The reaction to the loss of a significant relationship is intensified in the context of multiple losses, stresses, and problems.[146,199,203] Because perinatal losses represent not only a loss of the wished-for perfect child but also a threat to the parental self, self-concept, and self-worth, they represent situations of multiple loss.[188,189]

Helpful Interventions

Professionals have an opportunity to make a significant difference in the outcome after the crisis of perinatal loss for the individual, the couple, and the family. A care provider who is knowledgeable about the grief process and comfortable in sharing another individual's grief is equipped to assist the family and its members toward a long-term healthy adjustment rather than a dysfunctional and pathologic adjustment. Interventions that are helpful for family members also assist staff members in their own grief work.

Factors that influence an individual's personal experience of grief (and ultimately, appropriate interventions) are outlined in Box 30.4. Care for the grieving is individualized through assessing these factors, planning, and continually evaluating the individual.[61,62,146,155,159] Eliciting such personal information may not be as difficult as it first seems. Those in crisis often spontaneously share crucial data with little prompting. The importance of active listening to questions and comments or a more formalized therapeutic interview process may provide the needed encouragement and permission to begin communication.

A history of previous losses and their type and timing in the life cycle are important data for the care provider dealing with the current loss. Past experiences with a crisis or loss influence an individual's behavioral and coping style with current problems.[190] Experiencing a previous perinatal loss affects a subsequent pregnancy.[12,45,158] A recent nationwide cohort study in Finland found that parents with very or extremely premature, singleton infants (23 weeks to 27 completed weeks of gestation) actually have fewer subsequent children.[4] These pregnancies are characterized by guarded emotions, elevated levels of anxiety and depression, marking the progress of the pregnancy, and seeking out or avoiding various behaviors.[45,88,190] In a subsequent pregnancy, greater grief intensity as measured by the Perinatal Grief Intensity Scale (PGIS) is associated with symptoms of depression, higher pregnancy-related anxiety, posttraumatic stress and a poorer quality of the relationship with the intimate partner.[89] The PGIS is valid and reliable in predicting women who may have future intense grief associated with perinatal loss[89,90] and in predicting women in need of follow-up for severe anxiety and depression after perinatal loss.[91] A previous perinatal loss may compound the individual's reaction to a current loss. Dealing with problems alone, receiving help and support from others, and withdrawing altogether are possible ways of coping with the loss. Pregnancies after stillbirth or neonatal death require special emotional support from caregivers. A national United Kingdom survey of women with subsequent pregnancies found four themes relevant for caregivers to improve the quality of services: (1) sensitive

BOX 30.4 FACTORS TO EVALUATE IN INDIVIDUALIZING GRIEF INTERVENTIONS

1. Previous losses
   a. Type
      Separation
      Divorce
      Death
      Spontaneous abortion (miscarriage)
      Elective or selective abortion
      Period of infertility
      Relinquishment of child
      Perinatal loss
   b. Timing in the life cycle
      Distant
      Recent
   c. Coping styles[49] (of each individual and the family as a unit)
   d. Grief work
      Resolved
      Unresolved
2. Prenatal attachment
   a. Degree of psychologic investment in relationship with fetus or newborn
   b. Decision making about pregnancy and infant
      Planned or unplanned
      Wanted or unwanted
   c. Meaning of pregnancy and infant to individual and family
   d. Parental expectation about childbearing
3. Nature of the current loss
   a. Timing
      Sudden and expected
      Anticipatory grief
   b. Definition and meaning of the event (death, anomaly) to individual members of the family
   c. Multiple losses
      Self
      Perfect child
   d. Nature and severity
      Of loss
      Of defect
4. Cultural influences (also see Chapter 29)
   a. On experience and the expression of grief
   b. Societal expectations dictate acceptable and unacceptable behaviors of mourning
5. Strengths (individual and family)
   a. Support system (family, friends, religious, community, or social agencies) mobilized when necessary[37]
   b. Stable relationships: couple supportive of each other
   c. Financial stability
   d. Coping abilities: can evaluate, plan for, and adjust to novel situations
   e. Good health
   f. Receptive and intelligent
   g. Realistic expectations about childbearing and childrearing

communication and conduct from health care providers, (2) appropriate organization and delivery of services, (3) heightened monitoring and surveillance, and (4) perception of standard versus special care.[134]

The degree of attachment and the meaning of the pregnancy and impending parenthood to the family define expectations and influence reactions if an optimal outcome does not occur. The experience of grief depends on whether the loss situation was sudden and unexpected or if there was forewarning about a problem or complication. The definition and meaning of the crisis (e.g., the nature and severity of an anomaly, the finality of death, or the chronic sorrow of an infant with an anomaly) reflect the individual's and family's value system and previous crisis experience. The process of grief is affected by the event itself, the previous and current coping mechanisms, and the family's definition of the event. Consideration of all of these factors is crucial in instituting appropriate intervention.

Cultural practices among families and professionals often differ (see Chapter 29).[157] For example, in some cultures, it may not be acceptable to see or hold the baby (as in some Native American cultures). A literature review of the experiences of African American parents after the death of their child found four emergent themes: (1) emotional response to the death, (2) factors that added to the burden of death, (3) coping strategies, and (4) the health consequences of grief.[22] In the Muslim culture, the family is the primary system of support, and it is rare to see a Muslim family emote publicly. A phenomenological study of Muslim women experiencing perinatal loss found them to have experienced a lack of communication and privacy in the hospital during their initial grieving; feelings of confusion, emptiness, anxiety, anger, and guilt;

and agreement that husbands and families were the decision makers.[178] It is critical for health care practitioners to recognize cultural and religious differences to minimize misinterpretations and conflicts with families. With increasing immigration, practitioners must be able to respond with a more ethnic and culturally sensitive approach.[27,38,62,117,137,171] It is essential to be creative and flexible, thus respecting families' cultural and religious belief systems.[7,27,197] Studies show that cultural differences influence (1) parental emotional response to and perception of their infant's illness and disability, (2) parental use of services, (3) parental interactions with health care providers, (4) the ceremonies and rituals surrounding death, and (5) whether perinatal loss is culturally taboo or readily acknowledged.[24,27,62,117,124]

A review of published studies over the past 30 years of perinatal grief and loss in Latino parents has been published.[193] Latina women have a 1.5 times higher risk of experiencing perinatal loss due to (1) higher teen birth rates, (2) births to unmarried mothers, and (3) receiving no prenatal care or receiving prenatal care late in the pregnancy.[193] Grief responses among Latino cultures vary by country of origin, religious beliefs/practices, and acculturation (i.e., newer immigrants grieve in traditional ways, whereas subsequent generations incorporate the customs of the predominant culture).[193] Emotional expressions of grief, such as crying, are seen as healthy in Latino cultures. Because members of Latino cultures receive the majority of their emotional support from their families, numerous family members may be in attendance. Instead of the Anglo concept of "letting go" after a loss, Latina women believe in the concept of maintaining connections with the dead and are comforted by pictures, seeing/holding their dead infants, naming, and baptizing.

The national association SHARE: Pregnancy & Infant Loss Support, Inc. has revised the "Rights of Parents When a Baby Dies" and "Rights of the Infant" (Box 30.5). These documents serve as guidelines for the creation of protocols, checklists, and bereavement programs; affirmation and empowering tools for bereaved parents; and communication points for parents and care providers initiating the grief process.[148]

ENVIRONMENT

The first step in facilitating grief work is to create an ethical environment that is safe, supportive, permissive, and conducive to the expression of feelings.[31,41,146,156,194] This type of environment does not depend on physical surroundings but, rather, is created and maintained by a warm, receptive, accepting, and caring staff. Such an environment centers its concern more on the people giving and receiving care than on the tasks of care.[108] This type of environment is nonjudgmental and is characterized by an attitude of openness and freedom.[35,164] People feel safe enough to ventilate a full range of feelings—sadness, anger, despair, and even humor—without the fear of condemnation or rejection. Staff members become role models of open communication, facing grief, and feeling comfortable in an uncomfortable situation. The safety of such an environment generates feelings of acceptance and understanding so that grieving and healing may proceed.

Professional presence and support are essential to families in crisis because of the increased dependency needs that accompany grief and loss. Yet certain aspects of a conducive environment, such as privacy, quiet, and comfort, may be difficult to obtain in a noisy and busy perinatal setting. The recommendation to never leave the family alone must be balanced with their need for privacy and personal time alone with their infant (stillborn, ill, or dying). Simply saying "I will stay with you unless you ask me to leave so that you can have some private time alone with your child" or "Would you like me to leave for a while so that you can be alone with your baby?" offers both support and privacy. Many parents later regret not having time alone and not thinking to ask for that alone time.

A quiet place away from the hustle and bustle of the routine may facilitate both attachment and detachment. The mother of a stillborn child who is quickly shown her infant in the delivery room as her episiotomy is being repaired is not in an optimal physical (or psychologic) environment. Attaching to and saying goodbye to her infant are better accomplished in a quieter and more private setting with significant others present.[119,145] Active participation of parents at the death of their newborn may not optimally occur in a busy intensive care unit. Rather, adaptation of hospice concepts to neonatal care provides a private, homelike room, with focus on palliative (comfort) care, rather than cure, to the dying newborn and the family (see Chapter 32).[41,159,177,194] Optimally, parents are able to hold and comfort their dying infant. A recent

BOX 30.5 RIGHTS OF PARENTS, INFANT, AND SIBLINGS WHEN AN INFANT DIES

Rights of Parents

1. To be given the opportunity to see, hold, and touch their baby at any time before or after death, within reason
2. To have photographs of their baby taken and made available to the parents or held in security until the parents want to see them
3. To be given as many mementos as possible (e.g., crib card, baby beads or bracelet, ultrasound and/ or other photos, lock of hair, baby clothing and blankets, footprints and handprints, and/or permanent molds and record of weight and length)
4. To name and bond with their child
5. To observe cultural and religious practices
6. To be cared for by an empathetic staff who will respect their feelings, thoughts, beliefs, and individual requests
7. To be with each other throughout hospitalization as much as possible
8. To be given time alone with their baby, allowing for individual needs
9. To be informed about the grieving process
10. To be given the option to donate their baby's organs for transplant or to donate their baby's body to science
11. To request an autopsy; in the case of a miscarriage, to request to have or not have an autopsy or pathology examination as determined by applicable law
12. To have information about their baby, including autopsy results, presented in terminology that is understandable by the parents and family
13. To plan a farewell ritual, burial, or cremation in compliance with local and state regulations and according to their personal beliefs, religion, or cultural tradition
14. To be provided information on support resources that assist in the healing process (e.g., support groups, counseling, reading material, and perinatal loss newsletter)

Rights of the Infant

1. To be recognized as a person who was born and died
2. To be named
3. To be seen, touched, and held by the family
4. To have the end of life acknowledged
5. To be cared for and put to rest with dignity

Rights of Siblings

1. To be acknowledged and treated as individuals who have feelings that need to be expressed
2. To be given the choice/opportunity to see and hold the sibling before and after the death with parental input and support
3. To be considered in the choices parents are given (e.g., they may have ideas about names, funerals, memorials for their sibling)
4. To be informed and educated about grief according to their ages and developmental stages and offered the opportunity/choice to participate in support groups or counseling sessions
5. To be recognized by the family and society that they will always love and miss their sibling

Modified from *SHARE Pregnancy and Infant Loss Support*. http://www.nationalshare.org/about-loss/rights-parents. Accessed September 18, 2018.

phenomenological study of Scandinavian NICU nurses found a strong belief in offering skin-to-skin care for dying preterm infants and their parents as a way to provide mutual proximity and comfort.[80] When the family is too emotionally drained, they may elect to "say goodbye" and leave the hospital before life support is removed; the nurse then disconnects, holds, and rocks the baby so that the infant does not die alone.[146] In some situations (e.g., chromosomal anomalies), parents and professionals may opt to provide end-of-life care, ideally with hospice care at home.[135]

Supportive, Trusting Relationships. A relationship with a caring individual who offers consistency and support is the foundation of a therapeutic environment.[194] During periods of crisis, when there is a temporary increase in dependency needs and feelings of loneliness, it is an adaptive behavior to seek emotional support from family, friends, and professionals.[31,125,146] Even the crisis of normal childbearing prompts many cultures to provide a doula[152] to teach the new mother and give her emotional support. For a family in mourning, the relationships established with helpful professionals are more important than the physical care received.

Support, "sharing one's ego strength with another in a time of need,"[79] is particularly helpful in perinatal loss because of the threat to self-concept and self-esteem suffered by parents. Support may be as simple as remaining with the parents. "Being there" indicates not only a physical presence but also an emotional availability and willingness to share their

experience of loss. Professionals, family, and friends are often hampered by not knowing what to say. Usually, words are initially unnecessary or do not adequately describe the moment, and silent presence may better convey the message. Often it is not what is said but the mere presence of loving others that conveys empathy and support to parents and colleagues. Yet presence is not enough; meaningful interaction between parents and professionals is also necessary for a trusting relationship to develop.

The initial meeting with the professionals, including verbal and nonverbal cues, leaves a lasting impression on the family. Sensitivity and kindness of professionals are highly valued by grieving parents.[2] Addressing family members by name personalizes the encounter, and a brief touch or handshake represents an extension of self, a gesture of warmth, concern, and acceptance from professional to parents. An introduction that includes a brief explanation of the professional's role in relation to them and their infant helps orient them: "Good morning, Mr. and Mrs. Black. I'm Sue, your baby's primary nurse. That means that I will be caring for Jason while he is here and working with you." Orientation to the physical surroundings and technical equipment eases the transition to an unfamiliar and often intimidating hospital environment. Providing physical comfort, such as rocking chairs, privacy for interaction, and sleeping facilities for parents, demonstrates the philosophy of the parents' worth and importance to their infant.

Empathy, an emotional understanding of and identification with the plight of another, characterizes a helping relationship. In such a relationship, "How are you?" is asked with the emphasis on *you* and a genuine interest in the answer—unlike a social inquiry in which an automatic "Fine" is expected. Recognition of verbal and nonverbal cues of parental feelings (e.g., "You look tired" or "I hear that you are frustrated") communicates that these emotions are legitimate, understood, and accepted. A willingness to help, listen, console, and give encouragement and positive feedback establishes the professional as a sensitive, responsive person whom parents will trust.[194] Supporting any and all parental involvement, supporting damaged parental egos, and helping parents succeed in the tasks of attachment and detachment are goals of effective intervention.

A qualitative study examining maternal perceptions and experiences showed that mothers had feelings of both empowerment and powerlessness with professional care after the death of their newborns.[119] Feelings of powerlessness occurred when (1) mothers felt disrespected as a person and a mother, (2) good communication between mother and professionals did not exist, and (3) the mother did not feel treated as an individual.[119] Mothers feel empowered (e.g., more confident, able to ask questions, understood, and supported) when they felt that professionals (1) were "near," both psychologically and emotionally; (2) supported their self-esteem and confidence; and (3) provided empathetic, comforting support.[10,72,119]

The nursing staff often determines the tone of in-hospital perinatal settings. Generally, residents, interns, and specialists remain for short periods, and the private physician or permanent medical staff members are not available on a minute-to-minute basis. The development of a safe, trusting environment depends on viewing parents as essential partners in the care of their baby and not as visitors or "disruptors" of the ward routine.[44] Pleasant and relaxed surroundings convey the message of hospitality and "You are welcome here."

Both professional and nonprofessional support systems are available in the crisis of perinatal loss. Yet relating to many people during a crisis is difficult for parents. Primary care (both medical and nursing) uses the same care provider for both the physiologic and psychologic care of the infant and the family. Thus, the family only has to relate to as few professionals as possible. This special caring reassures parents that a few special people love, know, and are invested in their infant. Primary care providers share with the parents the joys of even small gains and the sorrows and tears of complications or death. Professionals and parents benefit from primary care systems in the emotional and psychologic satisfaction of such involvement. Yet this involvement is not without the price of vulnerability to an individual's feelings of loss and grief. Peer support on an individual basis or in a group setting is essential in dealing with the stress of continual attachment and loss.[1,52,54,57] An Australian study of volunteer peer supporters found that most often the callers to the 24-hour telephone support service were bereaved mothers who needed "to talk to someone who understands" in the early weeks and months after perinatal loss.[23]

Normal grief reactions may be facilitated by nursing and medical professionals using other professionals (social workers, chaplains, or counselors)

BOX 30.6 CRITICAL FINDINGS
Indicators of Pathologic Grief [116]

1. Overactivity without a sense of loss
2. Acquisition of symptoms belonging to the last illness of the deceased
3. Psychosomatic conditions
4. Altered relationships to friends and relatives
5. Furious hostility against specific others
6. Formal manner resembling schizophrenia
7. Lasting loss of social interaction patterns
8. Assuming activities detrimental to social and economic existence
9. Agitated depression

when necessary.[15,41,126,146] Interdisciplinary collaboration and consultation helps the staff gain insight into parental and personal behaviors and appropriate intervention strategies.[16,174] The staff also may benefit from the expertise of a trained counselor in dealing with their own feelings of loss and grief.

PATHOLOGIC GRIEF

Maladaptive responses to perinatal loss are indications for referral for specialized care (Box 30.6).[200] Involvement of clergy and religious organizations is often comforting and supportive to the family.[132,145,193,197] Religious rituals (e.g., baptism, prayer service, or anointing) may be advocated by certain denominations and provide a measure of comfort and hope. Often parents in crisis do not think to request infant baptism or to call their priest, minister, or rabbi. Offering to call a clergy member of their choice or the hospital chaplain may be helpful. A national survey of pastoral care providers noted barriers to providing spiritual care: (1) inadequate numbers of pastoral care staff, (2) inability of health care providers to assess spiritual needs, and (3) being called "too late" to give all the care that could have been provided.[68] The use of spiritual activities and coping strategies has been shown to help parents cope with grief and to help mothers to maintain their mental health and experience personal growth after the death of a child.[83] Spiritual and religious coping strategies were most often used by black mothers and Catholic and Protestant parents.[84] Among Iranian families, three spiritual themes have been identified: (1) belief in supernatural power, (2) need for comfort of the soul, and (3) human dignity for the newborn.[162] Negative religious coping (i.e., feeling angry or abandoned by God) is related to poorer family relationships, poorer family cohesion, and the use of denial.[25]

Primary care providers who have shared intimately with the parents the experience of their child's life and death may be invited to attend the funeral or memorial service. For both care providers and parents, this may represent the final act of caring for the infant.[57]

Nonprofessional support systems such as the couple, family, friends, and parent groups are often forgotten as sources of potential help to grieving parents. On the one hand, in our society of isolated, mobile, nuclear families, it may be erroneous to assume that a support system exists. On the other hand, it may be unrecognized because it does not fall into a traditional definition, such as the neighbor or other friend who may be more supportive (and available) than the grandparents. Biologic kinship is not the only valid criterion for a support system; an emotional kinship is the most important factor.

Because professional availability and involvement with the parents is not lasting, the professional has a responsibility to identify, foster, and facilitate a nonprofessional (social) support system. Simply identifying supportive others and expecting them to automatically help in a perinatal loss situation may be unrealistic. Unless those who constitute the support system are as well informed and instructed as the parents about the situation, they will not be able to offer emotional comfort. For example, if the parents wish to talk about their loss but the members of the support system empathically want to spare them by not discussing it, no help will be given or received.

The quality and quantity of ties one has with a social network are associated with improved health status and life satisfaction.[56,197] For parents experiencing a perinatal loss, the quality and quantity of ties with their social network (i.e., extended family, friends, and colleagues) may be profoundly affected. In one study, most families suffered a permanent loss of relationships because others were not sure how to react, avoided talking about the baby, or made comments that diminished the intensity of the loss.[51]

Fathers especially receive little personal attention as friends and colleagues focus their attention on the mother's grief.[51,56] Because grandparents grieve for their grandchild and may feel guilt and

grief for their own child, they may be emotionally unavailable to support the grieving parents. To prevent social network disruption for grieving families, health care providers can (1) share information with families about reactions to expect and reasons for these reactions, (2) support families and enable them to rebuild their networks, and (3) emphasize and support the family's belief in their strengths and capacities.[51,56,146]

Open communication between the parents is essential in preserving and fostering a close relationship by the giving and receiving of mutual support. Sharing the experience presents the couple with the opportunity for personal growth and growth as a couple. Yet the individual experience of grief within the context of a couple is too often fertile ground for misunderstanding and resentment.[156] One study showed that disruption of a couple's sexual relationship occurred after the death of a child.[168] A national study examining parental relationships after live birth, miscarriage, or stillbirth found an increased risk for dissolution of marriage or cohabitation in couples experiencing loss compared with a live birth.[75]

Parental support groups offer their members an opportunity to discuss their feelings with others who have been through similar traumas.[156,190] Knowing how others who have experienced perinatal loss have felt and dealt with similar situations is emotionally comforting and stabilizing to parents experiencing their own loss. Parents provide each other with validation for their feelings and a sense that they are not alone in their pain. Each individual has different needs, different ways of adapting to crisis, and different ways of giving and receiving support. It is essential that professionals use techniques that are real and spontaneous and not adopt words or actions that are foreign to one's own self. Interventions must also be gauged to the parents' needs and pace.

In one study,[188] and as reflected in clinical experience, fathers stated that they received most of their support from their spouse. They reported that little attention is paid to fathers by hospital staff, causing more denial and difficulty expressing their grief. So that the father's grief is not ignored,[128] it is critical for hospital staff to address the father's feelings when addressing parental grief.[163] Suggestions to assist fathers in their grief include implementation of all-male support groups; validation of their feelings; and asking direct, open-ended questions. These may include "What are you feeling right now?" "Tell me how your day is going," and "Tell me about your coping strategies." Health care providers can help a father by reflecting his statements, using his name, and assisting him with expressing his feelings. Fathers should be included and acknowledged in all discussions with staff[189] so that they are not "forgotten mourners."[107] One study documented that family adjustment after the NICU experience improved over time for mothers but deteriorated for fathers, especially if the infant had ongoing health problems.[40] Assessing the family as a unit rather than using the mother as a representative of the entire family, being cognizant of and responsive to gender differences in coping, and being supportive of family strengths and resources are recommendations for clinicians.[49,56]

Information. Information aids in intellectually understanding the crisis, thus facilitating a sense of control over it. Actively seeking and using information enable confrontation and mastery of the crisis. Knowledge about a situation strengthens the ego because it enables "worry work" and psychologic preparation for expected events. Because "the void of the unknown is more frightening than the known; facts are more reassuring than awesome speculations,"[32] a major role of the professional is to provide and clarify facts and information relevant to the perinatal loss situation (Box 30.7).[31,126] In the search for meaning that always accompanies loss, medical facts may help alleviate some parental guilt about causing the tragedy. Repeating to the parents that nothing they did or did not do could have caused this problem is reassuring. Sketchy or no information only serves to contribute to parental denial of the reality or to their fantasies of causation.[164] Confronting the crisis and realizing its real element of danger and trouble starts the process of grief by giving permission for the expression of feelings of fear, sadness, and loss.

Because the family as a unit, composed of the individual members, must deal with perinatal loss, professionals should encourage and support open interfamily communications. Keeping secrets, especially between the parents, should be discouraged because this eventually undermines trust and promotes asynchronous grief work. When parents are given the same information and talk with each other about their loss and their feelings, more

BOX 30.7 PARENT/CAREGIVER TEACHING
GRIEF

1. Grief is a normal reaction and is expected in perinatal situations: pregnancy, abortion, stillbirth, premature birth, when the baby is sick or has an anomaly, death, relinquishment, when the birth process does not meet parental expectations, and when there is postpartal depression.
2. Grief is a staged process that occurs over time and is characterized by stages: shock and disbelief, anger, bargaining, depression and withdrawal, and eventually acceptance.
3. Grief is an individualized process and may be experienced differently by the mother and father.
4. To facilitate grief reactions, the neonatal intensive care unit will provide a safe environment for the expression of feelings; information about the infant and the infant's condition; and supportive, trusting relationships with health care providers.
5. Seeing, touching, and holding the baby are as important to the parents of a sick or dying infant or an infant with an anomaly as they are to the parents of a healthy infant.
6. When an infant dies or is dying, parents and infant(s) have the right to interact with each other, to create memories, to involve extended family and friends, and to engage in specific religious and cultural practices.
7. Parents and families are informed about the grief process, encouraged to support and care for each other, and encouraged to identify and rely on social support systems (e.g., extended family, friends, professional support services).[37]
8. Providing both verbal and written information to parents is essential.[2]

synchronous grief reactions develop.[108] Telling parents together with the infant present prevents misunderstanding, misinterpretations, and "shading" of information to one parent.[145] Informed parents are better able to share their experience with each other and to participate in joint decision making with the professional.[14,28,42,194] A prospective cohort study found that the quality of the mother's relationship with her partner, secure attachment, and social support affect the course of bereavement after perinatal loss.[165]

The questions of when to tell and how much to tell the parents often arise. Parents should be told as soon as possible about perinatal complications or problems.[31,108] Receiving this information at the earliest possible time helps parents establish trust in the care provider, appreciate the reality of the situation, begin the grief process, and mobilize both internal and external support. Information must be given in its entirety because attempts to "spare" parents by staging the truth serve only to undermine their trust in professional credibility. The couple's relationship also may suffer if one parent colludes with the professional in a conspiracy of silence. This is best illustrated by the following incident:

> *To spare a diabetic mother from the truth about her infant's congenitally absent limbs, the physician and the father decided to tell her about his missing legs but not the missing arm. On arriving to transport the baby, the nurse asked if the mother had been told. "Yes" was the response, so she took the infant to the mother's room before transport. As she uncovered the infant, the mother gasped and looked at the physician and the father and said, "You lied to me. You didn't tell me about his arm, too."*

When given the unedited truth, parents can face reality and begin the grief process without fear that there is something else that they are not being told about. The individual's stage of grief influences not when or what will be said but how the information will be given and received. During the initial stage of shock, information, if processed, is processed slowly.[108] Often, events take on a foggy, dreamlike quality so that sensory information remembered is not believed. Yet to give no information only perpetuates this frightening feeling. Communication to those in shock and denial must proceed simply, slowly, and with much repetition and reinforcement. Giving information once does not ensure that it will be retained or understood. Repetition by the professionals is necessary for gradual acceptance of the reality of the situation.[14,28] This may be a nuisance for the professional who has already given the information and wonders why the parents cannot remember it. Parents are so shocked they do not hear what is said, and information must be patiently repeated.[194] Although early contact with parents almost ensures they will be in a state of shock, the tone and content of the first meeting are not forgotten.[31,108] Initial information about the infant and his or her condition may have long-term effects on the parents' ability to attach or detach. In the past, parents were given a pessimistic outlook with the belief that "It will be easier for them. They won't get so involved." Negative descriptions and initial pessimism only increase the amount of grief and detachment while effectively blocking attachment behaviors. If the sick infant or one with an anomaly survives, the parents may have detached to the point of, at least emotionally, burying

him or her. Knowledge of better survival rates and the quality of survival enables a truthfully optimistic outcome for many sick neonates. Therefore, information must be given clearly (not medical jargon), with a minimal focus on possible complications and medical odds.[108,203]

Volunteering information to parents is essential, but encouraging their questions is equally as important. As the normal mechanism for adapting to crisis and gaining mastery over a situation, questions help the professional "start where the parents are" and begin communication with their concerns. Questions and comments unrelated to the discussion may indicate either failure to comprehend or failure to send the information clearly.[203]

Direct questions deserve direct answers because they indicate a readiness and desire for information. Indirect questions or comments by the parents may indicate concern about their own infant that cannot be directly expressed. "Baby Stevie (who died yesterday) had severe respiratory distress syndrome, didn't he?" The parents want to be reassured that their infant will not die, too.

During the crisis of perinatal loss, interpersonal communication is difficult. Therefore, as few professionals as possible should relay information to the parents. Primary care providers (nurse and physician) should coordinate and provide continuity in giving information to parents because individual care providers will supply information about the same topic in different ways.[44,146] The use of varied terms, inflections, and attitudes by a multitude of professionals becomes a monumental source of confusion and anxiety for parents. A trusted relationship[28,31,35] with a primary nurse and physician through whom all communication flows minimizes unnecessary anxiety and concern for parents. It is essential that the nurse (or primary nurse) be present and assists the physician in communication with the parents. Any anxiety-producing information (poor prognosis, complication, or impending death) may not be heard or understood initially by the parents. The nurse must know exactly what information was given to the parents and how this information was delivered. After the physician departs, the nurse must be able to offer clarification, explanation, and support to the distraught parents. Nothing is more distressing than finding a crying, upset mother who is unable to relate what the physician said, why she is upset, or even if she understood what was said.

No family or parent should have to wonder and worry about a dreaded or feared outcome without being given the proper information. If the primary care physician is unavailable to speak with the family, then someone from the health care team must assume this responsibility. No mother whose infant is ill, deformed, or dead should awaken from an anesthetized birth to find her physician absent and the nurses unable to answer "How's my baby?" A plan of action for telling individual parents must be decided and agreed on by all care providers.

Parents are interested in the daily (or hourly) progress of their infant, including both positive and negative developments. It is important for parents to know about a crisis or negative development in an infant's condition as soon as possible. They are then able to participate and care for their infant through the difficulty and to trust professional communication. Parents should have unlimited access to phone or personal contact with the staff in the perinatal care setting. Phone calls to the hospital from concerned parents should be possible any time of the day or night. The knowledge that information about their infant and access to a caring professional are available at any hour often is enough to comfort parents of a critically ill infant.

Lactation suppression for the mother of a dying newborn often has been a forgotten aspect of care.[136] Engorgement creates a feedback mechanism to the maternal brain that leads to the cessation of milk production; however, painful engorgement should be avoided. Using a breast pump to remove enough milk to relieve pressure and discomfort but not enough to empty the breasts will gradually result in a decrease in milk production. If the mother pumps until she is comfortable, gradually prolonging the intervals between pumping and pumping for shorter periods, lactation gradually is suppressed. The use of a well-fitting and supportive bra relieves the discomfort/pain of heavy breasts. A recent study comparing the use of breast binding to a supportive bra found that the breast-binding group had greater breast pain/tenderness, leakage, and use of other pain-relief measures; the study recommendation was to discontinue breast binding for the more comfortable and efficacious supportive bra.[179] Mothers who have pumped and stored breast milk may wish to donate it to a mother's milk bank. A mother also may wish to continue pumping to

be a human milk donor.[40] These options should be sensitively discussed with the mother of the dying infant.

ENCOURAGING EXPRESSION OF EMOTIONS

Because grief is an emotional reaction to loss, expression of these emotions is necessary for grief work to begin and proceed. Verbalizing thoughts and feelings provides an outlet for the intense emotions accompanying grief and signifies to others that emotional support is needed.[31] For some, the open expression of emotions may be difficult because of the influence from their culture, gender-specific roles, and social status. Yet the containment of intense feelings uses a great deal of emotional and physical energy that could be more productively used in moving on with the grief work. Those who are stoic and noncommunicative experience symptoms of grief for a longer period than those who freely express their feelings and emotions.[18]

Experiencing the loss of an infant initiates an "ambivalent transition" into motherhood in a short period.[120] These women often feel totally confused, with broken expectations and elusive grief: "Have I or have I not become a mother?" Supporting families provides them with an opportunity to talk about their infant, confirming the baby's life as important, although short. This process assists parents to attach and subsequently begin the grieving process.[198]

Talking about the loss helps parents validate and assimilate the experience. Timing and events are clarified, including forgotten details, by discussion with each other and with their care providers. Confronting the reality enables them to work through the shock and disbelief, verbalize their fears and disappointments, and begin to cry and grieve. Expression of feelings gradually permits a clarification of the meaning of the loss to the parents. Talking lightens the burden of loss because every time the experience is shared with another, half of the experience and the accompanying emotions are given away. Telling, retelling, reviewing, and reliving the experience are all necessary ways to understand and gain mastery over a frightening and most often unexpected situation.[31,191]

Verbal and nonverbal cues tell professionals where the parents are in their grief process. To elicit feelings, the professional may verbalize his or her own perceptions and observations:

- "Mrs. Green, you sound tense (upset, tired) today."
- "Mr. Brown, you look worried today."
- "I'm sorry that your baby died."

These statements indicate the listening ear and observing eye of one who cares. They set the stage for communication: "It's okay to talk with me about how you are feeling because I acknowledge your pain."

Because they feel scared, alone, and out of control, parents often deny their feelings under direct questioning. Thus, "Do you think you did or didn't do something to cause your baby's problem?" may be answered negatively, despite parents being consumed with guilt. Direct questioning places parents in an awkward and vulnerable position of revealing their most personal doubts and fears. Direct questions may be reworded with safer and more indirect statements:

- "Most parents feel overwhelmed and sad when their baby is sick."
- "Many parents wonder if the cause of their baby's death is something they did or didn't do."
- "It is helpful to many parents to talk about their doubts and fears. These feelings are common and normal in such a difficult situation."

The professional gives information to the parents about the feelings and emotions commonly felt in similar situations. Because there is safety in numbers, if "most" or "many" parents feel this way and it is expected, then it might be safe to share their feelings. Validating parents' reactions as appropriate reassures them that they are not crazy. With this type of invitation, the feelings may be free to come spilling forth, or the parents may need time to establish a relationship with this professional before they are ready to talk about such personal emotions.

Empathetic actions and comments may open communication pathways with parents.[31] A professional presence that is warm and caring may facilitate more communication than any words. Touching or holding grieving parents may help feelings be expressed. Nonverbal cues such as nodding, direct eye contact, uninterrupted attention, and the physical closeness of pulling up a chair and sitting down give positive feedback to verbal communication and indicate active listening by the professional.

Crying is the expression of feelings of sadness, sorrow, and intense longing that accompany the

pain of loss.[116,203] A healthy catharsis, crying should be expected and encouraged in any loss situation. Yet the cultural, gender-specific, and professional taboos against crying have defined it as an unacceptable and inappropriate response and one that should be suppressed. Because tears are healing and therapeutic, professionals must learn to be comfortable with the crying of others. "Don't cry" is often heard from those attempting to comfort grieving parents (or colleagues). This is an admonition against the behavior rather than an empathetic comment. "It's okay to cry" or "Go ahead and cry; let it out" gives permission and acceptance to the behavior and the need for it.

By expecting tears, providing a safe environment for their expression, and encouraging the behavior by words and actions, the professional may facilitate crying in both mothers and fathers. Too often, tears are blocked in a relationship in which one partner (usually the man) is expected to be stoic and in control, whereas the other's (usually the woman's) tears are defined as too upsetting or difficult. Because the ability to cry is a healthy response, the couple must be encouraged to use this outlet together.

In the past, crying in the presence of patients and their families was defined as "unprofessional." Yet the cool, controlled exterior defined as "professional" was seen by others as not caring and not feeling. When the professional cries with the parents, it is an acceptable expression of genuine emotion, a demonstration of empathy, and a role model of the appropriateness of tears given the situation. Parents do not define the tears of care providers as weak or unprofessional. Rather, they feel a special bond of love and care with professionals who have been free enough to share their grief.[9,31,146,156] Instead of relearning that crying is acceptable, many parents and care providers must learn this for the first time.

Talking and crying about the loss are easier to facilitate than the expression of anger.[81] Because of the social expectations of dependency of the patient role and real or imagined consequences of retaliation (against the infant or job status), perinatal care settings are not safe environments for the expression of anger. Parents (and colleagues) will be able to vent anger only in an environment free of punishment or retaliation for their behaviors. It is the responsibility of the professionals to create an environment that allows open expression of negative criticism and anger.

SEEING AND TOUCHING

Seeing and touching are as important to the parents of a sick, deformed, or dead infant as they are to the parents of a normal, healthy one. In the past, fear that seeing a deformed or dead infant would intensify grief and be overly upsetting resulted in a lack of contact between parents and their newborn. Despite the fact that many mothers wished to see their infants, the prevailing practice was to discourage and prevent it. Often no information, including sex or physical characteristics, was given to grieving parents, who were left to fantasize about their newborn's problems or cause of death. Current practice indicates that parental contact with the infant does not cause "unduly upsetting immediate reactions or appear to result in pathologic mourning."[101]

Researchers in the United Kingdom have evaluated mothers and fathers who have seen and held their infants after stillbirth. In several of the studies, researchers correlated posttraumatic stress symptoms in both mothers and fathers[183] and disorganized maternal–infant attachment[184] in subsequent pregnancies to seeing/holding the stillborn infant. Although remarking that seeing/holding the dead infant is culturally entrenched and highly valued by parents, these researchers warn that this practice is associated, in their studies, with psychologic sequelae and based only on clinical impression without empirical evidence of benefit.[14] In a more recent study, most parents chose to see and hold their stillborn infant.[196] Among mothers who chose to see and hold their babies, more intense grief was not equated with poorer mental health, whereas fathers ($n = 9$) reported poorer mental health. The research cited in Table 30.1 shows how this small sample of well-adjusted and low-grieving parents valued holding their infants, being present at the time of death with family/friends, and keeping mementoes and the memory of their child alive.[28] The sequelae of seeing/holding a stillborn and the sequelae of seeing/holding a live infant who has died may not be similar; clearly, more research is necessary.

The British researchers[14] who found psychologic sequelae of parental contact with their stillborn infant state that many parents experience great meaning and treasure the memory of time with their dead infant. They concede that some parents would choose to have contact with their dead infants, regardless of potentially harmful outcomes. They also state that the parental decision to see/

hold the dead infant may be heavily influenced by attending staff who may expose reluctant parents to their dead baby. Clearly, the decision to see and touch their infant is ultimately a parental one.[14,203] Making decisions for parents is not the professional's role; making decisions with parents is the professional's role. The role of the attending professional(s) is to encourage families, provide information for appropriate decision making, and address parental uncertainty and/or apprehension in seeing/holding their baby during the hours after stillbirth because their "opportunity for contact (with their infant) is fleeting and final."[106] Seeing and holding their stillborn baby is associated with better parental psychological health and may be beneficial for their future well-being.[105] Each parent must make the decision for him- or herself; neither may decide for the other. Altruistic others, such as professionals, the spouse, or other family members, must not usurp the right to individual decision making. Often, in an attempt to protect the mother, the father or the professional decides that she should not have contact with her infant. They either actually discourage it or do nothing to facilitate it. Mothers who have not seen their infants always know who prohibited it. The couple's relationship may suffer irreparable damage if one decides for the other, even if the motive is altruistic. The professional's role is to facilitate a healthy decision by each parent so that their individual needs to see or to not see the infant are met.

Parents may not realize that seeing and touching their infant is an option, or they may just be too overwhelmed or afraid to ask if it is possible. Instead of waiting for parents to ask, the professional care provider takes a more active role by offering the possibility to the parents: "Would you like to hold your baby?"

Time is often necessary to make the decision because parents are initially ambivalent about seeing and holding a deformed or dead infant. Most mothers and fathers want to see their child but fear what they might see and how they may feel. The care provider may alleviate the parents' ambivalence by acknowledging that being with the infant will be difficult but that the professional will remain with them unless asked to leave. The emotional support of the physical presence of an empathetic professional may allay the fear of becoming out of control. The professional can reassure the family by explaining what they will see before they hold their infant. Making such a crucial decision in the initial stages of loss is difficult. Giving parents information about the positive aspects of seeing and holding the infant in facilitating their grief process helps make their decision an informed one.[203]

Seeing the infant brings the dreaded impossibility of perinatal loss into stark reality.[203] Parents confirm with their own eyes that the infant is alive or dead or normal or abnormal. Contact enables claiming behaviors and identification of the infant as their own. While holding their infant, parents examine her and begin to recognize familiar family characteristics: "She has my long fingers and her father's red hair." Even small, severely deformed, or macerated infants can be recognized and claimed by the parents as part of their family. What is remembered are the normal, endearing characteristics that identify the child as "mine."

Parental contact confirms the infant's own reality and eliminates the prenatal fantasy of the expected child. For the parents of an infant with an anomaly, grief work about the fantasized perfect child may begin so that the actual child may become the object of love. Early and frequent contact between the parents and the infant encourages a realistic perspective of the infant's problems. A stillborn or aborted fetus may be physically normal rather than the deformed infant imagined by the parents. Seeing the infant allays doubts and fears about the infant's normal state and about the parents' ability to subsequently have a normal child.[164] Seeing and touching enable parents to grieve the infant's reality rather than a feared and dreaded, and thus more frightening, fantasy. It is easier to grieve a real infant than a mystical, dreamlike fantasy of the infant.[108]

Whether the ultimate decision is to see or not to see the infant, the professional must honor and respect that choice.[203] Cultural taboos against viewing dead bodies may preclude some parents from seeing and touching their infant. Yet many such cultures support their members by formalizing the grief process in sanctioned ritual and ceremony. For those parents who decide not to see and touch, the professional should reassure them of their infant's normal condition (e.g., "He had 10 fingers and toes."). The infant should be described in as much detail as necessary to give parents a mental picture. Gender, size, hair color, skin, weight, and distinguishing characteristics should be included. A simple, realistic description of any anomaly is also helpful because the fantasy of the defect is worse than its reality.

Adequate preparation for the first encounter with their infant includes a description of everything parents will see, hear, and feel.[203] Verbal preparation for viewing an infant with a congenital anomaly includes not only a simple description of the abnormality but also the infant's normal characteristics. Seeing a picture of the abnormality first may help parents prepare for seeing their infant. Remaining with the parents at the initial visit, the professional should describe the anomaly and point out normal findings. Focusing by parents on the normal familial characteristics helps in attaching to the less-than-perfect baby. Although parents of a dead, deformed infant view the abnormality, they often focus on the normal traits and remember the infant not as "monstrous" but as beautiful.

For those who have never seen a dead body, the mind may invent frightening images and sensations. Certainly, "dead" is associated with the temperature sensation of cold. However, a newborn who has been placed under a radiant warmer or in an incubator may feel warm rather than cold shortly after death, hence the statement by a mother, "You couldn't be dead. You feel so warm." The professional must touch the infant and prepare the parents for the tactile sensation of warm or cold: "The baby will feel warm to you because she (or he) has been under the radiant warmer."

To prepare parents for seeing their infant, the professional must observe the baby. Color, skin condition, and size must all be described and are not shocking with adequate preparation: maceration, "peeling of the skin"; peripheral shutdown, "the blue-white discoloration"; and the small size, "as long as the length of my hand." Any equipment that must remain on the body should be described and explained before viewing. Even an umbilical cord clamp may cause concern in a parent who has never seen one. The reason for not removing equipment also must be explained. Respectful care[10] of the infant's body after death shows respect for the person of the infant and for the grieving parents. Attention to details, such as wrapping the infant in a blanket rather than a surgical drape or towel, cleaning the infant, and holding the infant in a cuddling position, indicates care and concern.

Parents whose infant has died, has a congenital anomaly, or is ill proceed with attachment behaviors of seeing and touching in the same manner as parents of normal, healthy infants.[108] Touching is important, but the distinction must be made between touching and holding. Cradling one's infant is quite different from merely touching with a hand. Holding the infant, whether healthy, sick, or dead, for the first time is a momentous event. Touching the infant who has died may not be sufficient; parents must be given the opportunity to hold and cuddle the child before, during, and after death. Other parenting behaviors, such as bathing and dressing their infant, also should be offered to parents.[94,99]

Parents of a dead infant may need more than one chance to see and touch the infant. The first time they do so, they attach to the reality of their infant. Subsequent encounters allow a final chance to see and hold their child. Parents have described the initial encounter as saying "Hello" and the subsequent one as saying "Goodbye." Some parents may be able to accomplish closure with one visit, whereas others who might benefit from a final visit may not ask or think to ask. Offering another contact with their infant leaves the decision with the parents.

The emotional effect of seeing the infant requires support, time, and permission to cry. Attaching is a process that occurs over time. Providing parents sufficient time with their infant takes precedence over paperwork, ward routine, or taking the infant to the morgue. Parents have indicated a need to hold their infant for a longer time and not feel pushed by care providers.[94,120] Even infants who have been removed to the morgue may be returned if parents need more time and contact for detachment.[119]

When an infant dies, opportunities for memories are limited. Professionals have the responsibility of helping parents make memories so that they will have a tangible person to mourn. Encouraging parents to name their infant gives the infant a separate identity, which helps facilitate the grieving process. Tangible mementos may include photographs, handprints and footprints, a lock of hair, hand/foot castings,[115,146] measurements of the infant, identification bands, the blanket the infant was wrapped in, a blessing or baptismal certificate, and birth and death certificates. Parents find most beneficial the interventions that acknowledged the infant (e.g., photographs, holding the infant, and receiving personal mementos).* Even when parents say they do not want mementos, the mementos should be kept in hospital files and the parents made aware that they will be available to them in the future if

*References 3, 28, 94, 99, 113, 115, 119, 176.

they want them.[119] Taking pictures of the infant, obtaining other mementos, and telling the parents that such mementos will be available to them on request not only respects their immediate decision to not see or have information on the infant but also provides a mechanism for them to "know" their infant at a later date if they wish to do so.

Before an infant is transported to a newborn special care unit, photographs should be taken and given to the parents to promote bonding. If the infant remains hospitalized for a long time or requires surgery, pictures taken at weekly intervals or before and after surgery can help confirm the reality of the child's condition and progress and assist with bonding, as well as the grief process. Despite the outcome, parents will appreciate some lasting record of their child's life.

The staff members who provide emotional support for parents must also receive support from each other. Expecting staff members to immediately return to work is unrealistic. Such an emotional experience takes time and space for decompression, which is facilitated by the use of exercise, crying, and being alone for quiet time.[57] Interdisciplinary staff often feel inexperienced, anxious, and fearful and experience dread when communicating with families about sensitive end-of-life issues.[5,28,61] Many received inadequate education and support to deal with these families and their own personal pain.[10,41,42,82] Even when providers feel comfortable with end-of-life issues, they often perceive the care given to families as inconsistent and variable.[42] Just as simulation teaches teamwork in clinical psychomotor skills, simulation of "delivering bad news" enables all members of the health care team to enhance their communication skills with families.[10]

OPEN VISITING AND CAREGIVING POLICIES

Perinatal care settings with open visiting and caregiving policies foster a shared family experience and support from others. Regardless of the type of perinatal loss, no mother should experience it alone—a spouse, friend, family member, or identified supportive other should remain with her.[94,189] Members of the mother's support system will also need an outlet for expression of their grief.

Women suffering the grief of perinatal loss should be given a choice about their room assignment. Arbitrary removal from the obstetric unit may deny the mother's maternity: "Am I a mother or not?" It also may escalate her feelings of failure, guilt, and worthlessness as a woman and a mother. Because she did not produce a normal, healthy infant, she may feel punished and banished from the maternity area by isolation on another floor. Her care may be entrusted to those without expertise in the physiologic and psychologic care of the normal postpartum period, much less a postpartum complicated by loss. Placement at the end of the hall far from the nurses' station, with the door closed and no company from staff and family, only increases her feelings of loneliness and isolation. Yet being on a happy maternity floor with normal, healthy infants and their mothers may be an exceedingly difficult and constant reminder of her loss and even complicate her recovery.[101] Information about the advantages and disadvantages of staying or leaving the maternity ward should be given by the professional. The mother, knowing what will be helpful, can then make the decision.[203]

The alternative to maternal hospitalization is discharge as soon as medically possible so that the mother may join her infant when the infant has been transported to another hospital. Early discharge also facilitates an easier mobilization of supportive others in the familiar surroundings of home. Removal from the constant reminder of one's failure (i.e., other healthy infants) may let the grief work begin.[203] Early discharge is not therapeutic when the professional assumes there is a support system to provide care and no one is available. Without a plan for follow-up care and contact, early discharge merely relocates the problem.

Caregiving is as important for the parents of a sick, anomalied, or dead infant as it is for the parents of a normal infant. Open visiting and caregiving policies increase interaction between the parents and their infant by actively involving them in the reality of their child's illness, anomaly, or impending death. Even if the child lives only a short time, parental access to and the ability to take care of the infant complete the attachment process and enable them to begin the detachment of grief work. Even minimal caregiving (i.e., holding, bathing, dressing)[10] helps parents overcome their sense of helplessness and be comforted by the thought that "We did all that we could have done. We cared; we made a difference to our baby." Active parental involvement decreases poor outcomes such as aberrant parenting styles, attachment problems, and unresolved grief.[28,108]

The loneliness and isolation of death are decreased for both parents and infant when they are together at the time of death. Parents often are comforted and relieved that their fantasy of the agony of the death scene is not borne out in the quiet, peaceful reality of death.[108] Having experienced the beginning of life together, parents who are present at the ending of life can feel a sense of closure and completion. Parents who can share even a brief life with their baby and the moment of death can face death's finality knowing they did not abandon their infant but provided him or her love and care.[119] Parents who are not present at death may take care of the infant afterward by seeing and holding him or her.

Parents should be given the opportunity to make final plans for their deceased infant.[146] The planning will help them face the death and facilitate the grief process. For many parents, this is their first experience with death and making final arrangements, and they are not aware of the options. It is helpful to provide the family with detailed, specific verbal and written information about cremation, burial, funeral, or hospital disposal.[34,94,146]

A funeral may be chosen for religious reasons or as a declaration of the fetus or newborn as a person befitting burial rather than disposal. Burial leaves a specific place of remembrance and recognition that this infant lived. Care for the infant after death may include funeral arrangements, such as choosing the clothes or bathing and even dressing the infant. If parents choose not to have a funeral, they may wish to have a memorial service or do something special, such as plant a rose bush or tree, in memory of their infant. Regardless of their decision, the birth and death of their baby constitute a life event for the family, and one must recognize it.

AUTOPSY

For parents who experience a stillbirth, spontaneous abortion, or neonatal death, knowing why the infant was deformed or died eases their recovery from grief.[108] In the search for a cause, many parents blame themselves for doing too much or too little to favorably influence the outcome. Neonatal autopsies reveal important new information and the cause of perinatal loss in only 10% to 40% of the cases.[43,194] Knowing why the infant died or the converse, that not even the "experts" know why the infant died, may help assuage their personal feelings of guilt and failure.

Primary care providers (physician and nurse) must use the utmost tact and show respect for the family's feelings when approaching them for permission to conduct an autopsy. Too often the permission for autopsy is denied because of the way the subject is broached by professionals. Telling the family about their infant's death in one breath and asking for an autopsy with the next is not appropriate. Parents need time to deal with the reality of the death, including seeing and holding their infant and being with each other and supportive others before they are even ready to think about an autopsy. Consideration of the family's feelings and stage of grief greatly enhances communication with the professional.[85] Reasons for the autopsy, including a possible answer to the question of why their infant died or had an anomaly, are important to discuss in a relaxed and unhurried manner.[8] Parents may feel rushed to make a decision without clearly understanding the advantages and disadvantages and resist the emotional topic of a postmortem examination. Time for discussion with an empathetic professional, as well as between themselves, facilitates an informed parental decision; sometimes consultation with a religious leader is necessary.

The professional who receives permission for an autopsy is then obliged to discuss all findings with the parents.[8,101,194] This may entail more than one meeting with the parents because they should be informed of the findings as soon as they are available.[145] Therefore, the professional may meet with them within 24 hours of completing the autopsy to discuss gross and preliminary findings and again 2 to 8 weeks later to discuss microscopic results.[108,130] A major complaint of parents is the "long wait" (i.e., longer than 12 weeks) for autopsy results.[85] Autopsy data may indicate either a condition that has implications for subsequent pregnancies or one that has little chance of recurrence.[8] The need for genetic counseling for future pregnancies may be evident from autopsy results.[43] Discussing the results with the report in hand and offering parents a copy for future reference are also important.

ANTICIPATORY GUIDANCE

Encounters with parents after the death of their infant give professionals the opportunity for anticipatory guidance/information about what to expect from themselves and from others.[94,99] Reactions to perinatal loss differ markedly, so family, friends, and acquaintances may not act as parents might

expect. Some will be supportive and emotionally empathetic, especially if they have suffered a perinatal loss. Others will be uncomfortable and, not knowing what to say or do, may choose to avoid the couple and never mention the loss, even in future conversations. Those who are unaware of the loss may question the newly nonpregnant parents about the new infant. These inquiries are both awkward and painful.

Knowledge of the universal feelings and behaviors associated with grief gives comfort and relief to parents. Knowing what to expect from grief (i.e., how it progresses and how long it takes) is valuable to those who are or will be experiencing it.[72,99,108,146,203] Knowing the stages of grief and that the accompanying behaviors and emotions are normal decreases the feeling of "going crazy." Recovery from the loss takes time and cannot be hurried or ignored. The most difficult time is immediately after birth and the first few months after the loss (2–4 months). The emotions of grief begin to lessen toward the end of the first year.

Parents should be encouraged to support and care for each other in their time of loss. Professionals should advocate mutual support by a free expression of feelings and emotions between the parents. Although parents need each other during grief, they also need an identified support system with whom to talk and cry. Reaching outside of the nuclear family to friends, extended family, and professionals should be encouraged.[28,37,56,146] Professionals have a responsibility to ask to whom parents turn for help and support in a crisis. If there are no identified supportive others, parents must know whom to call for help in the initial bereavement period.

Anticipatory guidance is also essential at the discharge of an infant with an anomaly, a preterm, or a previously ill newborn. Knowing what to expect when going home with an infant with a defect or an infant who has been hospitalized for months makes the transition from hospital to society easier for parents. Evaluation of the grief process, the attachment level of the parents to a less-than-perfect infant, and the presence or potential for postpartum depression (see Chapter 29) is vital.

LONG-TERM FOLLOW-UP CARE

Assessing the health and functioning of parents over the first year after the death of their infant is essential because of the effect of their loss.[201] Follow-up care and contact with professionals assist grieving parents.* A study of bereaved parents highlighted their needs for follow-up: (1) appointments should be scheduled with the neonatologist soon after the baby's death and certainly within 2 months, even if autopsy results are unavailable; (2) appointments should be held in a setting away from the hospital; (3) families value the professionals' efforts to determine how they are coping; (4) families value full, frank, sensitively delivered information and reassurance that enable them to understand what happened and to assess their future risks; and (5) families do not want false reassurances, half truths, and broken promises.[130] Follow-up meetings function as a catharsis for parents, as well as an opportunity for assessment, counseling (psychologic and genetic), and possibly referral. Primary care providers (physicians, nurses, and social workers) from the perinatal care setting may provide follow-up. One study documented a significant decrease in the intensity of a mother's grief after stillbirth when she received one telephone call from the physician.[144] For the family, relating to providers with whom a relationship has been established may be easier than establishing a new relationship with a stranger.[28,35,115,146] However, being with those who are associated with the loss event may be uncomfortable for the parents at the height of their grief. For the professional, the ability to continue to be a source of help and comfort to families with whom they have established a relationship may help complete the family's grief reactions. Maintaining contact with the family may be painful as the professional relives the feelings of grief and loss associated with sharing their tragedy. Although painful, this reexperience of intense feelings gives both parents and professionals another opportunity to work toward grief resolution.

When and where to provide continuing care for families are crucial questions. Contact in the perinatal care setting both at the time of death and daily until discharge provides immediate care. However, when discharged, too often the family returns home alone to face weeks and months of unsupported and lonely grief. Without feedback about their normal reaction and society's expectations that they will shortly be "back to normal," they are abandoned to their emotions. They suffer in silence and often drift apart in their misery. With their support system withdrawn but still feeling overwhelmed with grief, parents describe the period between 2 and 4

*References 28, 56, 94, 145, 146, 201.

months after the loss as the most difficult time.[101] At 2 months after perinatal loss, parents show increased symptoms of anxiety and depression that are reduced by 8 months but still higher than in parents not experiencing perinatal loss.[186] Follow-up care from professionals is most meaningful and needed by parents during this period when they feel deserted by previously supportive others.[94] Parents experience a need for spiritual support weeks and months after the loss. Meeting with families sooner (within weeks of their loss) may alleviate the effect of decreasing support as the months go by. The professional who acknowledges the withdrawal of others but can be relied on to be available provides the parents with the emotional anchor of long-term care and support.

Breaking appointments or continually not being available may be resistance to follow-up contact with the professionals but also represents a reluctance to return to the perinatal care setting with its painful memories. A visit from the professional in the home provides a nonthreatening, familiar environment for follow-up care. The more comfortable home environment enables assessment of family interactions and facilitates communication at the "feeling" level.

Each family member and the family as a unit must be assessed for their place in the grief process as follows:

- In what stage of grief is each family member?
- Is anyone "stuck" in a stage of grief?
- Are behaviors appropriate for normal grief reactions, or do altered behaviors represent pathologic grief reactions?
- Do altered behaviors warrant referral for further treatment and evaluation?
- Do the caregiving and attachment behaviors of the parents reflect resolution of grief over the loss of the perfect child and adoption of the less-than-perfect child as the love object?

Just because everything was progressing normally at previous encounters does not mean that it should be assumed to still be so. As the flood of initial grief subsides, problems and questions that were not considered suddenly become of great concern. For the first time in months, the regressive behavior of siblings not only may be noticed but also may be extremely annoying to parents. The beginning of grief resolution may allow future projections, such as "When can I have another baby?" or the dread of the painful anniversary of the loss.

Referral to public health nurses or visiting nursing services in the community for follow-up care is appropriate. However, a written referral alone is not enough. Involving them in the hospital care and discharge planning is essential for a smooth transition to home care. Having the new professional meet the family in the hospital with the primary care providers facilitates trust transference from the familiar to the unfamiliar. Traditionally, home care providers have been involved in the care of normal mothers and infants in the community. Involvement in perinatal loss situations requires knowledge about the process of grief and willingness to share the grief of the parents. Because these may be new skills for many, continuing education programs that teach the theory and skills of effective intervention help the professional be more comfortable with a perinatal loss situation.[2,82]

Additional expertise may be warranted when the professional recognizes signs and symptoms of pathologic grief, complicated or absent grief, or concurrent multiple stresses or losses. Parents may not be ready for genetic counseling, infant stimulation programs, or financial programs until months later. Between 3 and 6 months after their loss, parents may be ready to reach outside of the nuclear and extended family for help and support for the first time.[156] Suggesting a local hospital support group or the local chapter of a national support organization may at first be met with resistance. Leaving the names and phone numbers of such organizations ensures that the parents have the information at their disposal when they are ready to use it. Until their own support system has withdrawn, parents may not be ready for a support group of other parents.[156]

Throughout this section, examples of what to say and how to say it have been used to illustrate helpful interventions for grieving families. It is essential to state that there are no "scripts." Parents do not say something and the professionals answer with a parroted response. Each encounter is a unique situation consisting of distinct parental and professional personalities. Each situation must be evaluated separately and individual interventions instituted.[94,146] It is recommended that the professional learn by observing an experienced colleague with grieving families and that the professional "practice" with role playing and situation solving before actually attempting to intervene with the parents.[10] The use of formalized education about grief, loss, and bereavement is also recommended for health care providers.*

*References 62, 70, 72, 82, 93, 126, 160.

Innovative bereavement programs have been developed to provide families and staff with support and follow-up care.* Such programs[62,82,94] provide education and assistance to the health care providers who care for the family at the time of their infant's death. There is follow-up care to the family for up to 1 year after the death of their infant.[94] Perinatal bereavement programs may include intergenerational services in which parents, grandparents, and siblings participate together in education and services.[161] Bereavement programs provide the needed support, education, and help to families, as well as to staff. Use of a couples-oriented program enables the following[156]:

- Participation in the group at 3 to 5 months after the loss when most other support systems have ceased
- Ability of partners to share with the group and each other gender-related differences in grief experiences
- Opportunity for men to share and hear about other men's feelings and coping skills
- Opportunity for couples to learn to tolerate their differences in grief processing and to process their grief together
- Enhancement and preservation of the couple's relationship

A study of maternal perceptions of the quality of services they received after a perinatal loss was studied using qualitative analysis. The findings of the study included one major theme: "dissatisfaction with the quality of care received" and six categories: effective communication, expecting responsiveness, expecting to respect the patient's dignity, expecting better care, tension of medical expenses, and insufficient facilities.[170] Having an evaluation tool to assess and continually change and improve the program is essential.[2,94,156]

CHILDREN AND GRIEF

Explaining and helping a surviving child to understand the loss of an infant is an enormous task for parents. Facilitating the child's normal feelings of sadness, worry, and anger after a loss may be difficult for parents who fear being flooded with their own emotions. Unresolved grief from the parents' own childhood may prevent the expression of grief by their children.

To maintain the myth of childhood (innocent happiness), children are often shielded from any knowledge about death, even when it is an inevitable event in their lives. Thus, children are prevented from full realization, validation, and expression of their feelings and emotions. They cannot formalize and express their grief over the loss of a significant person; are at increased risk for the development of complicated grief and emotional and behavioral problems, including psychiatric issues, as children and adults; and are unable to process their grief into reconciling a future life without their sibling.[98,121]

Children are called the "forgotten mourners."[191] Although adults are encouraged to cry, talk, and gradually understand and integrate their feelings of grief, no one helps the child deal with the same frightening feelings. No one discusses the loss with the child, because "He might cry" and because of the adult's inadequacy and lack of understanding of how to respond and what to say. No amount of secrecy or denial of the situation will hide the fact that the child is being excluded from an important family event.

Attempts to protect children from feelings of grief and mourning because of death or other important losses isolate the child. Age and developmentally appropriate explanations include the child in the family's experience, rather than separating and excluding him or her from what is happening. Shielding children from the knowledge of death denies them the reality of life and the opportunity for personal growth and mastery of the experience. Often in America, the subject of death, like that of sex, is taboo for children.

A child's grief and mourning in response to perinatal loss depend on his or her cognitive and developmental level, the extent of prenatal attachment and expectation about the infant, the degree of ambivalent feelings, and the response of the parents to the death. Because the child's understanding of death differs from that of adults, knowledge of the stages of growing awareness is essential for both parents and professionals working with children experiencing grief (Box 30.8).[121,191] Regardless of age or developmental stage, a universal fear of childhood is the fear of separation and abandonment. For a young child (younger than 5 years), the loss of the infant is experienced indirectly through parental grief. A young child reacts to the emotional

*References 62, 82, 94, 115, 156, 161.

BOX 30.8 CRITICAL FINDINGS
A Child's Developing Concept of Death

Age	Cognitive Understanding	How Experienced
Infant (to 12 months)	None	Indirectly through parental grief expressed in: Emotional withdrawal Inability to provide concern and continuity in caregiving behaviors Overconcern for fear of recurrent loss Changes in eating, elimination, and sleep patterns; unresponsive to parental holding and cuddling[121]
Toddler (1-3 years)	Little understanding of cause and effect Death may be confused with sleeping or being away	React to changes in behavior of grieving parents and reflect their feelings and anxiety Changes in sleep and behavior (shy, aggressive, acting out, attention-seeking, angry), regressive behaviors (enuresis, loss of skills), and complaints of headaches and stomachaches[121]
Preschooler (3-6 years)	View death as a temporary state and not an inevitable occurrence Believe that they are the center of the universe and can do anything, and that thinking is doing (thoughts have the power of actions)	Expect the dead to return—ask questions about "when?" Changes in sleep and behaviors (shy, aggressive, acting out, attention-seeking, angry), regressive behaviors (enuresis, loss of skills), and complaints of headaches and stomachaches[121]
School age (6-12 years)	Understand that death is inevitable and irreversible; 6- to 9-years-olds personify death as a separate person (skeleton; bogeyman) About 8 years old: "death phobia," a normal developmental stage characterized by preoccupation with thoughts of own death and that of loved one Reasons concretely, with ability to see cause-and-effect relationships	Realize death occurs in adults, such as parents, and even in children; realize death is permanent, not temporary state May show interest in biologic aspects of death and details of funeral Changes in sleep and behaviors (loneliness, isolation, acting-out, sad, unhappy, depressed, anxious and fearful, aggressive, attention-seeking), difficulties with school work as a result of inability to concentrate, headaches and stomachaches, regressive behaviors (enuresis)[121]
Adolescent (12 years)	Able to think abstractly about death like the adult; philosophic reasoning	Similar to that in adult

Modified from American Academy of Pediatrics, Committee on Psychosocial Aspects of Child and Family Health. The pediatrician and childhood bereavement. *Pediatrics.* 2000;105:445. Reaffirmed in *Pediatrics.* 2013;132(1):e281; Gardner SL, Merenstein GB. Helping families deal with perinatal loss. *Neonatal Netw.* 1986;5(2):17.

withdrawal of grieving parents and fears loss of them (and their love).

Although children at different developmental stages have their own conceptions of death, adults must provide them with the facts about the situation in language that they can understand. They may benefit from guidance by the nurse, social worker, or other health professional about beneficial approaches to facilitate the child's grief work.[151] The professional serves as a resource, role model, and support system to parents and other family members in caring for their surviving children. Printed and videotaped materials are also available to assist parents in helping their other children understand death (see "Resource Materials for Parents" at the end of this chapter). Age-appropriate storybooks concerning death can facilitate grief discussion and elicit questions and feelings from children.

Just as grieving adults need repetition, children need repeated explanations and discussions about the loss. Constantly in a state of developmental flux, the child attempts to view the loss in new ways as a result of increasing maturation. Asking questions (usually at inopportune times) and making comments about the infant are ways the child continues to process the experience, often long after the parents have completed it.

These questions and comments may seem endless and resurrect the parent's own grief. The child's inquiries must be encouraged and supported so that he or she knows that talking about the loss or death is acceptable. Exploring the child's feelings for fears of causation, guilt, or the wonder if "death is catching" enables them to be dealt with appropriately. Truthful discussion with the child dispels the worst fears and fantasies and replaces them with reality that is "not too horrible to discuss" with parents. If the cause of the infant's death is known, it should be explained to the child in simple, direct terms: "Baby Bobby couldn't breathe by himself because his lungs were sick. His sick lungs only happen to little babies."

In one study, bereaved children had more frequent health care contacts for symptoms (e.g., abdominal pain, enuresis, headaches, insomnia) with no organic cause in the year after their loss.[118] Subsequent illness may precipitate worry by the child that he or she, too, will die. Often, this fear is not verbalized but acted out by significant behavioral changes such as withdrawal, clinging, whining, or overactivity that is uncharacteristic for the child. Verbal reassurance that the child will not die and a reminder that "the baby died of a sickness that only little babies get; big boys and girls can't get it" are helpful.

The normal feelings that accompany grief should be acknowledged and explained to the child. "Mommy and Daddy feel sad that Baby Jean died. Sometimes we will cry because we feel sad. It's okay to cry when you feel sad." Permission for the expression of the child's feelings should also be given verbally: "You might feel sad, too. It's okay for you to cry when you're sad. Then we will talk about how you are feeling." Encouraging children to draw or write their feelings is another way of giving them permission to express their grief.

Using words such as "went away," "expired," "lost," or "went to sleep" is dangerous in describing death to children. Because young children are concrete and literal, they think they might die if they "go to sleep" or that anyone who leaves them is in danger of dying. Children also relate current experiences to past ones and interpret "lost" quite literally. In the mind of the child, if the parent only searched well enough, the misplaced (i.e., "lost") child would be found.

Including children at funeral or memorial services facilitates their grief and prevents exclusion from a significant family event.[96,121] Consideration of the family value system, age of the child, and religious customs must enter into the decision to include the child. Adequate preparation includes a discussion of everything the child will see, hear, and feel, including the normal adult emotions of crying and sadness. An adult other than the grieving parents should accompany the child to reiterate what is happening and to meet the child's physical and psychologic needs. Adult support is necessary so that the child can express and deal with his or her feelings.

Helping children with their grief is also therapeutic for parents. Assisting children to master the crisis of loss ultimately augments the parents' self-esteem and restores confidence in their parenting skills.[108] Parents can deal in a healthy way with their own grief when they can facilitate the grief of their other children. Qualitative studies revealed parental spiritual needs and support of siblings after a perinatal loss:[95,132]

- Recognition and acknowledgment of the child's grief, which included listening and answering questions honestly; interpreting and acknowledging the meaning of the child's behaviors; shielding from the insensitivity of others; and knowing when support of the child would be more effectively handled by someone outside the immediate household
- Inclusion of the child in family events, rituals, and practices such as visiting, holding, and touching the baby in the hospital; attending the funeral/memorial service; and visiting the gravesite
- Keeping the baby alive in the family's memory by encouraging questions and comments about the baby; expressing feelings about the loss, including viewing photos and personal items of the baby; and recognizing the deceased infant in birthday/holiday celebrations

PATHOLOGIC GRIEF

The absence of grief when it would be expected is not a healthy sign but, rather, a cause for concern.[101] The emotions of grief and their expression are healing. Early and full expression of grief is associated with an optimal outcome.[101] However, many people in grief-producing situations attempt to avoid the pain of grief and the expression of emotions, the

result of which prolongs mourning, delays a return to the previous lifestyle, prevents the creation of new attachments and relationships, and ultimately results in pathologic grief (see Box 30.6).[101,191]

Not grieving precludes opportunities for growth and change. No new coping styles will be attempted. No novel alternatives to problem solving and adapting to a crisis will be added to the repertoire of behavior for future use. In other words, those who choose not to do grief work say "no" to their own potential and remain frozen in development.[137] Under the stress of not resolving their grief, some may even regress in their development.

Reproductive loss is a blow to self-concept and self-esteem, as well as a loss of the infant. Blocking appropriate feelings of loss, grief, and anger results in a significant decrease in one's sense of self-esteem.[48] After the death of their neonates, 33% of mothers suffered severe and tragic outcomes (including psychoses, phobias, anxiety attacks, and deep depression; see Chapter 29).[108,203] Those who cannot effectively resolve their grief may suffer lifelong emotional damage;[125] however, some empirical research shows that those who suppress feelings of grief may recover with relatively few difficulties.[14]

Not working through grief associated with repetitive contact with perinatal loss also affects the staff. To cope with feelings, they may hide behind a "professional" demeanor characterized by decreased spontaneity and withdrawal. Such a provider defends against the repeated pain of loss by emotional dissociation from the situation. The real self does not respond; instead, the professional stays in the role of the omnipotent, unemotional physician or nurse. The result, self-alienation, eventually desensitizes the professional to the experience and ultimately prevents any empathy with the experience of others.[97] Emotions that cannot be acknowledged or expressed healthily are vented in ways that may be destructive to relationships in personal and professional life.

Unresolved grief does not disappear and is not dissipated. The emotions accompanying grief may never be expressed but are not forgotten by the unconscious mind. Containment of these emotions through repression or suppression takes psychic energy. A conscious, intentional decision to postpone or dismiss grief to meet others' needs or to meet immediate demands of the loss situation (e.g., funeral arrangements/care of a surviving multiple) is called *delayed grief.*[116,125,146] For a period of time (days, weeks, or longer), there is little or no grief response when such a reaction would be expected and appropriate. Delayed grief also may be the result of repression—the unconscious content seems to have a life and energy of its own that become the sources of later emotional conflict.

Grief that is inhibited and never resolved is called *abortive.*[125] Those who have aborted their grief work often live bereft of *joie de vivre,* with no interest, concern, or enthusiasm for life. *Complicated grief,* a failure to transition from acute grief to integrating grief and resuming a fulfilling life, occurs when there is no movement (6 months after the loss) beyond the feelings of acute grief.[138] Inability to function in daily life accompanied by intense longing and yearning for the deceased, failure to accept the reality of the death, overwhelming guilt, and detaching from family and friends characterize complicated grief and must be distinguished from major depression.[104,138] Complicated grief is more common after the loss of a child, including a perinatal loss, and more common among women with preexisting psychological difficulties and/or use of psychopharmacologic therapy.[60,104] One year after a perinatal loss, higher grief levels are associated with (1) being the mother (mothers had more grief than fathers), (2) no previous living children, and (3) a low-level of socioemotional support from the father of the baby's family.[182]Although only 10% to 20% of those experiencing grief and loss have complicated grief, referral for intervention from mental health professionals is required.[138] Studies of internet-based cognitive therapy for perinatal loss showed a significant reduction in grief, PTSD, and depression in the treated group, thus preventing the development of complicated grief.[102,103]

Grief that is not resolved remains buried in the psyche, waiting for an opportunity to "rear its ugly head." A current loss may remind the psyche of the unmourned grief from a previous loss or losses.[63] As the two (or more) losses become intertwined and are experienced as one and the same, repressed emotions of unresolved grief pour forth. Grieving more than one loss or a lifetime of losses is more difficult and emotionally draining than grieving one event at a time.[45] Cumulative grief work also may be occurring when a current loss of seemingly little importance overwhelms the person with intense emotions.[63,125] This flood of emotions seems disproportionate to the current

BOX 30.9 CRITICAL FINDINGS
Symptoms of Unresolved Grief

1. Vivid memory for the details of the perinatal loss event
2. Flashback to the event
3. Anniversary grief (date of birth or expected date of delivery)
4. Emotions of grief (sadness, anger, or crying) when talking about loss
5. Intense emotions with subsequent loss or crisis

loss and is only peripherally related to it. The unconscious, unresolved grief is finally uncovered when the individual is flooded with emotions. Thus, aspects of unresolved grief from the past[190] may influence the emotional components of any grief reaction.

Grief and loss events of the perinatal period have been equated only for a relatively short time (about 30 years).[143] Because loss during the perinatal period is a common experience, many childbearing and older women (and men) have never grieved over their experience of spontaneous abortion, stillbirth, or neonatal death, even 10 to 20 years after its occurrence. Parents (or grandparents) in a current perinatal loss situation also may be dealing with unresolved grief from a previous perinatal loss. Unresolved grief (whether from perinatal or other loss events of life) may become available for resolution in subsequent crisis events. A mother who delivers a normal healthy newborn, yet is depressed in the postpartum period, may not have postpartum depression. Instead, she may be grieving the unresolved loss of a spontaneous abortion, therapeutic abortion, or other perinatal loss. The normal grief reaction accompanying relinquishment may persist and often leads to chronic unresolved grief that may present itself during and after a subsequent pregnancy.[13] Her depressed mood could also be resulting from unresolved grief from the loss of a parent, spouse, or child. Depressed menopausal women may be experiencing the cumulative effects of a lifetime of unresolved grief (Box 30.9).

Recognizing unresolved grief has implications for facilitating grief work in a current loss, episodic care, and health maintenance. The energy to keep unresolved emotions restrained could better be used in personal growth and development, grieving, and maintaining and establishing relationships. The lifelong stress of unresolved grief contributes to both psychologic and physical illness, including increased death rates and an earlier death.[150]

Not grieving a perinatal loss affects the individual involved and the relationships with significant others, including present and future children. Resolution of maternal grief about the infant's prematurity, as well as the quality of maternal interaction, are necessary for secure infant attachment.[172] Asynchronous grief and the absence of grief in one or more family members weaken and strain family relationships.[19,56,108,138] The irritability and preoccupation of normal grief may overly disrupt the family. Differences may be magnified to the extent that major rifts and disruptions in the relationship occur, resulting in an increased incidence of strained marital relationships, separation, and divorce.[19,104,108, 138]

Exclusive dedication to the care of a malformed or ill infant to the detriment of other family relationships is symptomatic of a pathologic grief reaction.[108,175,200] The parent who neglects other children, the couple's relationship, and social outlets is so overwhelmed with guilt about having caused the baby's defect that nothing else in life matters. This guilty attachment and exclusive dedication are ways of avoiding grief work.[175] Other forms of pathologic reactions include parental rejection and intolerance of the deformed or ill infant.[108]

The parent who is emotionally withdrawn and unavailable to the family because of chronic grief and depression cannot attach to and care for present or subsequent children. Aberrant parenting styles (resulting in a vulnerable, battered, or failure-to-thrive child) may be the result of prolonged separation, unresolved grief, or grief that has progressed beyond the anticipatory phase, resulting in the emotional ties with the infant being severed.[108] These difficulties with caring and parenting may affect the deformed or ill child and all the children in the family. In turn, these children may grow up unable to parent subsequent generations because of the type of ineffectual parenting they received. Parents who grieve inappropriately may leave their children a legacy of psychosocial problems, such as difficulty with separation, independence, and control (e.g., school phobia and toilet training); failure to thrive; and sleep disturbances.

Planning for a new pregnancy and another baby should begin after the grief process for the lost infant

is complete (about 6 to 12 months) so that parents are emotionally ready to invest in a relationship with another fetus/newborn.[108] A national survey of U.S. obstetricians found that two-thirds of the respondents endorsed a waiting time of less than 6 months for subsequent pregnancy after stillbirth.[74] The researchers concluded that this was a "provocative" finding because short interpregnancy intervals are associated with increased fetal risks for poorer outcomes.[54] Because the decision to become pregnant is highly personal and individual, many women are pregnant within 6 to 12 months after a perinatal loss.[158] Some women see a subsequent pregnancy as a "cure" for their overwhelming feelings of emptiness and failure,[192] whereas others are averse to a subsequent pregnancy. Pregnancy after a perinatal loss is characterized by (1) increased pregnancy anxiety, a heightened fear, concern, and vigilance about the pregnancy and baby; (2) comparisons of current and previous pregnancies; (3) less attachment to the current versus the previous pregnancy; (4) a desire to see and phone the health care provider more often; (5) a desire for more prenatal testing; and (6) the subsequent pregnancy possibly being the precipitating event for PTSD in both mothers and fathers.[11,20,58,183,190] Having a subsequent child may promote parental resilience and represent positive parental adjustment after a perinatal loss.[100] Mothers appreciate being educated by their health care providers about the benefits and risks of subsequent pregnancies so that they can make an informed choice.[58] Benefits of postponing pregnancy include (1) enabling physiologic recovery from pregnancy before another is attempted; (2) enabling psychologic recovery, progression of grief work, and an optimal state to emotionally invest in a new pregnancy and newborn; (3) avoiding anniversary dates with the second pregnancy/child; and (4) improving the maternal-infant relationship—less anxiety, overprotectiveness, overindulgence, and hypervigilance.[5,190] The time necessary for physical and emotional recovery varies widely, and parents may benefit from interconceptual counseling after a perinatal loss.[105,161]

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RESOURCE MATERIALS FOR PARENTS

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Videos, DVDs, and Professional Modules

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National Organizations

Association for Death Education and Counseling: http://www.adec.org.
Bereaved Parents of the USA: http://www.bereavedparentsusa.org.
Center for Loss in Multiple Birth, Inc: http://www.climb-support.org.
Centering Corp. and Grief Digest: http://www.centering.org.
Hygeia Foundation, Inc.: https://www.drberman.org/hygeiafoundation.
Mothers in Support and Sympathy (MISS) Foundation: http://www.missfoundation.org.
Parents of Stillborn: https://www.facebook.com/StillbornStillLoved/
Perinatal Hospice and Palliative Care: http://www.perinatalhospice.org.
Pregnancy Loss and Infant Death Alliance: http://www.plida.org.
Resolve through Sharing: http://www.gundluth.org/resolve-through-sharing/
SHARE Pregnancy and Infant Loss Support, Inc.: http://www.nationalshare.org
The Compassionate Friends: http://www.compassionatefriends.org.

31 DISCHARGE PLANNING AND FOLLOW-UP OF THE NEONATAL INTENSIVE CARE UNIT INFANT

ANGEL CARTER AND BRIAN S. CARTER

Parents with infants in the neonatal intensive care unit (NICU) have immediate worries about whether their newborn infant will survive but soon thereafter start having concerns about how their child will do through infancy and into adulthood. As the infant's convalescence begins, so does discharge planning; this brings to the forefront questions about outcomes. **Unfortunately, it is almost impossible to know the outcome of any individual infant at the time of discharge from the NICU. Caregivers within the NICU must be knowledgeable of the latest outcomes literature to respond to these questions and to guide parents in the importance of follow-up care.**[159]

Of the many reasons that newborns require neonatal intensive care, the most common one is preterm birth. Numerous publications report the outcomes of very-low-birth-weight (VLBW; birth weight <1500 g) and extremely low-birth-weight (ELBW; birth weight <1000 g) infants.[8,29,105] Many studies have focused on the survival and outcome of even more immature infants with birth weights below 750 g, or on infants born at the limits of viability, 22 to 25 weeks of gestation, often referred to as extremely low gestational age newborns (ELGANs).[29,91] **Late-preterm infants have been a topic of renewed interest because they are at risk for a unique set of problems with adverse outcomes.**[5,60] **Infants with intrauterine growth restriction (IUGR) are also vulnerable to a wide range of complications requiring neonatal intensive care, especially if they are also preterm and experience extrauterine growth failure.**[63,93,123] Full-term infants may also require intensive care because of perinatal or neonatal conditions and are at risk for health and developmental sequelae.[75] Finally, a number of infants with congenital anomalies require surgery and/or neonatal intensive care.

PLANNING FOR DISCHARGE

An organized, well-implemented discharge plan is the beginning of successful follow-up of the NICU graduate. A family-centered multidisciplinary team approach uses the expertise of many disciplines, along with the family, to formulate and implement the discharge and follow-up plan. The team can comprise parents, grandparents, other caregivers, physicians, nurses, case managers, dietitians, therapists, developmental specialists, and social workers.

Integrating family-centered principles into the discharge process, as a continuation of family-centered care practiced throughout the NICU stay, facilitates better parental adaptation to the transition to home.[65] For many infants, the NICU stay has been lengthy and complex, and **families may experience varying degrees of anxiety and stress as they prepare for the infant to come home.** In some cases, a long, complicated medical course may have affected attachment and bonding. **A survey of preterm mothers found that symptoms of psychological distress (fatigue, depressive mood, anxiety, physical symptoms) persisted up to 1 year after the birth of their**

BLUE type highlights content that is particularly applicable to clinical settings.

premature baby.[66] Families may need extra attention paid to these issues before they can successfully attend to the discharge process. A thorough assessment of caregiver needs, environmental issues, and knowledge of their infant's care before discharge is an important part of the planning process. Implementation of a parent educational-behavioral intervention program during the NICU stay may be one mechanism to reduce stress, depression, and anxiety and effect more positive interactions of parents with their infant, and a reduced hospital stay and associated costs.[102]

Considerations Before Discharge

INSURANCE

Many parents may need assistance to enroll their infant in their existing insurance policy or to identify the procedures necessary to apply for medical assistance. This process can take many weeks and must be accomplished before discharge so the parents can select a pediatrician for follow-up care and arrange outpatient subspecialty care as needed. Outpatient physician visits, therapies, medical supplies, medications, and nutritional supplements are often reimbursed differently from inpatient services. Out-of-pocket costs can escalate quickly and add additional challenges for families. Social workers, case managers, and financial counselors are valuable resources to assist families in this process.

IDENTIFYING A FOLLOW-UP PEDIATRIC HEALTH CARE PROFESSIONAL

A pediatric health care professional to follow the infant after discharge, trained in the care of NICU graduates, should be identified before discharge. Ideally, this clinician has been identified early in the admission to facilitate regular communications regarding the infant's medical course. In a 1992 policy statement, the American Academy of Pediatrics (AAP) attempted to define the concept of a medical home for children. Multiple challenges with implementation led to an updated definition with additional designations specific to medical conditions.[9] As defined, a medical home is considered to be the ideal practice for the health care management of children, although challenges remain with resource allocation, role definitions, and implementation.[9,14]

Immediately before discharge, a written summary should be provided to the outpatient primary pediatric health care professional, with follow-up recommendations regarding nutrition and growth, developmental surveillance, and subspecialty referrals, along with verbal notification of the discharge date. Parents should be advised to keep this summary with the infant at all times because this written documentation of the NICU stay is invaluable if the infant needs to be seen on an emergency basis shortly after hospital discharge. Providing families with a "care notebook" containing specialized forms and organizing tools can be a valuable addition to the discharge process, particularly for those with anticipated complex follow-up needs. Information to compile care plans for children with special health care needs can be found on a number of websites, for example, the National Institute for Children's Health Quality Medical Home (www.nichq.org), the AAP Medical Home (www..aap.org/en-us/professional-resources/practice-transformation/medicalhome/Pages/home.aspx), and others.

CAREGIVER EDUCATION

In a family-centered environment, families have been partners in caring for their infant throughout the hospital stay. Discharge teaching then becomes a process of reinforcing and attending to final details. In some instances, however, this teaching may be limited by the inability of the family to be present because of transportation and family or job constraints. In these cases, readiness of the caregivers and home environment should be thoroughly evaluated (Box 31.1). Infants with complex equipment and care needs at the time of discharge may require skilled nursing support in the home to be candidates for discharge from the hospital.

HOME EQUIPMENT

Any necessary durable medical equipment or supplies, such as an apnea monitor, pulse oximeter, feeding pump, ventilator, suction equipment, or oxygen for home use, should be delivered to the hospital before discharge to give parents practice using the equipment. When a home apnea monitor is used, a clear plan outlining the reasons for initiating home monitoring and the indications for discontinuing it should be discussed with the family and the primary care provider before discharge. The company supplying the equipment should provide training in its use and an agreement for maintenance and service support while equipment is being used in the home. NICU nurses or respiratory therapists should verify the parents' understanding of the

BOX 31.1 CAREGIVER EDUCATION

- Every encounter with the parents is a teaching opportunity. Assess each individual family's readiness for discharge.
- Inform parents verbally and in writing about the tests included in the newborn genetic screening and how they will receive the results.
- Teach parents the special nutritional needs of preterm infants after discharge, including nutritional supplementation, lactation support and intervention to promote breastfeeding, and use of alternative feeding methods, if necessary.
- Teach parents the importance of maintaining their infant on home oxygen therapy (e.g., for growth and development, sleep, and feeding) at designated pulse oximetry targets until pulse oximetry studies (e.g., awake, feeding, asleep) document that the infant can tolerate weaning and discontinuing the supplemental oxygen.
- Teach parents to dress their infant appropriately to maintain adequate axillary temperature.
- Teach parents appropriate safety precautions:
  - Proper positioning (supine) for sleep: "Back to Sleep."
  - Proper use of car seats.
  - Importance of a smoke-free environment.
  - *NEVER shake the baby!* Dangers of shaking infants include blindness, brain damage, developmental delays, seizures, paralysis, and death.
  - Information, in writing, about all medications for their infant including name, action, dose, route, side effects, and schedule.
  - Provide parents an opportunity to participate in an infant CPR class.
- Teach parents the importance of follow-up care and appointments:
  - Timely follow-up for infants with ROP provided verbally and in writing.
  - Timely follow-up for hearing screen and referral for rescreening.
  - Need for monthly RSV immunizations throughout the RSV season.
- Give parents the newborn immunization record.
- Teach parents the importance of their own self-care, and assist in identifying resources for support.

CPR, Cardiopulmonary resuscitation; *ROP,* retinopathy of prematurity; *RSV,* respiratory syncytial virus.

purpose of the equipment and its operation and also ensure that home caregivers for the baby have been trained in cardiopulmonary resuscitation (CPR). The family should be provided a clear contact number to the clinician who will be managing the home equipment.

ROOMING-IN

Whether or not an infant is going home with equipment, giving family caregivers the opportunity to provide "independent" care of their infant with professional caregivers nearby for assistance has been shown to increase parental competence and provide confirmation of readiness for independent care at home.[35,115] A recent meta-analysis demonstrated improved outcomes from rooming in for infants with neonatal abstinence syndrome (NAS), including a decreased need for pharmacologic interventions and reduced length of stay.[98]

DISCHARGE CRITERIA

Clearly defined discharge criteria provide both the family and the staff a point of reference from which to judge the infant's progress. Discharge criteria should be reviewed in a multidisciplinary team meeting with the family. Setting goals that the infant, parents, and staff must accomplish before discharge helps keep everyone focused and prevents important components of the discharge process from being overlooked.

For preterm infants, the attainment of a minimum weight is no longer the criterion for discharge. Rather, the ability of a preterm or recovering neonate to maintain physiologic stability and the ability of the family to care for the infant's physiologic and developmental needs dictate the infant's readiness for discharge (Box 31.2). There are significant variations across NICUs for specific discharge criteria, with assessment of apnea and feeding behavior significantly influencing the duration of hospitalization in a healthy preterm infant. The AAP policy statement, "Hospital Discharge of the High-Risk Neonate," provides guidance that should minimize such variations.[9]

TRANSFER

Some infants are not discharged home from the regional or tertiary NICU but, instead, are transferred from a regional referral center to a community unit or facility for the duration of their remaining hospital stay. Transfer to a community hospital may be beneficial to families because they are often closer to the parents' home (especially if the NICU is part of a regional referral center). Possible locations for transfer, as well as the criteria for transfer and financial implications to the family, should be discussed with the parents early in the hospitalization if this is an expected possibility. Communication of a comprehensive discharge plan should

BOX 31.2 SELECTED CRITERIA FOR DISCHARGE OF THE PREMATURE INFANT OR NEONATE WITH SPECIAL NEEDS

Infant

- Demonstrates sustained weight gain of sufficient duration
- Shows adequate maintenance of normal body temperature, clothed in an open bed, at normal room temperature (20°C to 25°C)
- Establishes and maintains competent breastfeeding or bottle feeding without cardiopulmonary problems
- Nutrition assessment and dietary management have been provided as indicated
- Hematologic assessment and management have been provided as indicated
- Physiologically mature and stable cardiopulmonary function of sufficient duration has been documented
- Parents have been given a report of neurodevelopmental and neurobehavioral status
- Metabolic, hearing, and indicated funduscopic screenings have been completed
- Infant has been appropriately immunized, including respiratory syncytial virus prophylaxis and plan for subsequent injections
- Car seat evaluation has been completed
- A review of the hospital course has been completed, pending medical problems have been noted, and follow-up plans have been established
- A home-care plan, individualized to the patient's needs, has been provided by all disciplines

Parents, Family, and Home Environment

- Identify and assess at least two caregivers for home.
- Assess psychosocial and parenting strengths and risks.
- Consider the home environment and on-site visit as indicated.
- Review resource availability (including financial, utilities, and transportation).
- Determine caregiver availability, ability, and commitment to the following:
  - Provide basic infant care: diapering, bathing, dressing, cord and circumcision care.
  - Maintain infant's thermal state: able to take temperature and dress appropriately.
  - Feed infant (breast, bottle, or alternative method—nasogastric tube, gastrostomy, parenteral nutrition), and demonstrate formula preparation if required.
  - Manage home feeding tube, infusion pump, intestinal stoma care, and other devices as indicated.
  - Manage home monitoring, oxygen, and other equipment as indicated; address initial problem solving; demonstrate CPR and initial emergency interventions.
  - Provide a safe environment (car seat, heat, electricity, telephone, transportation, smoke-free, emergency resuscitation).
  - Recognize signs of illness, and identify when to call the primary care provider or emergency services.
  - Have a support system identified to assist in the infant's care.
  - Demonstrate medication administration, and recognize signs of medication adverse effects (e.g., toxicity); understand the importance of follow-up care, and know whom to call for questions or concerns.
  - Obtain influenza vaccine at beginning of influenza season.

CPR, Cardiopulmonary resuscitation.

Modified from American Academy of Pediatrics. Committee on Fetus and Newborn. Hospital discharge of the high-risk neonate. *Pediatrics.* 2008;122(5):1119. Reaffirmed in *Pediatrics.* 2012;129(4):e1103.

take place with the receiving hospital before transfer.[73,91] As the capacity for back-transporting convalescing neonates to community hospitals has increased in the United States over the past 20 years, persistent issues of communication, trust, and psychosocial support remain for parents.[54]

EARLY DISCHARGE

Preterm infants are often discharged between 35 and 37 weeks' chronologic age after demonstrating cardiorespiratory stability, thermal stability, and adequate feeding skills.[9] Parental concerns at the time of discharge may include their own ability to have adequate rest, their readiness to learn and assume self-care and newborn care, their readiness to parent, and availability of support systems. Concerns about the newborn may include transition from the intensive care nursery to the home care environment, ability to feed and hydrate adequately, and the early development and recognition of complications.[135]

Late-preterm infants ($34^{0/7}$ to $36^{6/7}$ weeks' gestational age) are often the size of full-term newborns, but are physiologically and metabolically immature.[66] Timing of discharge of preterm infants should be individualized based on physiologic maturity and feeding competency. Late-preterm infants usually do not meet the necessary competencies for discharge before 48 hours of age.[60] A follow-up visit for medical assessment of these infants is recommended for 24 to 48 hours after discharge.[60]

Screening

GENETIC SCREENING

Initial screening of sick or premature infants is performed as soon as possible after birth, before the administration of blood products. Although it is common for these infants to have some relatively abnormal results—especially for thyroid function or amino acid profiles while on parenteral nutrition—early screening is recommended to identify in a timely manner those infants who may have an inborn metabolic disorder, congenital endocrinopathies, or hemoglobinopathies so that early treatment can be initiated.[16,40,52] **Subsequent screenings should take place according to established guidelines, depending on state requirements.** Recommendations for continued screenings after discharge should be clearly outlined in the discharge summary.

HEARING

All infants should be screened for hearing loss using otoacoustic emissions or automated auditory brainstem response testing before discharge from the nursery.[112] This initial screening should be performed once the infant is medically stable, and **if there are any concerns that warrant a secondary screen, rescreening should occur before 1 month of age.** Infants who do not pass (are "referred" after secondary screening) should have a full-scale auditory diagnostic evaluation by 3 months of age. **Infants with confirmed hearing loss should receive intervention by 6 months of age from an infant hearing specialist.**[15,18] Those infants with an increased risk for hearing impairment should be assessed by a pediatric audiologist with a follow-up schedule outlined for the parents (Box 31.3). **The goal of early detection and intervention is to maximize language, cognition, literacy, and social development of the hearing-impaired infant.**[137]

VISION

Development of severe retinopathy of prematurity (ROP) may still be a concern at the time of NICU discharge for infants born prematurely. Infants born at less than 30 weeks of gestation or less than 1500 g birth weight, and selected infants with a birth weight between 1500 and 2000 g or gestational age greater than 30 weeks with an unstable clinical course, should have a retinal screening examination with pupillary dilation.[17] Published tables make recommendations for timing of the initial examination dependent on postmenstrual age and chronologic (postnatal) age.[17] Timing of follow-up examinations should be according to the ophthalmologist's recommendations based on retinal findings. **Arrangements for follow-up examinations should be made before discharge.** Ophthalmologic follow-up for infants with any stage of ROP (whether they required treatment or not) is recommended at 4 to 6 months after hospital discharge.[17] **Current research indicates that the risk to visual development in preterm infants does not end when the risk for ROP has passed. All infants born prematurely, whether or not they develop ROP, are at increased risk for amblyopia/strabismus and refractive errors.**[117]

CRITICAL CONGENITAL HEART DISEASE

With as many as 30% to 50% of critical congenital heart disease (CCHD) cases diagnosed after discharge, pulse oximetry screening before discharge was recognized in the United States

BOX 31.3 CONDITIONS ASSOCIATED WITH INCREASED RISK FOR HEARING LOSS

- Neonatal intensive care unit admission for more than 5 days or any of the following regardless of length of stay: extracorporeal membrane oxygenation, assisted ventilation, exposure to ototoxic medications (gentamicin and tobramycin) or loop diuretics (furosemide [Lasix]), hyperbilirubinemia requiring exchange transfusion
- Syndromes associated with hearing loss such as neurofibromatosis, osteopetrosis, and Usher syndrome
- Family history of hereditary childhood hearing loss
- Craniofacial abnormalities
- Congenital infections such as cytomegalovirus, toxoplasmosis, bacterial meningitis, syphilis, herpes, and rubella
- Physical findings (white forelock) associated with syndromes known to include hearing loss
- Neurodegenerative disorders (e.g., Hunter syndrome) or sensory motor neuropathies (e.g., Friedreich ataxia and Charcot-Marie-Tooth syndrome)
- Culture-positive postnatal infections such as bacterial and viral (especially herpes and varicella) meningitis
- Chemotherapy
- Caregiver concerns regarding hearing, speech, language, or developmental delay

Modified from American Academy of Pediatrics and Joint Committee on Infant Hearing. Year 2007 Position Statement. Principles and guidelines for early hearing detection and intervention programs. *Pediatrics.* 2007;120(4):898.

as a critical component to discharge planning of the neonate.[139] Guidelines for this screening were developed and published in 2011 and recommend screening within 24 hours of life, or close to discharge, and should include preductal and postductal oxygen saturation with a "failure" receiving further evaluation by echocardiography and a pediatric cardiologist.[87]

IMAGING

Premature infants are at increased risk for injuries to the brain, potentially causing permanent damage. The most common form of damage and the leading cause of chronic neurologic morbidity is periventricular white matter injury.[20] Imaging techniques for routine screening for white matter injury has traditionally been cranial ultrasonography because of its availability and tolerance by the infant, though studies have shown magnetic resonance imaging (MRI) and advanced MRI to be superior at term equivalent age.[110,121] Woodward et al.[161] reported that **abnormal findings of MRI at term equivalent age in very preterm infants strongly predict adverse neurodevelopmental outcomes at 2 years of age.**[161] However an evaluation of the prognostic value of head ultrasonography versus MRI found that conventional near-term MRI did not substantially enhance the prediction of severe early school-age outcomes.[78] Another recent study of the effect of MRI on preterm infants and their families predicted moderate or severe motor impairment at 20 months of life only slightly better than ultrasonography, while also increasing costs.[58]

A review of MRI screening to identify risks of suboptimal neurologic outcomes suggests the following be considered as indications for screening by MRI at approximately 36 weeks' or greater postmenstrual age:[76]

- Grade III to IV intraventricular hemorrhage (IVH)
- Periventricular hemorrhagic infarction
- Cystic periventricular white matter injury
- Cerebellar hemorrhage or other abnormalities on ultrasonography
- Suspected white matter abnormalities on ultrasonography (echodensities/echolucencies)
- Posthemorrhagic hydrocephalus
- Abnormal neurologic examination
- Other conditions warranting detailed neuroimaging (metabolic disorders or suspected congenital structural abnormality)

Preventive Care

IMMUNIZATIONS

Infant immunizations are recommended for all NICU infants, according to the guidelines issued by the Centers for Disease Control and Prevention (CDC) and approved by the AAP.[41] **Immunizations administered in the NICU should appear in the discharge summary.** When immunizations have been declined by parents, this should be clearly indicated in the discharge summary, along with follow-up recommendations.

RESPIRATORY SYNCYTIAL VIRUS INFECTION PROPHYLAXIS

Respiratory syncytial virus (RSV) infection poses a risk for serious morbidity or even death of infants who were born prematurely, especially those with chronic heart or lung disease. In a study of 702 infants who were admitted for RSV infection, 42% were admitted to the NICU, with 20% requiring mechanical ventilation and the frequency intensifying with earlier gestational age and younger chronologic age.[25]

For qualifying infants, RSV prophylaxis should be initiated with intramuscular palivizumab before discharge into the community setting during RSV season. RSV infection prophylaxis should be coordinated with the follow-up pediatric care provider for subsequent monthly injections. Recommendations for qualifications have not changed since 2014 and include, but are not limited to those listed in Box 31.4.

BOX 31.4 RECOMMENDATIONS FOR PALIVIZUMAB PROPHYLAXIS[20,107]

- Infants born before $29^{0/7}$ weeks of gestation, given in their first year of life
- Infants born before $32^{0/7}$ weeks of gestation with chronic lung disease (oxygen requirement >21% beyond first 28 days), given in their first year of life
- Infants who qualified in their first year of life with continued need for respiratory medical intervention in their second year of life
- Other infants with compromised cardiopulmonary, neuromuscular, or respiratory systems

Assessments

CAR SAFETY

All 50 states require infants to be restrained in a safety seat while riding in a motor vehicle, although laws vary from state to state. Discharge of smaller infants from an NICU results in the use of car seat restraint devices that were designed for 7- to 8-pound term infants. **In these devices, preterm infants may experience oxygen desaturations and apnea and bradycardia caused by head slouching and airway obstruction.**[51] Infant car seats (rear facing) are now available for infants as small as 5 pounds, should be reclined to 45 degrees, and often come with tested and approved inserts for head or body support. **Supportive inserts that come with the infant car seats are preferable to the use of rolled diapers, blankets, or after-market inserts to support upright posture, prevent slouching, and enable the preterm infant to maintain stability while in the car seat.** In addition, infants with certain conditions (e.g., Down syndrome, osteogenesis imperfecta, myelomeningocele, Pierre Robin syndrome, cerebral palsy [CP]) may benefit from special-needs car restraints.[95] In 2018, the AAP published a technical report addressing the use of an algorithm to assist pediatricians and families in optimizing infant car seat safety.[57]

A car seat tolerance screening (CSTS) before discharge is recommended for all infants born before 37 weeks of gestation; this includes late-preterm infants (i.e., 34 to $36^{6/7}$ weeks) who are cared for and discharged from level I/normal newborn nurseries.[11,12] Although the CSTS has not been standardized, certain components are common: (1) using the car seat purchased by the parents, (2) positioning the infant in the car seat immediately before discharge while on cardiorespiratory and pulse oximetry monitoring, (3) using the car seat for a prescribed period (e.g., 30 to 90 minutes), and (4) recording respiratory/heart rates, oxygen saturations, and apnea/bradycardia events. Although this is a recommended practice, limitations have been identified. **First, little objective evidence supports the ability of this challenge to absolutely confirm safe travel for an infant.** Recent studies of CSTS failure have identified an association with being a full-term LBW infant,[49] and for preterm and late-preterm infants, an association with concurrent caffeine use, antacid use, and history of failure of a trial without respiratory support.[84] Failure of the initial CSTS is associated with a longer length of stay of 3.1 days but not with hospital readmission or 30-day mortality.[141]

NUTRITION AND GROWTH

Before discharge, safe oral feedings should be established, along with guidelines for advancing and monitoring growth, calorie, and nutrient supplementation. In studies of infants who experienced extrauterine growth restriction (EUGR), commonly defined as weight less than the 10th percentile for corrected gestational age (CGA) at discharge, the period from discharge to 30 months has been shown to be a critical period for growth.[134] **Nutritional intake at this time sets the trajectory for growth and neurodevelopment in childhood and adolescence.** VLBW children who have low weight gain in early years of life have a higher probability of cognitive deficits; conversely, those with excessive weight gain have a higher likelihood of obesity, cardiovascular disease, and diabetes.[39]

NEURODEVELOPMENT

Some premature infants may have recognized risks to their later development evident at discharge. **Identification of infants at high risk for poorer outcomes related to brain injury allows for timely referrals to early intervention therapies,** which improve cognitive outcomes into preschool age.[148] **Early intervention has been shown to improve neurobehavioral development with improved cognitive outcomes and parent-child interactions.**[31]

Technology-Dependent Infants

Infants who rely on long-term technologic support are being discharged home in increasing numbers.[153] In the past, children who were ventilator dependent; who had tracheostomies, gastrostomies, or jejunostomies; and even those who required long-term intravenous (IV) access for medications or parenteral nutrition would remain hospitalized, separated from their families and susceptible to other morbidities associated with long hospital stays (e.g., infection, delayed development, impaired mental health). **With this increase of technology-dependent children discharged into the community comes a greater need for support services for the parents, providers, and the infants themselves.**[34] Numerous investigators

have undertaken projects to understand the impact that caring for these children has on the individual child and the family as a whole. Toly et al. described the experiences of well siblings of technology-dependent infants, as told by their mothers.[152] Three themes were identified including (1) well sibling adjustment to a "new normal;" (2) upside experiences described as increasing empathy and compassion; and (3) downside experiences including anxiety/worry and feelings of resentment/jealousy. The implications illuminated are **the potential positive impact of whole-family intervention programs, including siblings, before discharge encompassing relationships and tips for managing everyday life.**[152]

Thorough assessment of families' understanding of their infant and caregiving requirements, extensive education of family caregivers, and early, clear, and consistent information addressing the skills, psychosocial impact, and identified supports are essential for successful discharge.[34] A discharge framework for these infants has been identified that addresses three areas of focus including (1) parental involvement in the early and ongoing care; (2) rooming-in experiences with customized education and frequency; and (3) outpatient care coordination with collaborating subspecialists and coordination of appointments.[34] **Rooming-in with their infant for one or more nights provides an important opportunity to evaluate their abilities and confidence in caring for their child.**

NEURODEVELOPMENTAL FOLLOW-UP OF HIGH-RISK INFANTS

Ideally, parents of all NICU infants would be offered comprehensive, coordinated, developmentally based, family-centered follow-up for their child through infancy and childhood (Fig. 31.1). Each infant is unique, as is each infant's family. **The following are the primary objectives of follow-up care:**

- **To counsel the family about their child's development so that they are empowered to optimize the child's health, growth, and development**
- **To recognize and diagnose (early) significant health conditions and neurodevelopmental disabilities to facilitate appropriate referrals for community services**
- **To anticipate future difficulties and needs so that optimal development is promoted and secondary complications are avoided or minimized**

The ultimate goal is to promote the child's integration into the family, school, and community.

In the current health care environment, follow-up resources are generally limited, and both public and private health insurance plans determine how children will access care. Consequently, criteria for developmental follow-up of NICU infants vary widely. Some high-risk infants are routinely referred to early intervention programs for developmental care, but implementation of these programs varies among states. **The dynamics of development are such that periodic assessments of the child's health and developmental progress are needed to determine whether current interventions are effective and sufficient.** Parents often need guidance to better understand what to expect from their child, how to interpret their own observations of their child, and how health care and community services can support their child's development. The AAP has emphasized that each child have a "medical home," especially the child with complex health and developmental needs, and has a policy statement regarding the recommended components of developmental surveillance.[8,12,14] **Unfortunately, the care of these children often is fragmented among numerous subspecialists and therapists.**[13] Well-organized NICU follow-up clinics can facilitate developmental and health care of the NICU infant in coordination with the primary care provider and the family.

Developmental Milestone Attainment

In developmentally based follow-up, much of the information about the child's development comes from a careful interview of the parent about the child's health status and developmental milestone attainment. **Noting the age of acquisition of the gross-motor, fine-motor, language, and adaptive-behavioral milestones helps determine a possible developmental delay.** Parents are very good historians of their child's current functioning and recent accomplishments, which is why eliciting a history of milestone attainment during serial clinic

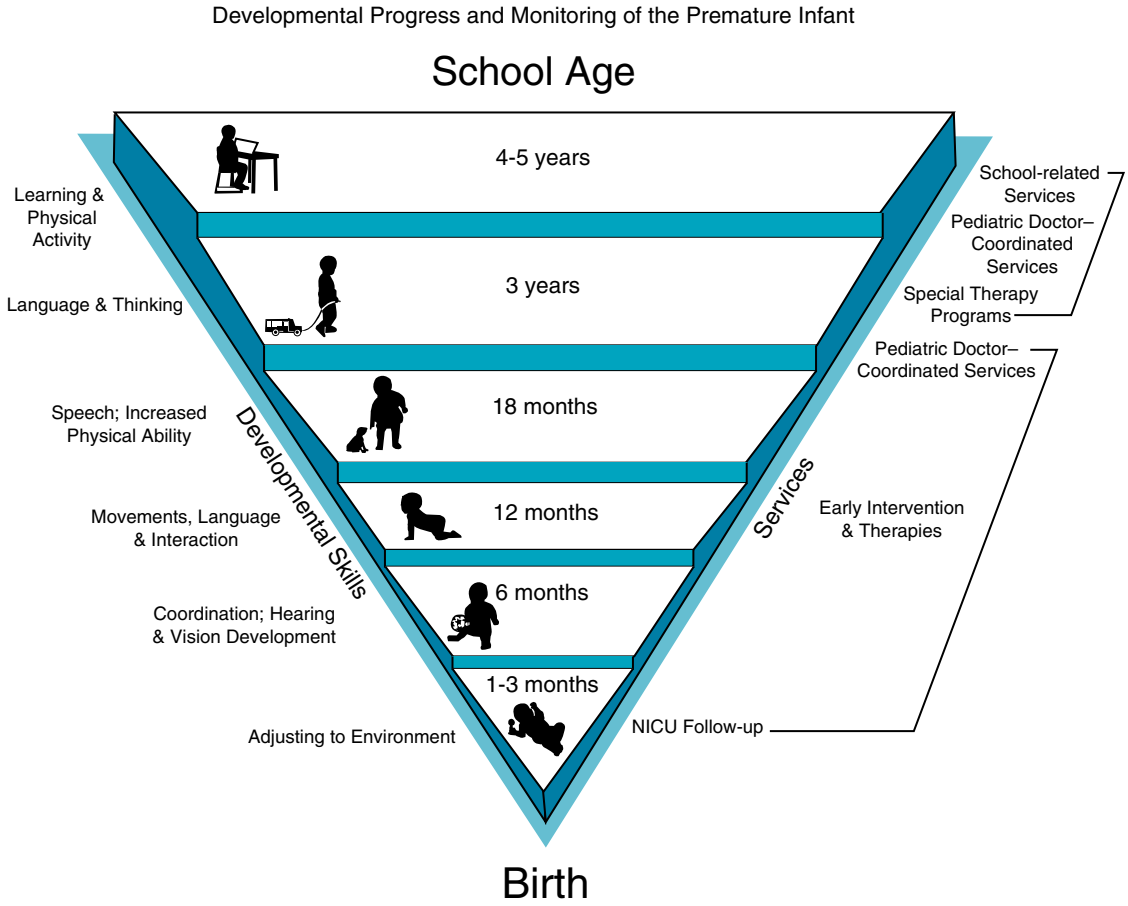

FIGURE 31.1 Developmental progress and monitoring of the premature infant. (Courtesy Angel Carter, Brian S. Carter, and Donna K. Daily. Vanderbilt University Medical Center, 2010.)

visits is so useful in assessing a child's rate of development. Sometimes additional explanation may be needed to clearly determine the age of acquisition, especially language milestones.

A number of accurate screening tools are available to monitor general developmental progress or domain-specific evaluation.[56] Early delay in language and self-help milestones raises concerns about cognitive development, language disorder, or hearing impairment.[2] Many NICU developmental follow-up clinics rely on **pediatric clinical psychologists to formally evaluate the cognition of high-risk infants, preferably with sequential assessments but sometimes with one assessment at a specific age (e.g., at 18 to 24 months' corrected age).** For infants, the *Bayley Scales of Infant and Toddler Development,* third edition, is the most commonly used assessment tool in NICU follow-up programs in the United States.[30] For preschool-age and school-age children, several cognitive tests are available, including the Wechsler Preschool and Primary Scale of Intelligence (WPPSI), the Stanford-Binet Intelligence Scales, and the Kaufman Assessment Battery for Children (K-ABC II).[86,132,160]

Adjustment for Degree of Prematurity

One controversy that arises in monitoring developmental scores of preterm infants is whether to adjust for degree of prematurity (i.e., whether to use the child's chronologic age, calculated from birth,

or to use adjusted age for degree of prematurity). **The best evidence supports adjusting for degree of prematurity**, but whether it is best to adjust throughout infancy is controversial, and **there is no agreement as to when one should stop adjusting for degree of prematurity.**[45] **By convention, most practitioners adjust through 2 years of age.** It is necessary to be very cautious when interpreting adjusted age scores at 12 months or less for ELBW infants. Parental understanding may lead to an overly optimistic outlook that will not be supported by testing at a later date.

Neurodevelopmental Examination

For high-risk infants, the standard pediatric neurologic examination is expanded to include a detailed assessment of posture, muscle tone, movements, reflexes, postural reactions, and functional abilities. Interpretation of the examination requires a thorough understanding of the normal pattern of development over time, the examiner's skill at assessing the infant's performance, recognizing deviations from the norm, and determining the significance of these findings.[2] An alternative to the standardized examination, the General Movements Assessment, has been found to have the best predictive accuracy for CP and, in one study, showed a positive predictive value of 87% to 100% for later spastic CP.[32] **Abnormalities of posture, muscle tone, movements, and reflexes are common in preterm and other high-risk NICU infants during the first year.** These abnormalities include asymmetries of movement, marked extensor tone through the neck and trunk with significant shoulder retraction or elevation, hypotonia, and lower extremity hypertonia and hyperreflexia. CP should be considered in infants with persistent abnormalities in tone, posture, movement, and motor delay. Mild delay and neuromotor tone variation suggest transient neuromotor abnormalities.

NICU Follow-Up Guidelines

The issue of how to do NICU developmental follow-up and how to conduct follow-up studies for high-risk infants has been complex. The methodology can lead to inadequate interpretation of published studies. The National Institute of Child Health and Human Development (NICHD), the National Institute of Neurologic Disorders and Stroke, and the CDC convened a workshop in 2002 to address these issues. Their purpose was to provide standardized guidelines for follow-up care, especially for tertiary care centers with neonatal fellowship training programs in the United States. The results of that workshop have been published and address topics such as risk factors that affect outcome, appropriate assessments, correction for prematurity, assessment tools, and research-related subjects.[14]

Again, these criteria may not fit the need or focus of every program. The resources available across states, within communities, and in individual hospitals and the commitment within the NICU strongly drive follow-up programs in different communities. Programs that wish to have developmental follow-up for quality care surveillance and to provide families with information about their high-risk infant can be resourceful in developing partnerships with local early intervention programs and community physicians. Programs that address scientific questions generally need a focused approach or a research network to approach the study.[156]

Survival to the end of the NICU stay is a very short-term outcome. Ideally, infants would be followed up to, and including, the beginning of school to best identify true developmental outcomes, but most programs do not have the resources to do this. Furthermore, it has become apparent that the effects of prematurity may extend throughout the life span. This is important to know but clearly goes beyond the capability of most NICU follow-up programs.

COMPLEX DISORDERS OF BRAIN DEVELOPMENT

Complex disorders of brain development are a group of chronic, nonprogressive disorders of central nervous system (CNS) function that occur as a result of a primary malformation or insult to the developing brain.[2] **There is a spectrum of neurodevelopmental impairments, from major disabilities (CP, seizures) and severe cognitive impairments (formerly referred to as *mental retardation*) to sensory impairments and other complex disorders of brain development** (Box 31.5).

BOX 31.5 COMPLEX DISORDERS OF BRAIN DEVELOPMENT

Neurodevelopmental Impairment
Major disability
Cerebral palsy
Global developmental delay and severe cognitive impairment

Sensory Impairment
Hearing impairment
Visual impairment

Other Complex Disorders of Brain Development
Language delay or disorder
  Expressive language delay
  Receptive and expressive language delay
Developmental coordination disorder
  Fine-motor incoordination
  Sensorimotor integration problems
Learning disability
  Variable cognitive abilities
  Visual-perceptual problems
Behavior disorders
  Attention-deficit/hyperactivity disorder
  Autism spectrum disorders

Modified from Accardo PJ, ed. *Capute and Accardo's Neurodevelopmental Disabilities in Infancy and Childhood.* 3rd ed. Baltimore, MD: Paul H. Brookes Publishing Co; 2008; Wolraich ML, ed. *Disorders of Development and Learning.* 3rd ed. Hamilton, ON: B.C. Decker; 2003.

Neurodevelopmental Impairment

Preterm infants are at an increased risk for major disabilities and also for other cognitive and behavioral concerns. Both may have a long-term impact on their life.[7,100] **The World Health Organization (WHO) has categorized disability, impairment, and handicap in the *International Classification of Functioning, Disability and Health* (ICF) and places emphasis on the interaction of functioning and disability, health condition of the individual, and factors of the environment.**[136,162] The ICF is structured around the following components: (1) body functions and structure, (2) activities and participation, and (3) additional information on severity and environmental factors.[162] This view has aided our thinking not only of the specific disability but also how it affects a child's ability to function physically and socially within his or her home and community.

Cerebral Palsy

CP is "a disorder of the development of movement and posture, causing activity limitations attributed to nonprogressive disturbances of the fetal or infant brain that may also affect sensation, perception, cognition, communication, and behavior."[130] **Important to this current definition is the recognition of the accompanying disturbances of secondary musculoskeletal problems and epilepsy.** CP is the most disabling motor impairment found in preterm infants and should be diagnosed as early as possible. A recent systematic review found that infants exhibit early signs and symptoms of CP before 2 years of age.[114] Early diagnosis includes a thorough medical history, neuroimaging (i.e., MRI), and standardized neurologic and motor assessments. Early diagnosis prompts referral for early intervention, with a goal of optimizing infant motor and cognitive plasticity, preventing and minimizing secondary complications, and optimizing caregiver well-being.[37,114]

CP has traditionally been classified by physiologic type (tone abnormality), topography (i.e., muscle groups involved), and severity.[2] Again, the most recent recommendation for definition and classification has been expanded and relates to the WHO ICF.[162] Components of the **currently recommended classification stress motor abnormalities, accompanying impairments, anatomic and neuroimaging findings, and causation and timing.** Because consensus has not been clear on the definition of level of severity, the Gross Motor Function Classification System is now commonly used to address motor function, and scales are being developed to more reliably measure other important areas of functioning, such as hand control, speech, and swallowing.[119,130] **Persistently increased muscle tone and increased deep tendon reflexes with persistence of pathologic reflexes (e.g., Babinski) are early signs of spasticity. Variable tone with persistent primitive reflexes, often with involuntary movements, is a sign of extrapyramidal CP.** The child may be 2 to 3 years of age before involuntary movements are seen. **Children who manifest signs of both spasticity and extrapyramidal CP have mixed CP.** Extrapyramidal CP is generalized, but spasticity should be further typed according to which limbs are most significantly involved.

Spastic diplegia, the most common form of CP in preterm infants, is characterized by spasticity in both lower extremities, with mild or minimal involvement of the upper extremities.[2] *Spastic hemiplegia* is characterized by involvement of one side of the body, with the upper extremity more involved than the lower. Because intrauterine and perinatal strokes are usually unilateral, children who had strokes often demonstrate spastic hemiplegia. *Quadriplegia* is the most severe form of spastic CP, with involvement of both upper and lower extremities and the lower more severely affected than the upper. Children with neonatal encephalopathy (whether caused by hypoxia/ischemia, metabolic disorders, or other causes) who develop CP are most likely to have spastic quadriplegia or severe mixed CP.[2]

Global Developmental Delay and Cognitive Impairments

Developmental delay is used to describe a deficit in any of the five developmental domains (cognition, motor, language, adaptive, social-emotional skills). *Global developmental delay* is used to define deficits in two or more areas of development with scores more than 2 standard deviations below norm referenced standards.[143] Currently in the United States, a child may receive services through his or her local school district special education program with a diagnosis of developmental delay until almost 8 years of age before the definition may be switched to severe cognitive impairment, again based on standardized testing. Standardized tests such as the Bayley scales have score groupings and definitions to match, such as *low average* and *borderline,* for each domain.[30] Early detection enables early intervention services for the high-risk infant because the early developing brain is most likely able to adapt or circumvent areas of injury.[31,56,118]

Severe cognitive impairment is a global impairment of cognitive functioning resulting from injury to or malformation of the developing brain that impairs the child's ability to adapt and function in society.[2,7,100] It frequently manifests with an early delay in language and problem-solving abilities. A diagnosis of severe cognitive impairment requires a comprehensive evaluation of the child, with neuropsychological testing of intelligence and assessment of adaptive (functional) abilities, which can be reliably done only at school age.

Neuropsychological testing includes an assessment of a child's intelligence quotient (IQ). Intelligence is not one entity but, rather, many different abilities, including auditory and visual memory, visual-perceptual abilities, and understanding complex language concepts. The older the child is, the greater the number of functions that can be tested and therefore the more accurate the tests are in assessing intelligence. Intelligence and functional ability tests for school-age children and adults consist of a variety of subtests. Most children with severe cognitive impairment have lower abilities for age across all domains of development, so the severity of cognitive impairment is easily classified. Many preterm children have a significant variability in cognitive functions, with high scores on some subtests and low scores on others, which makes them more difficult to classify and appropriate educational services more difficult to determine.

Cognitive impairment is classified in terms of severity, from profound (IQ below 20), severe (IQ 20 to 34), moderate (IQ 35 to 49), to mild (IQ 50 to 70).[2] Children with an IQ of 70 to 85 have borderline intelligence, not severe cognitive impairment. They are capable of academic learning but may have trouble keeping up with their class. The most important characteristics of children with cognitive impairments that enhance adult functioning are interpersonal skills and the ability to communicate and relate to other people.

Sensory Impairments

An NICU admission increases the risk of hearing loss. Most states require hearing screening for all newborns using a two-step process: initial screening with otoacoustic emissions, followed by auditory brainstem responses if the first test is failed.[15] Because of the risk for progressive hearing impairment, infants with congenital cytomegalovirus (CMV) infection, primary pulmonary hypertension, congenital diaphragmatic hernia, and infants treated with extracorporeal membrane oxygenation (ECMO) should have serial hearing evaluations during infancy and early childhood, as should infants with recurrent ear infections.[15,19]

Neonates demonstrate hearing thresholds similar to those of older children and adults. Even preterm infants as early as 24 to 25 weeks' gestational age demonstrate an immature brainstem waveform in response to sound stimuli, although the pattern of the waveform matures to a normal waveform as the infant reaches near-term equivalence. **Infants hear and process language throughout their first year, beginning at birth.**

ROP results from injury to the very immature developing retina caused by abnormal proliferation of retinal blood vessels. Severe ROP, which tends to occur in the most immature and sickest preterm infants, is usually treated with laser photocoagulation to try to prevent retinal detachment and blindness. Recent data indicate that intravitreal bevacizumab monotherapy in infants with stage 3+ ROP can significantly benefit zone I disease, but not zone II disease, compared with conventional laser therapy.[17] Preterm infants may develop medically related eye complications (retinal detachment, cataract, glaucoma) and are at increased risk for refractive errors, strabismus, and amblyopia.[116] Infants who have structurally normal eyes, no refractive error, and a history of no or low-level regressed ROP may be dismissed by the ophthalmologist after 12 to 18 months of age but should continue to receive routine childcare eye screening based on the AAP recommendations for routine preventive care.[117] Late-preterm and term infants with other neonatal complications and neurodevelopmental sequelae may also have visual impairments and need ongoing ophthalmologic follow-up.

Infants with congenital infections should be examined by ophthalmologists for chorioretinitis. Neonates symptomatic of congenital infection (e.g., TORCHES, HIV, West Nile and Zika viruses) have a high risk of visual and/or hearing impairment (see Chapter 22).[88] Preterm infants in the NICU with varying types of postnatal sepsis syndromes have also been identified as having an increased risk for neurodevelopmental impairment.[124] If infants with neonatal encephalopathy develop disability, they tend to have severe multiple disabilities, including cortical visual impairment or processing and hearing impairment.[129]

OTHER COMPLEX DISORDERS OF BRAIN DEVELOPMENT

Even if the NICU graduate does not develop major disability or sensory impairment, he or she remains at increased risk for disorders of higher cortical function (see Box 31.5). These disorders may be less evident in infancy and may be associated, initially, with only nonspecific symptoms (e.g., irritability, posturing, feeding problems). Diagnostic criteria, and even nomenclature, for these disorders vary widely, and few reports of preschool and school-age outcome studies have a comparison group evaluated in the identical manner.

***Language delay* may manifest as early as 6 to 12 months of age as a delay or deviance (i.e., nonsequential) in language milestone acquisition.[2]** Expressive language delay, either alone or in combination with receptive language delay, is common in preterm and other NICU infants. **Every child who manifests with delayed language should have a hearing test and neuropsychological testing to distinguish between language disorder, hearing impairment, and cognitive impairment.**

Developmental coordination disorder (DCD), also referred to as *minor neuromotor dysfunction,* **presents as mild delay or deviant motor milestone acquisition in conjunction with mild or transient neuromotor abnormalities.[50]** These children sit by 1 year of age and walk by 2 years, although they may have an atypical pattern to their motor progress (e.g., transient low or high tone, toe-walking, persistent wide-based gait). These **children generally have typical functioning by 3 to 5 years of age, although they may continue to have some balance or motor planning problems.** Fine-motor incoordination, visual-perceptual deficits, and sensorimotor inefficiencies may accompany DCD, but they may not be recognized until preschool or school age.[27] ***Visual-perceptual deficits,* often in combination with fine-motor incoordination, manifest as an inability to recognize and copy figures, letters, and numbers;** complete puzzles and mazes; or copy block designs; or as some level of difficulty with these tasks. ***Fine-motor incoordination* makes it difficult to button, zip, cut with scissors, draw, and write. *Sensorimotor inefficiencies* are characterized by difficulty following directions that include demonstrating an action (e.g., tying shoelaces) and tolerating motion through space (e.g., swinging on a swing) or different tactile sensations (e.g., clothing or food textures).** For children with DCD, fine-motor incoordination or sensorimotor inefficiencies and failures in school and on the playground erode self-esteem and peer relationships.

Language disorder, visual-perceptual problems, DCD, transient neuromotor dysfunction, and variable cognitive disabilities are associated with learning disability and other school problems.[2,27] Learning disability means difficulty learning one or more academic subjects (reading, writing, arithmetic) in children with normal intelligence who have had adequate exposure to school. Some children have more of a learning inefficiency, in that they do well in the early grades of school but have a relative inefficiency in reading or writing that causes them trouble as the work becomes more complex. **Their intelligence and resiliency help them make adaptations in learning, but they become overwhelmed in situations in which speed and accuracy are viewed as important.**

Behavior disorders are more common in preterm infants, late-preterm infants, and other children who were in the NICU as neonates.[1,85,122,149] **Some children have attention-deficit/hyperactivity disorder (ADHD), characterized by marked distractibility, short attention span, and impulsivity.**[82] ADHD can occur with or without hyperactivity; the child may be restless, always on the move, or constantly busy or may just demonstrate difficulty paying attention and impulsiveness. One must recognize these more subtle concerns as soon as possible. **Counseling parents and teachers can prevent the devastating effect these "mild" disabilities have on self-esteem, peer relationships, and performance in school and at home.**

Autism Spectrum Disorders

Expanding research indicates that the causes of autism spectrum disorders (ASDs) are multifactorial and include genetic, environmental, and epigenetic factors.[97,145] Risk factors for the development of ASD include advanced parental age, preterm birth, prenatal exposure to air pollution, and short intervals between pregnancies; more research into prenatal nutrients, metabolic conditions, and exposure to endocrine-disrupting chemicals is necessary.[97] In an effort to confirm prevalence rates, researchers followed a group of premature infants for 21 years and found the **risk to be five times greater for those infants born less than 2000 g compared with the general population.**[106] A more recent meta-analysis of 18 studies also found the prevalence of ASD to be significantly higher in children born preterm.[4]

The association between brain injury and the risk of ASD continues to be explored. Following 1105 LBW infants, Movsas et al.[106] **found strong evidence linking the occurrence of ventricular enlargement in the neonatal period with diagnosed ASD in those children by adolescence or early adulthood. Although any white matter injury significantly increased the risk for a positive screen for ASD, ventricular enlargement increased that risk sevenfold** with no associated increase with isolated germinal matrix or IVH.[106]

As research continues to explore potential explanations for causality, counseling for families and caregivers concerning the risks and prevalence is warranted. **Early attention to these risks, and potential, may provide earlier screenings, diagnoses, access to services, and behavioral interventions to the benefit of the child and family.**

Diagnosis of Disability

Major disabilities may be recognized and diagnosed in the first 2 years after birth. The more severe the disability, the sooner it may be recognized and diagnosed. Occasionally a child may have significant motor delay initially but seems to "catch up" by 1 to 2 years of age, with concomitant improvement in neuromotor abnormalities. These are often children with ongoing health problems (e.g., bronchopulmonary dysplasia [BPD]/chronic lung disease [CLD]) and are diagnosed with DCD **but have a high risk for learning disability at school age. Language disorders, visual-perceptual difficulties, and fine-motor incoordination are generally recognized and diagnosed during the preschool years (3 to 5 years of age). Specific learning disabilities and attention difficulties cannot be diagnosed until school age, usually around 7 to 8 years of age.** Mild learning disabilities or learning inefficiencies may **not be recognized until middle school or high school.**

Because there is so much overlap among the neurodevelopmental disabilities, whenever an abnormality in one area is detected, the child should have a comprehensive, multidisciplinary evaluation of all of his or her abilities. Services are now available to all children through the Individuals with Disabilities Education Act (IDEA 2004).[81] **Children from birth to 3 years**

of age receive services through their early intervention program, and after 36 months of age they receive services through their local public school's special education program.

PERINATAL RISK FACTORS FOR NEURODEVELOPMENTAL IMPAIRMENTS

Many conditions that require neonatal intensive care also increase the risk for neurodevelopmental disability. Perinatal risk factors can be used to identify NICU infants with a high risk for neurodevelopmental disability so they can be followed closely and referred for comprehensive evaluations and early intervention programs when appropriate (Box 31.6). **Broad categories of risk include the following:**

- Prematurity
- Maternal complications (chorioamnionitis, placental abnormalities)
- Birth complications (asphyxia, need for resuscitation)
- Infant conditions (IUGR, macrosomia, congenital anomalies)
- Neonatal illness (necrotizing enterocolitis [NEC], respiratory conditions, infection)
- CNS-associated conditions (brain hemorrhage, periventricular leukomalacia [PVL], stroke, structural defects)

Multiple risk factors increase an infant's risk for neurodevelopmental impairment, and the effects may be more than additive. As a group, preterm infants or full-term infants with IUGR tend to have a lower mean IQ than full-term appropriate-for-gestational-age (AGA) infants.[90,133,158] Infants with both prematurity and IUGR are vulnerable to the complications of each condition.

BOX 31.6 PERINATAL RISK FACTORS FOR NEURODEVELOPMENTAL DISABILITIES

- Maternal characteristics
  - Socioeconomic status
  - Education
  - Race/ethnicity
  - Obstetric/prenatal complications
- Maternal illness
  - Chorioamnionitis
  - Maternal ingestions (alcohol, drugs, medications)
  - Congenital infection
  - Multiple gestation
  - Labor or delivery complications
  - Placental abnormalities
- Physical characteristics
  - Prematurity
  - Postmaturity
  - Intrauterine growth restriction
  - Small for gestational age
  - Macrosomia
  - Gender
  - Microcephaly
  - Congenital anomalies
  - Dysmorphic features
- Condition at birth
  - Apgar scores
  - Cord pH
  - Meconium staining
  - Need for and response to resuscitation
- Neonatal complications
  - Hypoxia
  - Acidosis
  - Hypotension/shock
  - Apnea and bradycardia
  - CLD
  - Sepsis
  - Meningitis
  - Seizures
  - Hypoxic-ischemic encephalopathy
- CNS structure and function
  - IVH
  - Intraparenchymal hemorrhage or infarction
  - Ventricular dilation
  - Cortical atrophy
  - PVL
  - Burst-suppression pattern on EEG
  - Abnormal neurologic examination

CLD, Chronic lung disease; *CNS,* central nervous system; *EEG,* electroencephalogram; *IVH,* intraventricular hemorrhage; *PVL,* periventricular leukomalacia.
Modified from Taeusch W, Ballard R, Gleason C, eds. *Avery's Diseases of the Newborn.* 8th ed. Philadelphia, PA: Saunders; 2005.

SPECIFIC NEURODEVELOPMENTAL OUTCOMES

This section summarizes reported neurodevelopmental outcomes for some of the most frequently encountered conditions in the NICU. **A systematic approach (see Box 31.6) allows the clinician to assess the risk factors that may affect developmental outcome.** Preterm infants and their medical sequelae are most commonly encountered in neonatal intensive care. However, term infants with pulmonary disease, encephalopathy, or congenital defects also may require intensive care and have significant sequelae. Finally, although we have focused our attention in recent years on smaller and smaller babies in tertiary care centers, **it has become apparent that we have often neglected issues for larger "late-preterm" infants (see Chapter 5).** These infants are more typically followed in level II or transitional nurseries but are not without risk. It is beyond the scope of this chapter to cover **congenital malformations or genetic conditions (see Chapter 27), but it is well known that these infants often require complex multidisciplinary care,** and the principles of follow-up outlined earlier apply to them as well.

Prematurity

For more than 50 years, the medical literature has described the neurodevelopmental outcome of preterm VLBW infants (birth weight <1500 g). With the beginning of modern neonatal intensive care in the mid-1960s, tertiary care NICUs began reporting the incidence or prevalence of major disability—in survivors.

In a review of outcomes studies conducted from 2000 to 2013, Vohr[155] reported that, at 18 to 30 months' follow-up, cognitive impairment (scores >2 standard deviations below the mean) is the most common impairment of preterm infants, with incidences as high as 61% in the smallest survivors.[155] A more recent study also showed that parent-reported behavior problems were related to cognitive, language, and motor development in toddlers (22 to 26 months' corrected age) who were born extremely preterm.[96] By school age, 50% to 70% of VLBW children exhibit learning difficulties related to executive function, visual-motor skills, and memory, resulting in failed grades and special education requirements.

In ELBW children, a meta-analysis of the outcomes of infants delivered at 22 to 25 weeks of gestation reports that when followed at 4 to 8 years of age, all survivors had a likelihood of moderate to severe impairment, with decreasing severity rates in the higher gestational ages.[105] These authors report this to be a unique analysis of data from nine prospective cohort studies published after 2004 in that it is one of the first meta-analyses of studies reporting impairments from school-age children, rather than in the young toddler, where, because of still developing skills and adaptations, rates of impairment may be overestimated.

More recently, researchers suggest that the impact from prematurity extends beyond "merely" neurodevelopmental impairment, with a more broadly felt effect on long-term outcomes.[89,151] Areas of concern include (1) learning and cognition, (2) mental health, (3) physical health, and (4) quality of life.[55] Although 20% to 25% of extremely premature infants do experience moderate to severe neurodevelopmental impairment on evaluations at 2 years of age,[131] long-term outcomes in each of these four domains may be equally important and, perhaps, less considered in outcomes measurements.[77]

Although many challenges are possible for the infant born prematurely, particularly the smallest and youngest, the potential also exists to overcome or adapt to limitations. **Early intervention services, supportive home environments, and access to resources for the families can all help eliminate or mitigate many of the potential negative outcomes.**

Late-Preterm and Early Term Infants

Late-preterm and *early term infants* are defined as infants born between $34^{0/7}$ and $36^{6/7}$ and $37^{0/7}$ and $38^{6/7}$ completed weeks, respectively (see Chapter 5). **These infants are physiologically and metabolically immature, which places them at risk for medical complications and resulting adverse neurodevelopmental sequelae.**[61] Studies have identified **this group of infants to be at a higher risk for poor neurodevelopmental outcomes, which predisposes them to problems with school performance. Learning and behavioral problems, including ADHD and learning disabilities, occur at a higher rate than in term infants.**[74,122,149,154]

Short-term complications, such as fever, glucose instability, apnea, jaundice, and poor feeding, also occur in late-preterm infants at a higher rate than in term infants during the first few days of life.[60,68] Despite their increased morbidity, early discharge of late-preterm infants remains a practice in many centers.[68] Discharge should be individualized and carefully planned with parental input and education. **Long-term outcomes in late-preterm infants related to growth, higher use of health care resources, and developmental delay are outlined in Box 5.3.**

Maternal Complications

Maternal complications increase the risk for conditions associated with problematic birth, but also for long-term adverse outcomes for the infant. Placental abruption causes immediate threat of decreased oxygen supply to the fetus, potentially resulting in neurodevelopmental impairment.[128] Chorioamnionitis may result in adverse short-term outcomes including sepsis, IVH, need for ventilation, and others.[26] **Long-term outcomes associated with exposure to chorioamnionitis include cognitive impairment and death.**[120] Finally, other maternal conditions such as infection, preexisting health conditions, mother's weight, age, use of tobacco or other substances, and prior pregnancy and contraceptive history may increase the risk of prematurity or infant compromise (see Chapter 2). Infant outcomes related to prematurity or birth compromise are detailed throughout this chapter.

Birth Conditions

NEONATAL ENCEPHALOPATHY

The extent and nature of an initial hypoxic-ischemic event cannot be easily determined for many individual infants, leading clinicians to rely on recognizable signs and symptoms of neonatal encephalopathy to predict outcome. These signs and symptoms include the following:

- Poor feeding
- Hypotonia or extensor hypertonia
- Lethargy or hyperexcitability
- Apnea
- Seizures
- Abnormalities on neuroimaging studies, which are far more predictive than low Apgar scores
- The need for positive-pressure ventilation or CPR at birth
- Initial response to resuscitation

Many infants with congenital brain malformations or prenatal brain injury may present with perinatal cardiorespiratory depression. They do not breathe normally at birth and may require positive-pressure ventilation or further resuscitation. It is very difficult to distinguish these infants from those with encephalopathy caused by hypoxia or ischemia. Metabolic problems or neonatal sepsis may also present with these signs. **Therefore the term *neonatal encephalopathy* is preferred over the term *hypoxic-ischemic encephalopathy (HIE),* because etiology cannot always be determined with certainty.** However, the clinician must evaluate the history and relevant factors of each infant to address the etiology of his or her encephalopathy.[21] The etiology may be important in decisions about treatment, prognosis, follow-up, and family planning.

In the absence of a confirmed specific etiology, the stages of encephalopathy described in 1976 by Sarnat and Sarnat remain highly predictive of outcome.[137] Infants with *stage 3 (severe) encephalopathy* and coma, severe hypotonia or increased extensor tone, intermittent decerebration, decreased or absent reflexes, variable pupil reactivity, and abnormal electroencephalogram (EEG) **generally will die or have multiple severe disabilities. Only 20% to 30% of infants** with *stage 2 (moderate) encephalopathy* with lethargy or coma, mild hypotonia, overactive reflexes, seizures, abnormal EEG, and generalized parasympathetic function (constricted pupils, bradycardia, profuse secretions, and diarrhea) **will have multiple severe disabilities.** The remainder of newborns with stage 2 encephalopathy have lower scores on tests of cognition, vocabulary, reading, spelling, and arithmetic than children with *stage 1 (mild) encephalopathy* (hyperalert state, jitteriness, overactivity and easily elicited reflexes, increased sympathetic function, dilated pupils, and decreased gastrointestinal motility) or healthy control children. **Infants with neonatal encephalopathy should be evaluated with both EEGs and neuroimaging studies.** Very-low-voltage EEG patterns (signifying little brain activity) and burst-suppression EEG patterns carry an extremely poor prognosis, as does diffuse encephalomalacia detected by MRI.[42,129,146] **Infants with moderate encephalopathy may benefit from therapeutic hypothermia, commonly called *cooling,* leading to increased survival without disability (see Chapter 26).** The results from all published trials in North America and Europe

are most promising for encephalopathies of less than a severe nature, and cooling is considered to be a standard of care in many countries for infants meeting cooling criteria.[28,71,125,140] **Follow-up of infants receiving cooling therapy supports the therapeutic value of hypothermia.**[70,92,111,125,126] Mild encephalopathy with only a subarachnoid hemorrhage carries a favorable prognosis, although these children should be monitored for later learning difficulties.

Infant Conditions

INTRAUTERINE GROWTH RESTRICTION

Prenatal and postnatal growth can seriously affect neurodevelopmental outcomes of high-risk infants. The neurodevelopmental outcome of IUGR infants is strongly associated with the cause of IUGR; with the timing, severity, and duration of the insult; and with perinatal complications the IUGR infant encounters (see Box 31.6). Early severe IUGR often reflects a chromosomal anomaly, another severe genetic disorder, or a congenital infection that occurred early to cause organ malformation or significant injury. **Some causes of IUGR result in death** (e.g., trisomy 18) or severe disability. **Some carry a high risk for neurodevelopmental disability** (e.g., fetal alcohol syndrome). Others are associated with only mild disability (e.g., an increased incidence of attention and behavior problems in infants born to mothers who took narcotics or cocaine during pregnancy).

One of the most common causes of IUGR is uteroplacental insufficiency, generally a diagnosis of exclusion. **The fetus responds in many adaptive ways when the supply of nutrients or oxygen is limited.**[23,24] **There is first a decrease in subcutaneous tissue, resulting in lower birth weight, and then a decrease in length, before head and brain growth are affected (symmetric growth restriction).** Nevertheless, the problem may be severe enough to overwhelm these adaptations and lead to brain injury. In addition, a chronically compromised fetus, with decreased glycogen and nutrient stores, has more difficulty with the stresses of labor and delivery, leading to perinatal depression, cold stress, hypoglycemia, and hypocalcemia. Polycythemia may result from chronic intrauterine hypoxia but may result in the complications of hyperviscosity.[133]

Prospective studies of full-term IUGR school-age children compared with full-term AGA children showed that more IUGR children had language problems, learning disability, minor neuromotor dysfunction, hyperactivity, and attention and behavior problems. Postnatal growth may also be affected, but this will largely depend on whether the infant has symmetric or asymmetric IUGR. **Preterm IUGR children demonstrate the disadvantages of both prematurity and IUGR, but which is more important in determining outcomes is not clear.** The degree of IUGR may influence early delivery, either spontaneous or induced, because of concerns of fetal well-being. **The most striking findings in studies of preterm IUGR children and preterm AGA controls are the high rates of major disability (7% to 23%) and learning disability (36% to 50%).**[93,144]

CONGENITAL ANOMALIES

Cardiac. The presence of congenital heart disease (CHD) places children at an increased risk for developmental delays and neurodevelopmental impairment related to cyanosis, cardiac surgery itself, and more specifically cardiac surgery with cardiopulmonary bypass, or comorbid conditions such as prematurity.* Accumulated evidence for these risks led to the collaboration between the American Heart Association and the American Academy of Pediatrics to issue policy guidelines for the surveillance, identification, and interventions for these children.[22]

Early assessments of children with CHD show motor deficits as most common with language and cognitive deficits appearing later.[108] The most common indicator of later neurodevelopmental deficit was the failure to achieve full oral feedings without supplemental tube feedings; the presence of comorbidities and poor growth were the next most commonly identified risk factors.[108]

Periodic, longitudinal screening is indicated for children with CHD because evidence shows increased risk for motor, language, and cognitive effects. The American Heart Association developed a management algorithm to be used by the primary care provider, within the child's medical home. This algorithm assists with identification, evaluation, and management of potential neurodevelopmental challenges and allows for earlier access

*References 39, 45, 100, 109, 114, 149.

to potential intervention services for the child and family.[22]

Congenital Diaphragmatic Hernia. Congenital diaphragmatic hernia (CDH) increases the risk for poor neurodevelopmental outcomes, likely affected by the severity of CDH and associated hypoxemia (e.g., need for ECMO, prolonged ventilation). Most commonly reported deficits are neuromotor abnormalities (i.e., hypertonicity, hypotonicity motor performance) and neurocognitive dysfunction (i.e., language, cognition).[46–48]

CENTRAL NERVOUS SYSTEM INJURY

Infants with ischemic perinatal stroke are another group of infants with brain injury who are at risk for long-term developmental sequelae. This entity is generally distinctly different from the diffuse ischemia seen in the so-called "watershed" injury of perinatal HIE. Timing of the event may also be less easily determined, but the infant may present with focal or generalized seizures or less-defined clinical signs such as poor perfusion ("dusky" or "gray" spells), respiratory distress or apnea, poor feeding, or low neuromotor tone in the first few days of life. MRI is the most reliable method of diagnostic detection in the newborn period if timed appropriately. Neurologic deficits (i.e., cognitive, behavioral, motor, and language) have been reported in 50% to 75% of survivors, and hemiplegic CP is most commonly found.[94] Later difficulties with sensory impairment or learning difficulties also occur, thus requiring long-term follow-up.[127]

HEMORRHAGE

Although intracranial hemorrhage most commonly occurs in the preterm infant, it may also occur in the term infant, and any concerns need to be carefully investigated with infant outcomes closely monitored.[72] Subdural hemorrhage is the most common type in the term infant, with 44.4% of infants in a recent study having poor outcomes.[79] Impact of intracranial hemorrhage ranges from short-term feeding or state disruptions to severe disability and death (see Chapter 26 for the physiology of these hemorrhages). Attempts to associate the injury with disability have identified that ventricular dilation, as well as grade and laterality, can be predictive of the severity of any deficits, with bilateral grade IV IVH having the poorest outcomes.[43,67,83,103] Infants may experience cognitive and/or motor disability from the brain injury and the combined effects from risks associated with prematurity, comorbid medical conditions, or illnesses.

ILLNESS

Respiratory. Persistent pulmonary hypertension of the newborn (PPHN) and meconium aspiration syndrome (MAS) often overlap clinically, and many of these infants require neonatal intensive care technologies such as inhaled nitric oxide, high-frequency ventilation, and ECMO (see Chapter 23). Full-term survivors have an increased risk for major disability, neuromotor dysfunction, borderline intelligence, language delay, and attention problems.[80] Although the risk of acute neurologic morbidities is present with the use of ECMO for any population, neonates are the most affected, with neurologic morbidity rates of 20% to 50%.[101] Infants who experienced seizures while on ECMO were found to have a lower IQ score at school age and were at higher risk for CP and developmental delay.[101]

Bronchopulmonary Dysplasia/Chronic Lung Disease. BPD/CLD is the most common morbidity in surviving preterm infants.[64] The etiology of neonatal lung injury has changed over time and is now recognized to be an "arrest of lung development" rather than solely injury.[53] Complications of BPD/CLD are listed in Box 23.14.

Necrotizing Enterocolitis. NEC, with or without intestinal perforation, carries with it a high rate of neurodevelopmental impairments, especially in those preterm infants requiring surgery.[6] One study reported an incidence of neurodevelopmental impairments at 82% in infants requiring surgery.[157] Impairments include cognitive deficits, CP, nutritional compromise, and severe visual impairment, with rates significantly higher for those infants requiring surgery.[3,138]

Infection (Sepsis, Meningitis, and Other Non-NEC Related). The impact on neurodevelopmental outcomes from neonatal infection has primarily been studied by individual insult. A 2012 systematic review, however, attempted to define the global

burden of "intrauterine and neonatal insults" with individual sequelae identified per insult.[109] *Sepsis* was identified in five studies reviewed, with 40% of the infants affected (N = 977). The most commonly identified sequelae were cognitive, general developmental delay, or learning difficulties in 74% of the infants. *Meningitis* was identified in 11 studies, with 42% of the infants affected (N = 209) and 100% reporting cognitive deficits as the sequelae. *Cytomegalovirus* identified 377 infants with deafness or hearing loss (67%) and cognitive deficits (66%) as the identified sequelae. *Herpes* affected 116 infants, with 94% of them experiencing cognitive sequelae, and *rubella* was a cause of sequelae in 720 infants, with deafness or hearing loss reported as the most common impairment (80%).[109]

These data support the need for high surveillance, primary prevention, and close monitoring of follow-up for infants born with or acquiring infection in the neonatal period.

TRACKING HEALTH OUTCOMES: THE PRIMARY CARE PROVIDER

Primary Care Follow-Up

At the time of discharge, the NICU staff must provide the primary care provider and the parents with a complete and accurate history of the child's NICU course, including recommendations for ongoing care (Box 31.7). Special health concerns that are specific to the premature infant should be closely monitored, and surveillance of these should supplement the AAP guidelines for preventive, "well-child" care.[33] These additional areas of special concern for the premature infant include the following:

- Neurodevelopmental follow-up
- Visual and hearing outcomes
- Growth, nutrition, and feeding issues
- Osteopenia of prematurity
- Dental enamel defects
- Sequelae related to issues during hospitalization, including pulmonary, gastrointestinal, hematologic, and surgical conditions

Along with subspecialty medical follow-up, the primary care provider will also need to coordinate other supportive services such as early intervention programs and developmental follow-up through an NICU follow-up program, if available.[36] Recommendations for specialized follow-up of the late-preterm infant have also been proposed with the focus on feeding, sleeping, temperature regulation, jaundice, and infection in an effort to reduce postdischarge morbidities and rehospitalization of these infants.[60]

BOX 31.7 POSTDISCHARGE CARE NEEDS FOR NICU GRADUATES

Central nervous system: IVH/PVL imaging before discharge; consider value of MRI instead of, or in addition to, ultrasonography for predicting developmental challenges; plan for ongoing developmental assessment.

Vision: Complete ROP monitoring and treatment in a timely fashion as indicated; visual acuity evaluation between 6 and 12 months of age.

Hearing: Universal screening and recurring screening for high-risk groups (CMV, PPHN, HFV, ECMO, CDH); specific evaluation and augmentation, if indicated, by 6 months of age.

Cardiac: Pulse oximetry screening to rule out critical ductal-dependent cardiac lesions (usually completed in first 1 to 2 days of hospital admission) completed before discharge. Outpatient follow-up of cardiac issues identified during hospitalization (other structural defects, PPHN, or other functional problems).

Pulmonary: Evaluation of BPD classification at 36 weeks' corrected age; outpatient management of BPD, management of oxygen and monitoring of needs; management of additional support, including tracheostomy and ventilators as needed in select patients.

Gastrointestinal: Management of feeding regimens and close attention to growth; management of enteral feeding needs if oral intake is inadequate. Referrals for evaluation and management of oral eating problems.

Development: Early referrals for therapies as indicated for speech, motor, and cognitive development.

BPD, Bronchopulmonary dysplasia; *CDH,* congenital diaphragmatic hernia; *CMV,* cytomegalovirus; *ECMO,* extracorporeal membrane oxygenation; *HFV,* high-frequency ventilation; *IVH/PVL,* intraventricular hemorrhage/periventricular leukomalacia; *MRI,* magnetic resonance imaging; *PPHN,* persistent pulmonary hypertension of the newborn; *ROP,* retinopathy of prematurity.

Growth, Nutrition, and Feeding

Premature infants are at increased risk for growth deficits after discharge; many are discharged below the body weight of their healthy term counterparts. The failure to achieve adequate growth is known as *extrauterine growth restriction (EUGR)*

and is defined by weight less than the 10th percentile for CGA at the time of discharge.[134] **EUGR also occurs commonly in ill preterm newborns.**[39,135] **In the NICU, infants with lower somatic growth who did not also experience a preservation of head growth (head sparing) had a higher incidence of neurodevelopmental impairment** at 18 to 22 months' follow-up in the NICHD Neonatal Research Network.[59,104]

Postdischarge growth failure for preterm infants is also a common problem, especially in those with associated BPD/CLD. Transitional formulas, occasionally with enhanced caloric concentration, may be needed to optimize growth and subsequent development.[69] Recommendations from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition support breastfeeding of AGA infants or formula with long-chain polyunsaturated fatty acids for formula-fed, appropriately grown infants.[62] **For those infants with evidence of growth deficits present at discharge (EUGR), breast milk should be supplemented with a human milk fortifier. Formula-fed infants should receive a special postdischarge formula, with increased protein, minerals, and long-chain polyunsaturated fatty acids, for at least the first 9 months.**[10] Serial measurements of head circumference, weight, length, and weight/length ratio should be closely monitored.[150]

Some infants do not achieve full breastfeeding before discharge. It is essential, therefore, to provide **clear verbal and written instruction to the breastfeeding mother about how to assess her infant's hydration status if the transition from partial to full breastfeeding is to occur at home, along with ensuring that the mother has access to medically sound breastfeeding support from the child's pediatrician or a qualified lactation consultant.**

Although premature infants are at an increased risk for childhood obesity and the metabolic syndrome associated with excess weight gain, this risk is thought to be small compared with the risk for growth failure and should be considered with other risk factors such as parental size, adolescent weight, and lifestyle factors.[69] Nutritional status should be monitored closely to intervene for either deficient or excessive weight variations.

Gastroesophageal reflux (GER) is a frequent complication of the VLBW infant postdischarge, and it can affect growth and increase family stressors.[142] Management of these symptoms is often variable and may include medications, formula changes or thickening, and further assessments of potential allergies, insensitivities, and oral feeding skills. Delays in diagnosis and management often lead to caregiver frustration and may negatively affect the infant and development.[142] The use of a screening algorithm has been suggested as a way to more effectively assess and manage these symptoms and reduce caregiver stressors.[142]

Medically Fragile and Chronically Ill Infants

Increasing survival of infants with post-NICU morbidities, including those associated with CDH, short bowel syndrome, and others, has increased the need for detailed parent training, home health care arrangements, and comprehensive, coordinated, multidisciplinary follow-up. The AAP has issued extensive follow-up guidelines for infants with CDH, including monitoring neurodevelopment, managing pulmonary morbidities such as pulmonary hypertension and CLD, assessing hearing function at regular intervals, providing early therapies for feeding difficulties such as oral aversion and gastroesophageal reflux, and monitoring for hernia recurrence, which has been reported in 8% to 50% of CDH infants.[19] Brodsky and Ouellette[36] recommend close monitoring of infants with a history of NEC and/or short bowel syndrome, including neurodevelopmental delays; growth, nutrition, and feeding concerns; dehydration and electrolyte imbalances; and signs of associated complications such as infection, late strictures, and cholestatic liver disease.

LONG-TERM NEURODEVELOPMENTAL FOLLOW-UP

During hospitalization, parents may ask questions about outcome that simply cannot be answered. **Although the infant's risk for cognitive and motor impairment should be discussed, parents must understand that the certain diagnosis of developmental delay or disability cannot be made before 12 to 24 months of age. This need to "wait and see" creates an additional burden**

for families that the NICU staff should help the family anticipate. Referral to a multidisciplinary developmental follow-up clinic should provide the family with ongoing information about their child's progress and give parents the opportunity to speak with professionals about their concerns. **These clinics often provide families with concrete, focused tasks to undertake with their child that may optimize infant development and help parents feel they are contributing to their child's success.**

An additional concern that has more recently surfaced is even longer-term outcome issues for high-risk children. Because many children may be seen once for a multidisciplinary evaluation (18 to 24 months' corrected age) or may not be followed beyond 3 to 5 years of age in the NICU follow-up clinic, it is important that **parents be informed before release from specialty follow-up care about longer-term concerns regarding health and development, especially possible challenges with academics and social-emotional issues.**[7,100]

Pediatric health care professionals need to be aware also that recent reports delineate some more lifelong effects on the former NICU patient's quality of life as a child and adolescent, daily personal and social functions, and overall experiences with health and disease. Although much of this information may be speculative and studies remain ongoing, it is nonetheless important to inform the family that their child's long-term health and quality-of-life issues may relate to their child with a history of prematurity, regardless of the developmental status of the child when seen in the first few years of life.

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32 ETHICS, VALUES, AND PALLIATIVE CARE IN NEONATAL INTENSIVE CARE

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Clinical decision making is influenced by the values of the individuals involved. In the neonatal intensive care unit (NICU), these values include preserving life, decreasing morbidity, relieving pain and suffering, and, at times, end-of-life care. Sound clinical skills and judgment, combined with ethical reasoning and supportive palliative care, result in the art of care in the neonatal intensive care setting. Technologic advances in medicine have benefited many patients. We are better able to prolong life; at the same time, we are more often in a position to make deliberate decisions about when and how death will occur. Concomitantly, it has become necessary for society to reassess whether the value of prolonging life conflicts with other values, such as relieving pain and suffering and enhancing end-of-life care. In such cases, values of society, the family, and the health care professional necessarily enter into and influence the decision-making process.

Ethical reasoning and palliative care insist that we understand the role of values, as well as medical data, in making decisions.

HISTORICAL OVERVIEW

Historically, ethical concerns in neonatal care focused on the risks and benefits of available technology (Table 32.1). An example is oxygen therapy with the offsetting dilemma that treatment could cause degrees of blindness or residual lung damage, whereas nontreatment might result in death or brain damage (1960s). Treatment of premature infants and those with birth defects became technically possible in the 1950s with development of infant incubators, ventilators, and refined surgical techniques. Because these new technologies not only failed to eliminate all bad outcomes but also added new problems, controversies developed over when and how much to use them. Care of newborns with spinal cord defects is illustrative.

Zachary[114] and Shurtleff[97] advocated aggressive management, which increased survival rates but offered questionable quality of life for those more severely affected. Lorber[72,73] was less optimistic about the effects of aggressive management of infants with meningomyelocele and is recognized for his selective nontreatment of some of these infants. Today, open neural tube defects are routinely closed in the immediate neonatal period, and research is ongoing to assess the potential for fetal surgery to close these defects to mitigate long-term morbidity in what is clearly acknowledged as a nonlethal condition.[10,29]

Discussion of treatment of seriously ill newborns was stimulated by the 1973 publication of Duff and Campbell.[36] Their seminal article described the selective nontreatment or withdrawal of treatment for 43 seriously ill newborns at Yale–New Haven Hospital (between 1970 and 1972) whose "prognosis for meaningful life was extremely poor or hopeless." According to Duff and Campbell[36]:

> *Both treatment and nontreatment constitute unsatisfactory dilemmas for everyone. When maximum treatment was viewed as unacceptable by families and physicians in our unit, there was a growing tendency to seek early death as a management option,[20] to avoid that cruel choice of gradual, often slow, but progressive deterioration of the child.*

They recognized that most survivors of NICUs are healthy; however, they also recognized that some infants remain severely disabled by congenital

BLUE type highlights content that is particularly applicable to clinical settings.

TABLE 32.1 SELECTED ISSUES IN PERINATAL/NEONATAL HISTORY OF ETHICAL IMPORT

TIME	FETAL DIAGNOSIS	FETAL THERAPY	NEONATAL THERAPY
1900s (early)			Temperature regulation, nutrition; limited survival in low-birth-weight and anomalous infants Recognition of congenital rubella syndrome Cardiovascular surgery in the newborn period Modern incubator developed Oxygen therapy for respiratory distress
1950s		Tocolysis (EtOH)	EBF (Rh) incompatibility recognized Oxygen toxicity recognized: retrolental fibroplasia/blindness in treated infants; cerebral palsy and death in those untreated Other iatrogenic diseases Antibiotic usage broadens
1960s	Placentocentesis Early ultrasonography Fetal heart rate monitoring Fetal scalp pH assessment Amniocentesis Chromosomal analysis	Intraperitoneal blood transfusion for EBF	Birth of "modern" neonatal intensive care units Field of teratology develops after thalidomide disaster Improved outcome for infants <2500 g Surgical management of meningomyelocele becomes an issue
1970s	Fetoscopy Real-time ultrasonography Improved structural, chromosomal, and metabolic diagnostics	Intravascular blood transfusion for EBF Beta-adrenergic agonists for tocolysis Corticosteroids for lung maturation Legalization of abortion	Continuous positive airway pressure, modern neonatal ventilator Improved outcome for infants <1500 g Bronchopulmonary dysplasia recognized Problems of the very-low-birth-weight infant: intraventricular hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis TPN/HAL becomes available Improved pediatric surgery Newborn metabolic screening
1980s	Chorionic villus sampling Cordocentesis Doppler flow studies of placenta and umbilical vessels New reproductive technology Alpha-fetoprotein monitoring	Fetal surgery Prophylactic penicillin for group B streptococcus infection Treatment of fetal dysrhythmias via maternal medications	High-frequency ventilation Surfactant replacement therapy Improved survival in infants <1000 g Extracorporeal membrane oxygenation Intravenous immunoglobulin
1990s	Fetal cell isolation in maternal blood Polymerase chain reaction and genetic amplification	Treatment of twin-to-twin transfusion syndrome	Liquid ventilation Recombinant erythropoietin Nitric oxide therapy
2000–2010	First-trimester high-resolution ultrasonography	Further advances in fetal surgery (including that for nonlethal anomalies)	Head cooling; total-body therapeutic hypothermia to mitigate HIE

TABLE 32.1 SELECTED ISSUES IN PERINATAL/NEONATAL HISTORY OF ETHICAL IMPORT—CONT'D

TIME	FETAL DIAGNOSIS	FETAL THERAPY	NEONATAL THERAPY
2010–2019	Ever-expanding genetic testing (including noninvasive fetal testing from maternal blood) Expanded perinatal, genetic, and metabolic screening	Potential genetic treatments	Prostanoids, endothelin-receptor antagonists, and phosphodiesterase inhibitors for pulmonary hypertension Orphan drug approval for some rare metabolic conditions Erythropoietin to mitigate HIE Rapid genomic testing: facilitation and influence on parental decision making, especially during the acute distress of their infant's diagnosis; justification of cost and resource allocation.[13,49]

EBF, Erythroblastosis fetalis; *EtOH,* ethyl alcohol; *HIE,* hypoxic-ischemic encephalopathy; *TPN/HAL,* total parenteral nutrition/hyperalimentation.

malformations that, until recently, would have resulted in premature death. They were legitimately concerned about the quality of life for these infants and their families.

The majority of newborns treated in NICUs do grow up to lead active, productive lives, but not all fare well with even the most aggressive treatments.[42,43] Consequently, there is increasing concern over what is "appropriate" treatment of newborns, particularly seriously ill or disabled ones. Recognizing the risks and benefits of technology over 40 years ago, Eisenberg[38] stated, "At long last, we are beginning to ask, not *can* it be done, but *should* it be done."

Baby Doe (1982) and Baby Jane Doe (1983) became the focus of controversy over the issue of withholding treatment and nutrition from handicapped infants.[9,23,83,105] Today, new issues require our attention. Advances in fetal surgery continue to raise the question of whether interventions for nonlethal conditions warrant the attendant risks of preterm birth and treatment postnatally in the NICU.[10,29] Further, assisted reproductive technologies (ARTs) contribute to increasingly greater numbers of very-low-birth-weight (VLBW) infants born as multiples (twins, triplets, and higher-order multifetal gestations) in NICUs. At what point these well-intended services should be restrained or curtailed to prevent prematurity and its associated morbidities continues to pose new ethical questions.

Throughout this short but focused "history" of ethical issues in neonatal care, it has become increasingly apparent that there are significant issues about appropriate treatment and the limits of treatment.[47,84] The role of palliative care has become increasingly recognized. Diagnosis, prognosis, and the meaning of palliative care to families are important factors in clinical decision making. Not only numerous issues but also many individuals are involved in the decision-making process about treatment and nontreatment options. More people become involved as technologic advances increase treatment options. Parents have always been presumed to be the best decision makers on their child's behalf. Health care providers also have been committed to providing what is in the best interest of their patients. Historically, decisions were made privately between parents and their physician. In the modern NICU, treatment goals and decisions are made in the context of a health care team composed of professionals from various moral communities who offer specialized input into the care of the neonate and the family. Parents must be included in the team, because their values are of paramount importance in establishing goals and making decisions about their infant's care. Societal concerns generally have focused on protecting infants against decisions that are detrimental to their best interest by statutes on child abuse and neglect. Professional groups such as the American Academy of Pediatrics (AAP),[4,16,73] the American College of Obstetricians and Gynecologists (ACOG),[7] and the Canadian Pediatric Society (CPS)[68] have now addressed these concerns in published guidelines for care of critically ill infants. The National Association of Neonatal Nurses (NANN) has published guidelines on neonatal palliative care.[27] Community groups[35,37,110] are addressing limitations of interventions for critically ill infants as well. Clinical decision making is affected by parents, the health care team, professional groups,

and society. Bioethics and palliative care advocate a shared decision making model in which parents and clinicians decide together, seeking to balance the appropriateness of interventions and the protection of children against harm.

DEFINITION OF BIOETHICS

Ethics is the study of rational processes for determining the most morally desirable course of action in view of conflicting value choices. Ethics is a branch of philosophy that considers competing values to obtain the best possible outcome to a given situation. When values conflict and each value is morally justifiable, an ethical dilemma exists. For an ethical dilemma to exist, a real choice between possible courses of action must exist.

Bioethics seeks to determine the most morally desirable course of action in health care given the conflicting values inherent in varying treatment options.[8] Most often, when a conflict of values does not exist, moral conflict does not exist. That is, when the health care providers and parents all agree that it is most beneficial to an infant to not treat the infant aggressively and to allow the infant to die, no dilemma or conflict between them exists. Of course, that they agree does not mean that conflict does not exist with moral views of outside parties or principles. Regardless, the goal is to determine the most morally desirable course of action under a given set of circumstances.

THEORIES OF ETHICS

An ethical theory provides a basis for making morally appropriate decisions. There are many theories or approaches to ethics to consider. *Principle-based ethics* identifies fundamental principles that form the foundation of ethical deliberation. This approach emphasizes the centrality of principles and rules to determine moral duty. Principles commonly recognized are autonomy, beneficence, nonmaleficence, and justice.[17] *Virtue ethics* is character based, and as such, identifies the virtues of the moral agents involved, rather than the applied principles, as essential to ethical outcome. Various views of the moral life emphasize different virtues as more primary than others. In modern bioethics, primary virtues include respect, fidelity, honesty, and benevolence. *Casuistry* is *case-based ethics* in which the claims, grounds, and warrants of a particular case are compared with similar cases. The basic question for moral casuistry is how a general moral precept is to be understood in similar sets of circumstances. *Narrative ethics* is story based, in which the narrative itself is a method of ethical reasoning. Every case has different "narratives" to consider, such as medical knowledge, personal identity, patient experience, and the doctor-patient relationship. Although the medical model may focus on disease, psychopathology, objectivity, and diagnosis, the narrative model may focus correspondingly on illness, "the person," subjective experience, and caring. *Feminist ethics* is relationship based and considers primarily the ethics of care. All of these approaches are important to consider. Deciding which moral theory is operative is important to proceeding.

CLINICAL DILEMMAS IN THE NEONATAL INTENSIVE CARE UNIT

Personhood

Decision making in the NICU often revolves around the concept of personhood. When is one a person? Determining what this means depends on which moral community is consulted. Designation of personhood is morally significant because it determines whether and what duties and obligations are owed to a particular newborn.

Some communities believe personhood is present at the moment of conception; they equate "human" with "person." Shelp[96] refers to this as the "genetic theory of personhood." Others believe personhood depends on the presence or absence of certain basic human qualities. Shelp calls this moral theory "property based." Although with the latter theory there is agreement that the concept of personhood is nongenetic, there are differences about which qualities qualify for "person" status.

Fletcher[46] and Engelhardt[39] support the "property-based" stance. They believe that there are human lives that are "subpersonal." Fletcher states, "It is not what is natural but what is personal which has the first-order value in ethics."[46] Both researchers believe that neocortical function is necessary for personhood. Engelhardt[39] relates qualities such as self-consciousness, rationality, and self-determination

to personhood. He distinguishes between persons in a moral sense and persons in a social sense. Infants are deemed persons only in a social sense, not a strict sense by which societal rights are obligatory. The rights of the infant, according to Engelhardt, are held in trust by his or her parents; therefore "decision(s) about treatment belong properly to the parents because the child belongs to them in a sense that it does not belong to anyone else, even to itself."[39]

Tooley[104] suggested that "The ability to see oneself as existing over time is a necessary condition for the possession of a right to life."[62] If Tooley's reasoning is correct, no infant has a right to life, at least not for some time. Although the "pro-life" moral community assigns person status to all with potential life, Tooley denied that potential has anything to do with a right to life. He advocated a quality-of-life standard. When a life is full of intractable pain and suffering, death is seen as a morally acceptable option. In fact, it is sometimes considered a relatively more favorable outcome than continuing life.

Ramsey[91] and Robertson[95] hold a contrasting view. For them, death is never better than life; quality-of-life assessments are not part of their moral reasoning. Life is considered sacred, an absolute good. Both the fetus and newborn are considered persons with a right to live. Therefore "death must always be imposed nonhumanly by God or nature or some other cosmic arbiter."[46] This "pro-life" position supports the moral right of all fetuses and newborns to the same care, implying that abortion and infanticide are morally reprehensible.

If one is deemed a "person," society owes one certain obligations and expects certain duties. If one is not deemed a "person," it is morally reasonable for societal benefits to be withheld or withdrawn. Whatever justification is needed for a particular moral dilemma in the NICU extends from this beginning. Clearly, there is no final definition of personhood, and differing definitions must be considered.

Patienthood

A primary problem confronting a perinatal clinician is this fundamental question: Who is the patient? The adult patient is generally competent and worthy of respect as a moral agent. However, in the case of a newborn, the newborn, the family, and, in some circumstances, society have been variously considered the "patient." The accordance of rights to the newborn as an independent agent is a relatively recent occurrence. Neonatal cases are inextricably bound in the context of varying definitions of personhood and of complicated family and societal situations. This fundamental question remains: To whom is the moral duty owed? To the infant? To the family as "patient"? To society? If there are competing moral obligations, it is essential to determine to whom the primary moral duty is owed.

Professional-Patient Relationship

The importance of the professional-patient relationship cannot be overestimated, because this is the human context in which decision making occurs. With neonates, this includes a relationship between parents as surrogates and the health care team. This is especially recognized in bioethics and palliative care.

When the four major bioethics principles—autonomy, beneficence, nonmaleficence, and justice—are applied to health care relationships, several moral rules can be derived. These moral rules include fidelity, truth telling, and confidentiality. The professional-patient relationship is considerably affected by the meaning and extent of these rules.

Fidelity, or promise keeping, may be derived from the principle of autonomy. The duty to keep promises may promote the greatest good (utilitarian) or be seen as an obligation (formalist). Many relationships between professionals and patients (or surrogates) involve promises or contracts, whether implicitly or explicitly made. For example, once professionals have established a relationship with a patient, their duty of fidelity includes not abandoning or neglecting that patient. An obvious problem in dealing with surrogates may be conflicting duties to the surrogates and the patient. Promises made by professionals are binding except when they are superseded by stronger obligations.

Truth telling, like fidelity, can be derived from the principle of autonomy or respect for persons. It assumes an implicit contract between parties that the truth will be told. At the heart of truth telling is trust, which gives professional-patient relationships their integrity. Lying violates implicit contracts, respect for persons, and trust. It also impedes informed consent.

Utilitarians and formalists may agree on the duty to tell the truth, although they may disagree on the duty not to deceive. Cases have been made for "benevolent deception," when intentional deception is morally justifiable if its primary intent is for

the benefit of the patient. In such cases, telling the truth may be a violation of *beneficence and nonmaleficence.* Others argue that deception, benevolent or not, is morally wrong, because it violates respect for persons and trust. Ultimately, the professional-patient relationship erodes. Respect for persons involves acknowledging patient autonomy to know or not to know the truth of his or her particular situation. It is important to ask individuals how much they want to know.

It is generally agreed that *confidentiality* should prevail in professional-patient relationships. With minors, confidentiality extends to the parents or legal guardians. Part of the implied contract is that information gained by both parties will be kept confidential. From the earliest days of medicine, protecting the patient's privacy has been a fundamental tenet of clinical practice. There are, of course, instances in which confidentiality is justifiably breached. It is at this point that many ethical dilemmas arise.

Breach of confidentiality may be morally and legally justified to protect the life of a patient or the lives of others who may be endangered. The value of human life overrides the relationship, but the professional should be able to demonstrate clear danger before violating a patient's privacy. This also may be seen as a violation of autonomy. "The health care professional's breach of confidentiality thus cannot be justified unless it is necessary to meet a strong conflicting duty."[17]

Obviously, health care professionals can be torn between conflicting moral obligations, such as between the patient and society. Such instances in which a breach may be justified include child abuse and neglect and certain communicable diseases. However, there is strong justification among both utilitarians and formalists for maintaining the privacy and confidentiality of patient information. Most important, the genuine integrity of the professional-patient relationship will be enhanced and preserved when confidentiality, like fidelity and truth telling, is respected and upheld. This integrity of relationship then becomes the basis of the decision-making process.

Informed Consent

The issue of valid informed consent is repeatedly raised in the environment of the NICU. All relevant information for a decision must be given. Voluntary consent, free of coercion, by competent persons must be obtained. Information given to parents may be poorly understood for many reasons, including the complex nature of the information; the emotional or physical state of the parents after the birth of a sick, premature, or anomalous infant; physical separation of the parents from their newborn; and feelings of bewilderment and intimidation leading to uncontested paternalism. Indeed, there are indications that valid informed consent is an ideal toward which we work but one that, within the realities of practice, may rarely be obtained. Consent should be sought, however, and open lines of communication and parental education established to facilitate some level of understanding and enable more than token participation in decision making by the parents.[80,109]

One standard that has been put forth in an effort to accomplish informed consent is the "reasonable person standard." It asks, "What would a reasonable person want in this circumstance?"

Both bioethics and palliative care may enact the *reasonable person standard* in multiple ways in the NICU, thus ensuring that more valid informed consent is obtained. First, early contact should be made with the parents or family about the expected prognosis, interventions, and potential meaning of the prognosis. This consultation may be initiated even before delivery. Advanced care birth planning is recognized as vital to delivery room decision making for the at-risk infant. Second, information should be provided by the clinical staff in a factual, compassionate manner. Parents may need continued orientation or reorientation to the NICU environment. This may be necessary, especially for parents who are geographically separated from their infant. Third, phone calls and photographs are important means for parents to maintain emotional involvement with their baby. Fourth, social workers, chaplains, or other support resources should be contacted and used early to manage emotional distress and facilitate communication. Fifth, regular patient care conferences with the parents should be scheduled. This will keep parents apprised of the newborn's status and will keep the staff informed about the parents' level of understanding, perspectives, and values. Additional efforts to communicate must be made at the time of special procedures, tests, or therapies to enhance everybody's understanding and the informed consent process.

An integral part of the informed consent process and one that directly affects decision making is the

principle of fidelity, commonly called *truth telling,* as discussed earlier. Issues of what to tell, how and when to tell, and whom to tell become a daily part of the staff's interaction with each other and the families of affected newborns.

In practice, the issue of truth telling is considered an essential component of the professional-patient relationship. Information should be shared among staff members and presented to the family truthfully, compassionately, and without bias. However, it is often best for a single voice (e.g., the attending neonatologist, neonatal nurse practitioner, or primary care clinician) consistently to relate information and interpret facts for families to minimize confusion or misinformation.

Double Effect

The principle of "double effect" asserts that an action may be considered good if the intent of the action is a positive value, even if the secondary effects of the action might be considered harmful if undertaken as the primary goal; further, the good effect should be commensurate with the harm. Double effect is used frequently in the NICU. An example is the use of opioids (morphine or fentanyl) in a newborn for whom there has been a compassionate life-support withdrawal from assisted ventilation; the positive goal is reduction of air hunger and suffering, even at an acknowledged low risk for causing some degree of respiratory depression.

Problems of Uncertainty

A major difficulty in ethical decision making and palliative care is the uncertainty that exists around medical and prognostic outcomes. Supportive palliative care should always be provided. It is difficult to determine what may be in the best interest of the child when the prognosis remains unclear. Even when the prognosis may seem clear, there are always those children who confound science, whose developmental outcomes are far from expected.

Some of the most frequent problems in working with perinatal cases arise as a result of this uncertainty. Parents always ask, "Will my baby be okay when he (or she) grows up?" Answers are often unsatisfying or incomprehensible. In most cases with premature infants, truth telling may compel an answer that, when reduced to its simplest form, says, "I don't know." A statistical approach to answering the question may be "Most babies like yours grow up to be normal" or "Some babies like yours have serious problems." These answers are often followed by a litany of statistical probabilities of each morbidity. Neither approach answers the parents' question of what their particular baby will be like. Such approaches serve to complicate the clinician's relationship with parents over issues such as expertise, veracity, and disclosure. The statistical approach may answer the NICU staff's question of quality of care, but few parents understand such statistics or are willing to apply them to a loved one. Nonetheless, uncertainty is a way of life in many perinatal cases, and this observation significantly compromises the resolution of ethical problems in the NICU. This uncertainty should be incorporated in a holistic palliative care approach.

In considering medical uncertainty, it may be helpful to recognize two general classes of perinatal cases. NICU patients can be generally classified as either premature infants without known anomalies or near-term infants with major anomalies, either syndromic or nonsyndromic. Neonatal deaths, by definition occurring in the first 28 days of postnatal life, are principally associated with prematurity or anomalies and account for about two-thirds of all infant mortality cases (death before the first birthday). For infants with known syndromes or major anomalies, prognoses from the literature are describable with reasonable accuracy. This assists with some certainty.

A detailed review of neonatal outcome is beyond the scope of this chapter, but several conclusions appear justified. First, the infant mortality rate has declined rapidly since the establishment of NICUs, and the major mortality groups are in lower weight and younger gestational age groups.★ Second, coincident with the decline in mortality rate have come improvements in neonatal morbidity (both neurodevelopmental and pulmonary).† Third, the absolute number of normal premature survivors has increased dramatically, and the absolute number of moderately and severely affected survivors appears to have increased as well.‡

Despite this, "extreme prematurity, on the other hand, is characterized by an enormous uncertainty. In these cases, predictions of outcome at birth

★References 14, 33, 40, 58, 87, 93, 99.
†References 3, 34, 67, 82, 90, 100, 113.
‡References 1, 2, 11, 52, 56, 60, 75, 79, 92, 99, 101.

are probabilistic at best."[94] Accordingly, attempts have been made to establish guidelines for treatment of extremely low-birth-weight (ELBW) infants.[7,21,35,37,110] The morbidities in premature survivors are variable in nature, but central nervous system morbidities generally include visual impairment and blindness, speech and hearing impairment, neuromuscular impairment, and serious cognitive impairment.[101] Few premature survivors require long-term institutional care. The combined risk for one or more of these disabilities is in the range of 15% to 20%.[32,50,51,111] Most people agree that these are indeed serious disabilities, with major effect on the patient and family. However, do they justify withholding or withdrawing treatment? If so, under what circumstances?

For perinatal clinicians for whom quality of life is a major consideration, it remains an exceedingly difficult practical problem to predict which particular child will be significantly impaired and in what manner. The predictive value of postnatal evaluations in estimating long-term disability is low.

The intent of raising these questions is to underscore the complexity of ethical discussions as particularly applied to problems in the modern NICU. This in no way reduces the enormity of such problems for the patient, family, health care providers, or society. Technologic advances may resolve old uncertainties but often seem to carry new uncertainties that are equally perplexing. Supportive palliative care should continue to be provided to incorporate these uncertainties and to coordinate care.

Setting Goals

Clinicians should discuss diagnosis, prognosis, and the meaning of the prognosis of the newborn as early as possible for parents to consider their goals for their baby. Parents should be involved, not just informed, in determining the overall goals of treatment based on their values for their child. Treatment goals should be established so that incremental decisions can be made. Decisions toward that end then can be made. Goals expressed by parents may be living a "normal" life, living with a debilitating outcome but without persistent pain or suffering, existence without any notable "quality of life," and so on. Accordingly, treatment goals may be to improve an infant's health, help the infant to maintain the current state of health, or help the infant die with supportive palliative care. Too frequently, decisions are made before the treatment goal is established. The parents and health care team members may be working toward different goals. The physician, health care team, and parents all should be guided by established goals so that beneficial treatment can be offered. There should be a model of shared decision making. The AAP Committee on Fetus and Newborn has stated that although the role of parents in goal setting and decision making must be respected:[7]

> *The physician is not obligated to provide inappropriate treatment or to withhold beneficial treatment at the request of the parents. Treatment that is harmful, of no benefit, or futile and merely prolonging dying should be considered inappropriate. The physician must ensure that the chosen treatment, in his or her best medical judgment, is consistent with the best interest of the infant.*

Treatment and Nontreatment

For parents to be involved in determining overall treatment goals and the decision-making process, they must be fully informed to consent to or refuse treatment for their child. Infants should be treated humanely and with respect in an environment that is conducive to maximum comfort and healing. Humane judgments should be made in determining how infants can most benefit from treatment in any given situation. Palliative care should be provided to all infants at all times.[18] As noted in Chapter 12, sufficient analgesic should be administered to infants having surgery because they can indeed experience physical and psychological pain. Staff and parents should maximize the development of premature infants and offer every possible benefit to them. The nursery environment should be as free from excessive overstimulation as possible (see Chapter 13).

Other perplexing ethical questions arise when the benefit of treatment is unclear. Even the most perfunctory of decisions should be based on the patient's best interest, yet "best interest" is often difficult to determine. Should a baby born with anencephaly be resuscitated or receive life-sustaining interventions solely for the purpose of organ transplantation? Should an ELBW infant receive aggressive ventilatory therapy? Should an infant with trisomy 18 be treated with aggressive life support or surgery? Medical and ethical decisions involve considering not only what kind

of treatment serves the patient's best interest but also whether the treatment is appropriate at all. Limited or nontreatment decisions are agonizing and regularly result in ethical and palliative care discussions. A nontreatment decision is sometimes incorrectly called withholding or withdrawing *care*. Only *treatment* may be withheld or withdrawn. *Care* always should be provided, whether curative or palliative.

"Nonbeneficial" Treatment

The concept of "nonbeneficial" (or futile) medical treatment may be as perplexing as the concept of benefit. It does, however, deserve attention, because there are increasing circumstances in which treatment may be considered to be nonbeneficial and thus withheld or withdrawn. There is no ethical obligation to offer nonbeneficial treatment, yet there is no one definition of "nonbeneficial."

Most often, judgments about benefit are based on medical or physiologic data. It may be medically nonbeneficial to resuscitate an infant under certain conditions, because the treatment cannot alter the course of the illness or problem, yet there are psychological, social, and religious reasons that such treatment might be offered. If, because of the treatment, the family has time to hold the infant and say goodbye, the resuscitation may not be considered by them to have been nonbeneficial. Of course, the opposite is also true; that is, what may not be physiologically nonbeneficial may be considered to be nonbeneficial by the family or surrogates based on religious or other reasons. Again, there is no ethical obligation to offer nonbeneficial treatment. It is possible to get a medical effect but not a medical benefit. The distinction can be significant. Determination of the appropriateness of treatment should be based on medical benefit as determined by family goals for the patient, which include physiologic, psychological, social, and religious data.[65] By attending to all of these aspects of care, which include staff and family input alike, a determination of what is nonbeneficial therapy and thus what is beneficial therapy can be made.

Research Ethics

A persistent and controversial issue in neonatal care has been the introduction of new therapies or procedural interventions into the NICU without appropriate research into their safety, efficacy, net benefit, and long-term outcomes for those critically ill infants who receive them. Appropriate studies in animal models ideally are followed by randomized, controlled clinical trials in human newborns (see Chapter 1). Extracorporeal membrane oxygenation, high-frequency ventilation, and recombinant erythropoietin all have been examples of interventions that crept into neonatal care before controlled trials were conducted. In recent years, the use of glucocorticoids either to enhance fetal lung maturity antenatally or to prevent or treat bronchopulmonary dysplasia postnatally is an example worth evaluating.

Although the benefits of a two-dose regimen of antenatal steroids was demonstrated in 1972,[71] the development of recent practice patterns in which multiple doses of steroids were used over successive weeks of pregnancy was unsubstantiated by randomized clinical trials designed to address the efficacy or safety of such practices. Subsequently, the National Institutes of Health held a Consensus Development Conference and published a statement advising that repeat courses of steroids not be used routinely.[84] Research conducted after these practice patterns were established demonstrated increased maternal infection and suppression of the normal hypothalamic-pituitary-adrenal axis and both fetal and neonatal decreased somatic and brain growth, adrenal suppression, neonatal sepsis, chronic lung disease, and increased mortality rate. In addition, neurodevelopmental outcome studies suggested an increase in psychomotor delay and behavioral problems.

The acute, seemingly beneficial effects of administering systemic steroids to newborns with lung disease, however, were not met with significantly improved mortality rate or long-term outcome. It is also associated with a number of acute side effects (e.g., gastrointestinal perforation, hypertension, hyperglycemia) and possible long-term harmful consequences on lung and central nervous system function (see Box 23.13). Studies that caution about the poor postnatal brain growth among some ELBW NICU survivors raise additional concerns about the wisdom of adding risks associated with steroid treatment to an already at-risk newborn. Research into the future use of steroids in premature infants should be well designed and adequately powered to provide answers and should include an evaluation of long-term neurodevelopmental outcome.[44]

Recent concerns have been publicly aired in the lay and professional media over the conduct of neonatal research, the adequacy of the informed consent process for parents of newborns, and the overall safety and conduct of neonatal research.[53] As stated by Lantos, "the clinical judgment of conscientious and knowledgeable physicians is only as good as the evidence on which it is based."[63] This matter is clear, and the requisite evidence-based practices we all seek require carefully acquired evidence from well-conducted and safe studies (see Chapter 1). But there are other lessons in the SUPPORT legacy, not the least of which is the need for transparency and honest communication of what we *do not* know—hence the difficulty in explaining to parents and colleagues alike that the involvement in clinical research may or may not affect the risk of bad outcomes—or good! And that is why the research is being done.[64] Parents are vulnerable, their babies are critically ill, and everyone in the NICU—including clinicians—is hopeful. But these truths can make the informed consent process, and the conduct of research, challenging in seemingly unapparent ways.[78,80,109] If parents of critically ill children respond to the challenges present in decision making for clinical care by wrestling with multiple influences beyond any simple explanation or exchange of clinical information and attendant risk/benefit analysis, they likely are no less inclined to do the same in the context of clinical research.[23]

DECISION MAKING IN THE NEONATAL INTENSIVE CARE UNIT

In the NICU, decisions of serious proportion are encountered regularly, based on medical facts and nonmedical values.[85] Both bioethics and palliative care advocate for a model of shared decision making aligning values with the expected outcome for the infant. From the moment of birth, and in some cases even earlier during the antenatal period, a foremost issue is that of determining the appropriate level of intervention treatment of sick or anomalous newborns. Entire texts have been devoted to this issue.[62,108] Primary concerns are when to treat, when and how to intervene, when to limit intervention, and who should be involved in the decision-making process.[74]

A frequently encountered treatment problem requiring attention, other than the much-publicized anomalous infant, is the extremely premature or VLBW infant whose course is marked by slow or absent progress despite appropriate and seemingly heroic intervention. Together, these may portend a guarded or very poor prognosis.

These cases may prompt "quality of life" and "ordinary versus extraordinary treatment" discussions. The President's Commission[88] noted that "there is no basis for holding that whether a treatment is common or unusual, or whether it is simple or complex, is in itself significant to a moral analysis of whether treatment is warranted or obligatory"—a view that had been voiced previously by moral philosophers. The AAP has published a strategy for the initiation and withdrawal of treatment for high-risk newborns.[4,6] General recommendations include the importance of ongoing evaluation, parental participation, establishing the goals of humane care, and upholding the best interest standard seeking to benefit the infant: "It is inappropriate for life-prolonging treatment to be continued when the condition is incompatible with life or when the treatment is judged to be futile."[4,6] The AAP Committee on Bioethics further "supports individualized decision making about life-sustaining medical treatment for all children, regardless of age. These decisions should be jointly made by physicians and parents."[4,6] If we are honest about our professions, we must realize that "quality of life" is what we are all about. Health care professionals are entrusted by society to advance the health and well-being of the mind and body of all persons so that they can lead their lives and function as part of the human family, individually or collectively. No individual is capable of establishing what is an acceptable "quality of life" for all persons in all circumstances. Each case requires our collective efforts to facilitate the best decision for that particular patient.

Steps in Ethical Decision Making

The approach to decision making should follow a method that clearly demonstrates the practice of applied clinical ethics and supportive palliative care. Palliative care also includes the principles of ethical decision making in supporting decision makers as they make informed decisions regarding the care that the infant receives. The goal of both applied ethics and palliative care is to make the best decisions

BOX 32.1 APPROACH TO ETHICAL DILEMMAS IN NEONATAL CARE

1. Consider who is involved in making and implementing the decision (family, guardians, clinicians, society).
2. Decide who will make the final decision. Is referral to an ethics committee indicated?
3. Clarify all medical facts within the case; consider indications, alternatives, and consequences of each action or inaction.
4. Understand significant human factors and values (for patient, family, and health care team).
5. Identify the ethical dilemma or conflict.
6. Make a decision:
   a. List options as solutions to the problem.
   b. Weigh and prioritize values.
   c. Make a decision.
7. Check for moral and rational defensibility.

Data from Brody H. *Ethical Decisions in Medicine.* Boston, MA: Little, Brown; 1981; Francoeur RT. From then to now. In: Harris CC, Snowden F, eds. *Bioethical Frontiers in Perinatal Intensive Care.* Natchitoches, LA: Northwestern State University Press; 1985.

for and with a particular patient. Such a decision requires first that a decision maker be determined. The decision maker, whether a parent, health care provider, or other, must understand his or her own (1) relationship to the patient (or family), (2) interpretation of ethical principles and values, (3) theoretical basis of ethics used (e.g., utilitarian, deontologic), (4) source from which morality is derived, and (5) palliative care goals.

Ethical decision making involves identifying and working through substantive issues based on values and goals, resulting in a decision.[103] Implementing decisions requires determining who will decide, by what criteria they will be allowed to do so, and subsequently how the decisions or actions are to be implemented.

Box 32.1 presents the essential steps to decision making in neonatal cases in which a dilemma exists. Consider all involved values and possible solutions to the problem, realizing that alternative solutions may uphold different principles and result in different (positive or negative) consequences. Options that may appear acceptable to the family may be unacceptable to the health care team, or vice versa. There may be societal (legal) constraints on certain actions. In some instances, only one option will be consistent with the rules and principles to which the decision maker subscribes. Other options may present apparent conflicts between competing values or result in unacceptable consequences. In a decision, there will probably be some give and take. A shared decision-making model embraces all parties and viewpoints. Some priority must be assigned to a certain set of values, rules, principles, or resultant effects of any action or inaction. A decision should be made in light of these issues. This process need not always be invoked in full. Often, when the case is carefully dissected and medical facts, values, treatment alternatives, and expected prognoses are revealed, issues that at first seemed in question are clarified, and it becomes apparent that no real dilemma exists.

Good ethics, then, starts with good facts and effective communication. A viable patient-professional relationship that clarifies facts (taking into account uncertainties and the difficulties of prognosticating), human values and feelings, and the interests of all relevant parties is essential to ethical decision making. Decisions made should reflect a moral choice that is beneficial to the newborn as determined by the established, informed decision makers.

Although it may be arguable whether the patient is the neonate, family, or another societal group, it is prudent to develop a consensus wherever possible and thus minimize conflict among the interested parties. Efforts should be made by interdisciplinary team members to involve the parents and family early in the care of their child and listen carefully to their values, goals, and dreams. Clinical information should be presented sensitively and thoroughly. These efforts may help minimize the stresses on the parents and prepare them to participate in decision making about the care of their child. These efforts will also assist staff as they participate with the parents in the decision-making process. With careful attention to the needs of patients, families, and staff, many conflicts can be resolved at an early stage before positions are hardened and emotional investment is high.

In most cases, consensus is reached. In a minority of cases, conflict is unavoidable. In some cases, medical care raises issues that are highly controversial either within the group of clinicians providing care or in the broader context of societal problems. In many cases, the family is far from homogeneous in its expression of wishes. Many parents are young and in the process of achieving independent adulthood with well-developed values. Single-parent families are not uncommon. The birth of a critically

ill infant may serve as a focus to crystallize disagreements between spouses or may aggravate conflicts between the parent (or parents) and the extended family. In such cases, a more formal process, such as a formal family care conference, appeal to an ethics committee, or even involvement of the legal system, may help resolve or minimize conflicts of values. It is preferable, however, that decisions be made by involved parties as close to the bedside as possible.[98]

Proxy Decision Makers

In dealing with newborns who are, by their very nature, incompetent and cannot make decisions for themselves, value conflicts must be resolved with the input of a proxy or surrogate decision maker acting on the infant's behalf. This may be the parents, a family member, a friend, a guardian ad litem, or the physician. To be considered a valid surrogate, the person should be competent, knowledgeable of integral values of the patient or family, free from conflicting interests, and without serious emotional conflicts in dealing with the case.

Society has for many reasons allocated to the parents the primary authority role in collaboration with health care providers in making decisions about their newborn's care. In most instances, the parents are best suited for deciding such matters and have the infant's best interest in mind. They are usually present when possible, are concerned for their infant's well-being, and are willing to hear the facts of their infant's condition and learn about needed therapies. Of all people, they also know best the values of the family culture or environment in which the infant will be raised.

Yet parents may be less understandably overwhelmed at times, both physically and emotionally exhausted, and baffled or intimidated by the high-technology environment of the NICU and the complexities of their infant's care. Amid feelings of grief, fear, anxiety, and wonderment over their premature or anomalous infant, they may be uncertain of their proper role and responsibilities as parents. Some parents show signs of acute stress disorder and posttraumatic stress disorder. Health care providers should give daily updates on the infant's condition and anticipated course. Parents' needs for emotional support and avenues to both vent their frustrations and explore their concerns over economic, marital, family or sibling, and career effects of their predicament make resources such as nurses, social workers, and chaplains essential in providing assistance to allow them to participate in goal setting and difficult decision making. Occasionally it will be necessary to assess the level of parental competency in assuming the role of surrogate, recognizing when additional help or support for them is needed to fulfill this role.

Reliance on clinicians as decision makers is yet another option. Clinicians know and understand the complexities of the medical condition and treatment more than parents do. They may be more objective about individual cases and are not emotionally overwhelmed, as the parents might be. Also, based on experience, they offer a perspective of effectiveness of treatments and can be consistent in treating similar cases.

However, clinicians also may encounter problems when they act as the principal decision makers. Although their knowledge of medical facts is the most complete of all persons, it is at the same time, unfortunately, incomplete. Accurate diagnoses and certainty in prognoses are elusive at times. Medical knowledge does have limits. Statistics are helpful for groups of similarly affected patients, but individual outcomes are difficult to predict. Further, although physicians have an advanced degree of specialized information and knowledge, they do not necessarily possess any more moral expertise than that of parents or others.

Treatment versus nontreatment decisions are ultimately moral, not simply medical, decisions. These decisions are weightier than most clinical decisions that clinicians make. More is involved than a rote, rational process employed in isolation from the family or health care team. The clinician must contend with his or her own values and emotions, as well as the medical facts, in each individual case. He or she must facilitate parental and health care team communication and interaction and ultimately order the level of intervention.

Fortunately, physicians and nurse practitioners do not work in isolation from the health care team when making decisions about patients. Nurses, child life workers, social workers, and chaplains are vital members of the decision-making team. A potential problem with each of these clinicians as surrogates is that a conflict of interest may exist between them and the infants for whom they are deciding. Members of the health care team may be biased toward the prolongation of life, have preconceived and strong biases about euthanasia, or be influenced by issues unrelated to the infant, including

advancement of care, financial issues, or societal issues. Hence they may not fully consider the best interest of the patient or the values of the involved family. In contrast with parents, they do not live with the results of their decisions and actions. Also, consistency in their application of principles to similar cases may be lacking, and they may give in to strong pressures (real or perceived) exerted by the law or very assertive parents.

Various factors should contribute to minimizing the potential problems in parents and health care professionals reaching morally defensible decisions in the best interest of the premature or anomalous infant. The professionalism of health care team members who are committed to serving the health and interests of their patients is a foremost consideration that serves this purpose. A sense of duty leads these professionals to assist families in achieving their life goals through facilitating open communication and discussion of their varied concerns. A great sense of personal and professional satisfaction may be derived by helping families accept and deal with their emotions, questions, and concerns for their infant and their own circumstances.

For many years, hospital ethics committees have facilitated ethical decision making for sick neonates. Generally, their roles are to provide education, policy interpretation, and clinical consultation. Clinically, ethics consultants function to clarify the ethical dimensions of various treatment options and serve in an advisory capacity only. They do not make clinical decisions. Clinical decisions are best made at the bedside by parties who are involved with the sick infant. At times, however, clinicians and parents need clarification and support. Ideally, ethics committees facilitate the resolution of any conflicts between parents and clinicians in matters of treatment. They help work through ethical aspects of treatment decisions. One important role they play is to improve effective communication between staff and families. Finally, they may prove to be a safeguard for infants for whom parents and professionals are working toward an end that may be perceived as contrary to the infant's best interest.

Surely, much reflective thinking should be invested in our decisions, as individuals, parents, or members of a committee. However, a small number of cases will proceed beyond institutional review to a court. Every effort should be pursued before going to court. Courts may employ many of the criteria for being proxies. They can ensure that all relevant facts are presented and considered, and judges are capable of exercising unmatched control of data collection, investigation, questioning of experts, and seeking of alternative solutions. A judge also can appoint a guardian ad litem to be the patient's advocate when necessary.

There are at least a few weaknesses in courts as proxies. They are removed from the NICU and have no contact with the case, patient, staff, or family whose problem they are deciding; hence they are more remote than other possible proxy decision makers. Working through cases may be time-consuming, which may result in additional problems, changes in pertinent facts, or prolongation of suffering. Sometimes the consequences of court proxies are that they become the decision maker for the infant instead of the parents and/or clinicians. Although the best interest of the infant may override the rights of the parents, this can result in the rights of the state's legal system overriding the rights of the parents and even the best interest of the infant.

Standard of Best Interest

The best-interest standard has been advocated by the President's Commission and others seeking to accomplish valid moral decision making in difficult neonatal cases.[68,81,88,91] We are obliged "to try to evaluate benefits and burdens from the infant's own perspective."[68] This standard requires a balance of beneficence, nonmaleficence, and justice. It is accepted in the case of newborns over "substituted judgment." Because newborns are, by definition, never competent, substituted judgment can only be applied hypothetically. The best-interest standard is accepted as the best method available for parents and clinicians to decide on behalf of newborns.

The potential for self-seeking by the decision maker is easy to understand and has been recognized. The interests of parents, siblings, clinicians, hospital staff or administration, and society may all seem to compete with those of the newborn. But the interests of others—be they emotional, economic, or otherwise problematic—cannot justifiably override those of the patient[12,61] based on the actual or potential personhood of the critically ill neonate. Individual or societal problems or perceived burdens generally are not viewed on the same moral plane as a person's claim to life.

Certainly some cases stretch the best-interest standard to its limits. Cases of protracted treatment

with uncertain prognoses beg the question of quality of existence (in which nonmaleficence is the principle of concern) and require consideration of more than mere suffering and pain.[61] Indeed, in the words of Arras,[12] "Sometimes circumstances may be so extreme and the consequences so dreadful that the priority of justice can no longer be maintained." In this sense, we have to find the best balance of beneficence, nonmaleficence, and justice.

We also must consider other morally relevant concerns of neonates who may be doomed to brief lives with less than recognizably "human" existence. Human capacities (e.g., ability to think, be aware of self, relate to other people) may be different from biologic human life. The preservation of biologic human life bereft of the benefit of distinctly human capacities is controversial and has been challenged in quality-of-life decisions.[12,36,62,72,108] Walters[107] has written of the "proximate personhood" model. Arras[12] suggested the "relational potential standard" (Does this child have the ability, or potential, to relate to physical space and time and to communicate to others?) as a means to address these concerns more aptly than the "misapplied best interest standard," calling on society itself to inquire "into the conditions of valuable human life."

Priority should be given to attempts at effecting a cure in these ill infants. Whether or not a cure can be achieved, patient comfort should be sought. Some maintain that life itself may not always be an absolute good; thus it may be morally justifiable to withhold or withdraw futile treatment associated with inhumane risks or harms that would prolong dying. Mitchell, while a member of the American Nurses Association Committee on Ethics, has stated[83]:

> *Some infants are so premature and underweight, so profoundly impaired, so hopelessly diseased, or so severely asphyxiated that their foreshortened lives are full of misery for them and those around them. For infants who are so impaired that medical therapies are futile or would only prolong suffering, invasive medical procedures and surgery are morally, as well as medically inappropriate.*

She calls on nurses to shift their focus in such cases to "seek primarily to provide comfort, relieve suffering and help a grieving family."

Creating an Ethical Environment

Ethical decisions do not happen in a vacuum. Environments should exist that promote ethical behavior and deliberation and include integrated palliative care. Such environments should be institutional (the NICU, the hospital, the community, social and political structures) and attitudinal. In effect, these environments portray an ethical culture of the institution. Attitudes include those in which families and staff are empowered to express their opinions and engage in the decision-making process, all voices are valued, information is openly and honestly shared (including uncertainties), respect for all individuals is upheld, and the predominant concern is to benefit the patient, whether that be minimizing overstimulation of patients, administering the appropriate analgesic, or providing appropriate palliative care. Routine ethics rounds or ethics committee and palliative care consultations, along with family care conferences and generally good family communication, are recognized means of enhancing such an environment in the NICU. Yet none of these replace the responsibility of all staff members consistently to promote an overall ethical milieu in the NICU in which ethical practice and integrated palliative care are the standards of care.

Recent literature has focused on the concept of moral distress, particularly among nursing staff. Moral distress occurs when conflict exists between personal values and treatment being given. The most commonly reported cause of distress is following orders to support patients at end of life with advanced technology when palliative or comfort care would be, from the perspective of the caregivers, more humane.[42] A more recent study among clinicians in NICUs and PICUs found that moral distress was positively associated with burnout and uncertainty.[66] Among the clinicians surveyed, nurses reported higher moral distress intensity than physicians. Only in nurses was moral distress positively associated with more years of ICU experience and uncertainty about whether their care benefited the child.[66]

Some clinical settings hold weekly staff conferences for education, clarification, and open and informed communication among staff members. Information can be clarified, and family care conferences can be arranged. When the NICU staff enter into these dialogues with parents or when an ethics consultant joins in, it enhances the ability to clarify the goals of care and understand the present condition of the patient and potential future concerns of all parties as they view the patient.

ETHICS COMMITTEE OR PALLIATIVE CARE CONSULTATION?

Generally in practice, it is preferable to keep the shared decision-making responsibility within the professional-patient relationship. In the vast majority of cases, members of the health care team and the parents do have the infant's best interest in mind. Yet in view of the vast dimension and difficulties of some of the required decisions, many clinicians will consult with a hospital ethics committee (HEC), infant bioethics committee (IBC), or palliative care team (PCT). Some institutions have all three of these committees—the IBC falling under the HEC—but many do not have an IBC, PCT, or palliative care consultant. For those who have both ethics and palliative care consultation available, it is reasonable to question whom to call, and when, for consultation. These intersecting processes enhance clinical care. When there is agreement about a treatment plan, both the ethics committee and palliative care might be consulted for confirmation of that plan. When there is a dispute about a proposed course of treatment, the HEC (and/or IBC) may be consulted for clarification of ethical principles, values, and various treatment options that would be consistent with ethical and legal standards.[59] The PCT or consultant may also be used for consultation on goals clarification and the development of a comprehensive palliative treatment plan to include comfort measures, specific symptom management, and support to the infant, family, and caregivers. Palliative care provides comprehensive management of physical, psychosocial, spiritual, and existential needs of patients and families facing life-limiting illness.[6]

The stimulus to the establishment of IBCs in the United States was the controversy over and death of Baby Doe in Bloomington, Indiana, when society (and government) became acutely aware of the moral issues surrounding what many perceived to be wrongful nontreatment of a handicapped newborn.[86] Resulting government regulations, along with AAP policies, have focused on the importance of ethics consultation to promote quality decisions about treatment of ill newborns. HECs, composed of members from different disciplines, are a resource for consultation and advice. They are not a decision-making body, although some groups are moving toward a consensus model. Different committees have different procedures.[45,68,81] Ethics consultation should be sought for values clarification and decision making. Committee functions and responsibilities may include (1) offering counsel and ethical review, (2) educating hospital personnel, (3) retrospectively and prospectively reviewing pertinent government guidelines, and (4) developing appropriate institutional policies. In most institutions, *anyone* involved in a particular case may request a consultation from the HEC.

Palliative care is both a philosophy and an approach to care delivery.[6] It focuses on comprehensive, compassionate comfort and support. Many domains of palliative care are appropriate for all patients. Palliative care may, however, be especially important—and become the predominant paradigm of care—when an infant is on the threshold of viability, is gravely ill or has an uncertain outcome, or is dying despite appropriately applied intensive care measures.[18] Many clinicians are comfortable and skilled at providing palliative care to their patients and families, and others prefer consultation with a palliative care specialist. Palliative care consultation should be considered (1) any time there is a question about comfort or support, (2) any time there is a question about pain and symptom management specific to the realm of comfort and end-of-life, and (3) when an infant has a life-threatening condition or is dying despite life-sustaining interventions. Palliative care services generally work collaboratively with HEC members and the clinical team to ensure maximum comfort and minimal suffering for newborns whether their conditions are improving or worsening. Such consultations, along with good family communication, enhance patient care and the ethical environment of the NICU.

COMMUNICATING WITH FAMILIES

The most important element in communicating with families is listening to them. Indeed, consistent, sensitive, and thorough communication of clinicians with families is essential to good patient care. Active listening, clarifying treatment goals, and addressing emotional stress of parents and families are import tasks at the heart of palliative care and bioethics. The more complex the medical situation, the more crucial it is that parents receive consistent information. This requires concentrated efforts among staff to clearly communicate the care plan within the

interdisciplinary team to facilitate clear, consistent communication with the parents. Parents often are confused by the various prognostications offered by multiple subspecialists and cannot synthesize the data into a "larger picture" of what is happening to their baby. Yet in the urgency to communicate information, clinicians sometimes forget to listen to the grief, fears, and concerns of parents for their child (see Chapters 29 and 30.) These feelings can profoundly influence decisions that are made and how they are made. Ethics and palliative care must also consider the range of human emotions involved in life-and-death issues, not just clinical information. What parents would not be distraught over the premature birth of their infant? Overwhelmed by their severely disabled infant? The prospect of lifetime rehabilitation? The reality or prospect of suffering? The prospect of death of their newborn?

Clear, consistent communication with parents is essential, because parents play a vital role in the decision-making process. They, along with the infant, are the most affected.[19] No matter what their religious or sociocultural background, almost all parents experience shock and grief over their infant's need for intensive care (see Chapters 29 and 30). They deal with this in better and worse ways. For many parents, the ability to participate in ethical decision making is impaired while they are in such an acute stage of shock. Usually, prenatal diagnosis of anomalies gives parents time to adjust to their baby's condition before birth or before decisions have to be made. This adjustment time can be most valuable. To participate in shared decision making, particularly decisions about withholding or withdrawing treatment, parents must have achieved some degree of emotional reorganization and acceptance. Interdisciplinary team assistance in helping them move from emotional disorganization to reorganization is crucial to further decisions that should be made. At this point, parents may be better able to absorb medical data, ethical values, and principles. Although a theoretical difference may not exist between withholding withdrawing treatment, there is a large emotional difference. The sound clinician, as well as the ethicist and palliative care provider, must be sensitive to this distinction.

Choices about treatment and nontreatment do affect the grieving process. Questions such as "Am I just prolonging suffering by keeping her alive?" are countered by "Am I not giving her a chance and playing God by allowing her to die?" Duff and Campbell[34] report that families experienced "a normal mourning for their losses" after allowing their seriously ill infants to die. What remains for many parents are doubts that their choice was correct. For some, decisions based on certain religious principles or other value criteria offer moral justification of behavior that assists in the mourning process. For others, the justification may be logically but not emotionally clear. In these instances, grieving can become more complex and difficult.

A valuable role of an ethics committee and/or ethics consultant may be to offer input into, if not confirmation of, the parents' decision in a way that helps allay guilt that can interrupt normal grieving. Ethics, although at once highly theoretical and intellectual, must consider that the situations with which it most intimately deals are highly emotional. For parents, the psychological trauma will affect their ethical considerations, and ethical decisions will have further psychological effect. A valuable role of the palliative care provider may be to assist parents and families in their bereavement and other dimensions of emotional strain.

A real value of an interdisciplinary health care team is the particular attention paid to the many complex aspects of a patient's living and dying. When parents are facing the death of their baby and the goals of care become more palliative than curative, the entire team may be involved in providing palliative care to assist them. Nurses and physicians, social workers, chaplains, and psychologists may all be intimately involved with monitoring the patient's comfort level and deteriorating course and with comforting grieving parents. Baptisms (when appropriate) and especially funerals are important ritualistic ways of organizing the meaning of the traumatic event. The entire staff should encourage parents to offer all that they can to their dying infant. They should provide active palliative care—maximum comfort for the patient and maximum support to the family. Helping patients and families cope with death is a privilege. It can be personally and professionally satisfying, and ultimately immeasurably helpful to everyone involved, to enter emotionally into this process. Often care of the living means care of the dying.

Good communication among staff members is also important. The effect on the health care team members of helping an infant die also should be recognized because their concern and involvement with the infant usually are significant. Helping someone

through the dying process can be a difficult, though rewarding, experience. In such instances, professionals may agree with the decision (preferably the parents') to withhold or withdraw treatment. Professionals may also disagree with the decision but may place a higher value on the parents' autonomy to decide than on the decision itself. Respecting this, they may abide by the parents' wishes for their infant. No one should be forced to compromise personal or professional integrity, however, and in cases in which one's ethics or integrity is being violated, the case may be transferred. Staff support is essential to address bereavement and to alleviate any more distress that may be occurring. Preferably, professionals can learn about the range of ethically defensible options and can support the parents in choices different from their own.

How does the clinician discuss such sensitive issues, especially dying, with parents? In many ways. First and foremost, listen to their thoughts, feelings, and concerns as they express them. Clinicians should consider the vulnerability of parents who are frequently overwhelmed by the delivery, their baby's condition, and other related stressors. Clinicians should be compassionate not only in their listening but also in their communication to parents. What are they feeling, perceiving, wondering about, fearing, hoping for? Box 32.2 suggests some questions to engage in empathic conversation. Such questions are relevant to the parents of the infant whose condition is improving, the infant whose future is uncertain, the infant for whom parents must make agonizing decisions, and the infant who is clearly dying. Empathic communication with families is a critical component of good palliative care and the ethical environment of the NICU.

BOX 32.2 SUGGESTED QUESTIONS TO ENGAGE EMPATHIC CONVERSATION

- What do you understand is going on with your baby?
- Who is your main doctor? What has he or she told you?
- Do you have the medical information you need, or do you want more?
- What kind of information would help you the most right now?
- What are you expecting for your baby?
- What do you think your baby feels?
- What do you see your baby doing?
- Who is your very best support person right now?
- Is he or she available?
- What is your greatest concern about your baby?
- What would give you a sense of peace or comfort in the midst of this, if that is possible?
- What is happening at home?
- Faith and beliefs can be very important in the grief and healing process. Is there anything about your faith or beliefs that we should know to be able to take care of you and your baby?
- Who or what is helping you get through this?
- This may be or is the best condition your baby will ever be in. When this is the case, we usually focus on keeping him or her warm and comfortable until he or she dies rather than on curing. How do you feel about this for your baby?
- Our goals in health care are to (1) improve health, (2) maintain health, and (3) help someone die.
- How can we ease this experience for you?

SOCIAL ETHICS

Social ethics reflects on the sociocultural aspects of human life. It considers how individuals as moral agents are accountable for their behavior in social structures and public policy issues. It also can refer to shared patterns of moral judgment. Moreover, it focuses on how social contexts influence individual moral behavior and the range of moral responsibility.

In a pluralistic society like the United States, there is no one social ethic. Some believe in rugged individualism; others believe in equality of opportunity, worth, and treatment; still others believe that we bear mutual responsibility for one another. An underlying concern of most socioethical systems is concern for both the individual and the common good.

In NICUs, bioethics and social ethics converge. Treatment decisions have social implications; societal values influence treatment decisions. As described, government regulations highlight the paradox of societal values about the treatment of disabled infants. These federal guidelines advocate the use of "reasonable medical judgment" in treating disabled infants, yet their effect may be seen as increasing the perceived obligation to treat—to the point of "unreasonable." Through government, society expresses the determination to treat, yet societal commitment to the long-term care of special-needs NICU graduates and families is wholly insufficient. Public funds for such care have been reduced while the expressed urgency for treatment of all babies has increased.

The values inherent in our public policy decisions about initial and long-term treatment are curiously disparate.

After comparing the health care and social policies of the United States with the seemingly more equitable policies of Great Britain and Sweden, Young[112] concluded, "We need to strive for a better balance between aggressive treatment in the neonatal intensive care units initially, and the resources currently allocated for the long-term care of the disabled." Such a balance might include being more selective about aggressive treatment and learning more about prematurity and trying to prevent it. Young continued, "To the extent that society fails to ensure that seriously ill newborns have the opportunity for an adequate level of continuing care, its moral authority, to intervene on behalf of a newborn whose life is in jeopardy, is compromised."[112]

Recognizing this disparity, various community groups have attempted to establish guidelines for standards of care that are fiscally, morally, and medically responsible to guide parents and clinicians in goal setting and decision making. They have recognized the high cost, in every respect, of neonatal and pediatric intensive care. Their impetus has been to determine community "agreed-on" values for treatment and nontreatment of disabled infants to effect a standard of care for the extreme premature, severely disabled, and critically ill infant. Managed care organizations are also assessing the ethics of reasonable care and the limits of treatment to be offered. Although not wholly able to determine "agreed-on" values for treatment and nontreatment standards of care, these community and professional groups have offered important social voices to the complexity of neonatal care.

INTEGRATING PALLIATIVE CARE IN THE NEONATAL INTENSIVE CARE SETTING

The majority of newborns admitted to the NICU are in critical condition and need life-supporting interventions. Parents anxiously wait for any news concerning the life of their newborn infant. Could palliative care be included in the life-supporting care for the newborn? Would parents benefit from the additional support that palliative care offers during this critical time and for the days and weeks that follow? When palliative care is offered concurrently with life-sustaining cure-oriented care and continues throughout the infant's intensive care stay, it is referred to as an *integrated* or *mixed model of care delivery.*[6,28,55]

BOX 32.3 GOALS OF PALLIATIVE CARE PROGRAMS[54]

- Improve quality of life and prognostic understanding of problems/conditions.
- Relieve pain, distress, and uncertainty.
- Help clarify and address patient and family goals and associated treatment preferences.
- Strengthen communication, decision making, and family satisfaction/well-being.
- Coordinate medical and practical needs across settings.
- Reduce resource utilization and costs by matching treatment to patient and family goals.

Palliative care for infants and children emerged from the adult palliative care model and is defined as an interdisciplinary team approach to care for all seriously ill patients and their families. The goals of care are focused on quality of life and the relief of suffering (Box 32.3). By offering an integrated model of neonatal care, parents and clinicians will begin to dispel the prevailing myth in health care and in the public that palliative care can only be offered when death is certain.[28] Palliative care focuses on the needs of the infant and family rather than the prognosis of an infant's condition.

THE UNMET NEEDS OF INFANTS/PARENTS IN THE NICU

In 2003, the Institute of Medicine (IOM) assessed the care received by seriously ill and medically fragile infants and children.[43] Approximately 400,000 infants and children were living with unmet needs related to the conditions, which in the majority of cases, were first identified at birth (neurologic trauma, extreme prematurity, congenital or chromosomal abnormalities). Many of these children spent months in the confines of the NICU receiving the most modern technologically advanced treatment in neonatal care. However, parents and caregivers reported that they received little, if any, support from the pediatric health care community; they

felt abandoned and struggled alone to manage the complex needs of their child. Additionally, the IOM report acknowledged the high incidence of infant death in the NICU as 34% of all childhood deaths occur in the first 28 days of life.[25,43]

After the IOM report, a majority of neonatal peer-reviewed literature focused on improving end-of-life care for neonates and their families.[48,70] Pioneering efforts in neonatal palliative care recognized and attended to the reality that the death of an infant leaves a profound lifelong imprint and trauma on parents, siblings, extended family, and the community. However, these early efforts did not encompass the spectrum of care management that is needed for support of parents and coordination of care from the intensive care setting to the home setting. Confusion continues to exist in the literature and in practice as to which newborns are critical enough to receive palliative care and when is the right time to include palliative care in the infant/family care plan.[20,48,76,102] Often which infant receives palliative care is dependent on the attitude and awareness of the neonatal team.

Currently little evidence suggests a standard of care or established protocol for an integrated model of care delivery in the NICU.[15,30,89] Among 17 articles reviewed, only one reported on an integrated model of care for all neonates admitted at 28 weeks or less of gestation.[89] The integrated model uses a clinical algorithm that clearly integrates palliative and cure-oriented approaches in care.[30] This algorithm was initiated when the newborn was admitted and continued until discharge or death.

Another integrated model of neonatal care includes all newborns at risk for neurologic trauma or birth malformations.[69] This model outlines areas in which palliative and neonatal care interventions overlap in providing comfort and bonding for the newborn and parents, such as swaddling, non-nutritive sucking, light reduction, and minimal stimulation. The addition of palliative care expertise in symptom management, navigating prognostic uncertainty, communication with families, and shared decision making is a more comprehensive approach to caring for neurologically challenged infants, children, and parents.

Recent articles enumerate the goals of neonatal and palliative care from a historical and value-based perspective.[25,57,77] From this perspective, the future of palliative and family-centered care can merge to offer neonates and families the comprehensive support that is needed for families of the medically fragile newborn and continue postdischarge from the NICU. The delivery of palliative care in four US NICUs has been described and is seen by the neonatologists as an intricate and necessary part of the care offered in the NICU, in outpatient clinics, and in the home.[26] Three NICUs initiate the integrated care model on admission to the NICU and continue after discharge. The palliative care team consults and advises the primary neonatal care team. When an infant requires extensive care coordination and community services after discharge or is expected to die, a referral to the palliative care team is made by the primary neonatal team, usually the attending neonatologist. At Children's Mercy Hospital, palliative care clinicians (i.e., nurse practitioner or physician) are part of the neonatal care team, make rounds daily with the intensive care team, and are always available to staff. Coordination of the infants care on discharge from the intensive care setting to the community is facilitated by the palliative care team.

MANDATED PALLIATIVE CARE EDUCATION FOR ALL HEALTH CARE PROVIDERS

In 2015, the IOM published another study that found that the majority of seriously ill children (and adults) were not referred to a palliative or hospice care and most primary care providers were ignorant about the benefits and services offered by palliative care. The IOM report encourages healthcare educators to include palliative care knowledge and skills in basic education of all health care providers. Clinicians and educators are also encouraged to begin the process of integrating palliative care skills into clinic settings where death occurs frequently (i.e., intensive care settings) and for patients with chronic, complex conditions.[55]

NECESSARY SKILLS TO INTEGRATE PALLIATIVE CARE INTO NEONATAL PRACTICE

Box 32.4 lists the requisite attitudes, knowledge, and skills to integrate palliative care into neonatal practice. An integrated model of care delivery also includes a palliative care team specialist (clinicians

who have advanced education and experience in palliative care) who is available to the primary care team as an advisor.[24] In the NICU, the primary neonatal integrated team can seek the advice and consultation from a specialist on the palliative care team for complex symptom management, complicated family situations, or when coordination of care after discharge is required. The specialist team is available to the neonatal staff in a similar fashion as the ethics consultation team.

NICU professionals must evaluate their current practice and make adjustments that include palliative care in the model of care delivery. Most importantly, neonatal clinicians and educators must gather evidence on what works and what does not work with an integrated model of neonatal care, so that each setting can adjust the model for their specific needs. Although an overall shift in how neonatal care providers view palliative care takes time, resources, and often-moral courage, a few committed and dedicated clinicians and educators can create a climate of change that would benefit all infants and their families. A step-by-step process is needed to begin the integration of palliative care in the neonatal intensive care setting (Table 32.2).

BOX 32.4 REQUISITE ATTITUDES, KNOWLEDGE, AND SKILLS FOR INTEGRATING PALLIATIVE CARE INTO NEONATAL PRACTICE

- Advanced communication skills
- Shared decision making
- Awareness of variables pertaining to cultural/religious sensitivity
- Coordinating care across settings and in the community
- Additional pain and symptom management skills

THE COMMUNITY PALLIATIVE CARE SPECIALIST

The integrated model continues after discharge in outpatient clinics and at home. The care coordinator (nurse, social worker, or case manager) is a bridge between the inpatient setting and community pediatric primary providers. Care coordinators support parents in adapting to their role of primary care provider, while ensuring that care continues as prescribed on discharge from the inpatient setting.

Offering palliative care concurrently with life-supporting care to all newborns on admission to the NICU promotes continuity of care from diagnosis to discharge or the death of the newborn. Integrated care acknowledges the family's decisions about care, even when it means that the child is

TABLE 32.2 STEPS IN IMPLEMENTING AN INTEGRATED MODEL OF NEONATAL CARE[55]

STEPS FOR IMPLEMENTATION	COMMENTS
Step 1: Identify champions (Neonatal Palliative Care Champions)	Neonatal educators and clinicians committed to the goal of integrating palliative care into neonatal care-delivery model. Begin by exploring domains of care delivery:[55] 1. Patient care 2. Organizational concerns—legal, economic 3. Education 4. Research
Step 2: Create a mission statement	Mission statement communicates the goals of an integrated model of care that are specific to the setting. Mission statements are usually written in terms of the philosophy and values of the parent organization. Encourage all neonatal care providers to become involved in focus groups that explore knowledge, attitudes, and priorities of staff toward creating an integrated model of care.[106]
Step 3: Examine how to disseminate knowledge, skills, and attitude	Develop concrete and sustainable change in how palliative care is integrated in caring for infants/parents. How can the knowledge, skills, and change of attitudes begin to take shape for neonatal clinicians in the setting?

indefinitely dependent on life-prolonging interventions. An integrated model of neonatal care recognizes the profound and long-term emotional impact that a child's complex condition and/or death has on a family unit and a community.

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End-of-Life Nursing Education Consortium pediatric palliative care training program, from the American Association of Colleges of Nursing. Available at: www.aacn.nche.edu/ELNEC/Pediatric.htm.

End-of-Life Physicians Education Resource Center. Educational resources for physicians (includes pediatrics). www.eperc.mcw.edu.

Initiative for Pediatric Palliative Care. A comprehensive resource on educational resources including videotapes and other resources. Available at: www.ippcweb.org.

Resolve Through Sharing (RTS). Available at: www.bereavementservices.org/resolve-through-sharing/conferences-and-workshops/perinatal-death-training.

Together for Short Lives. ACT—clinical pathways for perinatal/neonatal palliative care. Available at: www.acponline.org/clinical-information/clinical0resources-products/end-of-life-care-physician-education. Accessed September 16, 2019.

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NEWBORN METRIC CONVERSION TABLES (CONT'D)

Length

INCHES TO CENTIMETERS

1-inch increments Example: To obtain centimeters equivalent to 22 inches, read "20" on top scale, "2" on side scale; equivalent is 55.9 centimeters.

INCHES	0	10	20	30	40
0	0	25.4	50.8	76.2	101.6
1	2.5	27.9	53.3	78.7	104.1
2	5.1	30.5	55.9	81.3	106.7
3	7.6	33.0	58.4	83.8	109.2
4	10.2	35.6	61.0	86.4	111.8
5	12.7	38.1	63.5	88.9	114.3
6	15.2	40.6	66.0	91.4	116.8
7	17.8	43.2	68.6	94.0	119.4
8	20.3	45.7	71.1	96.5	121.9
9	22.9	48.3	73.7	99.1	124.5

One-quarter (¼) inch increments Example: To obtain centimeters equivalent to 14¾ inches, read "14" on top scale, "¾" on side scale; equivalent is 37.5 centimeters.

	10–15 INCHES					
	10	11	12	13	14	15
0	25.4	27.9	30.5	33.0	35.6	38.1
¼	26.0	28.6	31.1	33.7	36.2	38.7
½	26.7	29.2	31.8	34.3	36.8	39.4
¾	27.3	29.8	32.4	34.9	37.5	40.0

	16–21 INCHES					
	16	17	18	19	20	21
0	40.6	43.2	45.7	48.3	50.8	53.3
¼	41.3	43.8	46.4	48.9	51.4	54.0
½	41.9	44.5	47.0	49.5	52.1	54.6
¾	42.5	45.1	47.6	50.2	52.7	55.2

NOTE: 1 inch = 2.540 centimeters. Centimeter equivalents rounded one decimal place by adding 0.1 when second decimal place is 5 or greater; for example, 33.48 becomes 33.5.

Weight (Mass)

POUNDS AND OUNCES TO GRAMS

Example: To obtain grams equivalent to 6 pounds, 8 ounces, read "6" on top scale, "8" on side scale; equivalent is 2948 grams.

	POUNDS														
OUNCES	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
0	0	454	907	1361	1814	2268	2722	3175	3629	4082	4536	4990	5443	5897	6350
1	28	482	936	1389	1843	2296	2750	3203	3657	4111	4564	5018	5471	5925	6379
2	57	510	964	1417	1871	2325	2778	3232	3685	4139	4593	5046	5500	5953	6407
3	85	539	992	1446	1899	2353	2807	3260	3714	4167	4621	5075	5528	5982	6435
4	113	567	1021	1474	1928	2381	2835	3289	3742	4196	4649	5103	5557	6010	6464
5	142	595	1049	1503	1956	2410	2863	3317	3770	4224	4678	5131	5585	6038	6492
6	170	624	1077	1531	1984	2438	2892	3345	3799	4252	4706	5160	5613	6067	6520
7	198	652	1106	1559	2013	2466	2920	3374	3827	4281	4734	5188	5642	6095	6549
8	227	680	1134	1588	2041	2495	2948	3402	3856	4309	4763	5216	5670	6123	6577
9	255	709	1162	1616	2070	2523	2977	3430	3884	4337	4791	5245	5698	6152	6605
10	283	737	1191	1644	2098	2551	3005	3459	3912	4366	4819	5273	5727	6180	6634
11	312	765	1219	1673	2126	2580	3033	3487	3941	4394	4848	5301	5755	6209	6662
12	340	794	1247	1701	2155	2608	3062	3515	3969	4423	4876	5330	5783	6237	6690
13	369	822	1276	1729	2183	2637	3090	3544	3997	4451	4904	5358	5812	6265	6719
14	397	850	1304	1758	2211	2665	3118	3572	4026	4479	4933	5386	5840	6294	6747
15	425	879	1332	1786	2240	2693	3147	3600	4054	4508	4961	5415	5868	6322	6776

NOTE: 1 pound = 453.59237 grams; 1 ounce = 28.349523 grams; 1000 grams = 1 kilogram. Gram equivalents have been rounded to whole numbers by adding 1 when the decimal place is 5 or greater.