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Newborn Nursery Care

JAMES A. TAYLOR, JEFFREY A. WRIGHT, AND DAVID WOODRUM

KEY POINTS

- Interventions for newborns during the newborn nursery stay should be limited to those for which the evidence of benefit is clear.
- The short-term and long-term benefits of breastfeeding are clear. The effects on breastfeeding rates from interventions such as formula supplementation, frenotomy, and restriction of pacifiers are controversial.
- Comprehensive guidelines for management of common newborn conditions such as jaundice, risk of sepsis, and hypoglycemia are available. However, whether use of these guidelines improves outcomes is unclear.
- Online aids are available to clinicians to help guide individualized management of jaundice and weight loss in both breastfed and bottlefed newborns.
- With the implementation of universal maternal screening for group B streptococcus and the use of intrapartum antibiotic prophylaxis, rates of sepsis in term newborns have fallen significantly. Online aids are available to guide clinicians in assessing the risk of sepsis.
- Prenatal ultrasonography can diagnose multiple newborn conditions early. However, the natural history of many common ultrasound findings is variable, and the findings may, or may not, represent markers for serious disease.
- Pulse oximetry screening for critical congenital heart disease is recommended for healthy newborns. False-positive rates are low, but there is a substantial false-negative rate.

Two central paradoxes underlie the care of normal newborns. First, although birth is, almost by definition, the most natural of all human processes, until very recently the newborn mortality rate has been extraordinarily high. The second paradox in providing newborn care is that neonates are both the healthiest and the most vulnerable patients in medicine. Recent medical history is replete with examples of the pendulum swinging too far in each direction around these paradoxes. The promotion of scheduled feeding using infant formulas rather than breastfeeding is an example of the overmedicalization of neonatal care. Conversely, recent resistance to treatments that prevent uncommon, but disastrous, conditions represent a denial of the benefits provided by medical care.

Thus optimal care of a normal neonate is an attempt to balance these competing forces. Systems of care should be designed to support the concept that newborns are extraordinarily healthy and require little intervention beyond promotion of breastfeeding. Those interventions for which there is clear evidence that the benefits outweigh the risk should be provided as unobtrusively as possible. Simultaneously, while promoting "natural" care for these newborns, healthcare providers need to be vigilant for the early identification of neonates who are at risk of conditions such as dehydration, sepsis, and severe hyperbilirubinemia.

The goal of this chapter is to provide an evidence base for the promotion of normal newborn care by parents, the rationale for monitoring term neonates for various conditions, a risk–benefit analysis of common treatments, and the significance of common prenatal and postnatal findings. Rather than providing a comprehensive prescription on how to care for these newborns, we hope that the reader will integrate the information provided in this chapter with expert opinion and his or her own clinical experience to determine the proper management of normal newborns.

Initial Assessment

The timing of the initial assessment of a term newborn is dependent on the condition of the newborn and parental preference. In most instances a healthcare professional who is present at the birth will make a general appraisal of the newborn and alert the child's provider if there is an acute problem necessitating an immediate evaluation. Usually the neonate will be healthy, and the assessment can be timed so as not to interfere with breastfeeding, bonding with the family, and routine care.

Before a well newborn is examined, the mother's medical history should be reviewed to identify issues that could affect the care or prognosis of the newborn. For example, a history of diabetes in the mother would lead to glucose testing in the neonate. Maternal drug use should be assessed for possible teratogenic effects, possibility of symptoms of withdrawal in the newborn, and compatibility with breastfeeding. It is important to review the pregnancy history, focusing on estimated gestational age (GA), the results of screening for genetic conditions, and the results of prenatal ultrasound examinations. Perinatal events such as the type of delivery, length of time that membranes were ruptured, and Apgar scores should also be reviewed. Finally, it is critical to review the mother's social history to ensure that the newborn will be raised in a nurturing environment and to identify high-risk situations for which interventions are needed before, or shortly after, discharge from the newborn nursery.

The results of several laboratory tests commonly performed on pregnant women will determine the need for treatment and/or monitoring during the newborn nursery stay. These include maternal HIV and hepatitis B (HBV) surface antigen status and syphilis testing. The mother's blood type, Rhesus (Rh) status, and antibody test results are useful in identifying newborns with an increased risk of hyperbilirubinemia. It is important to note the results of testing for maternal colonization with group B streptococcus (GBS)

and the type and timing of antenatal antibiotic prophylaxis in mothers who are GBS positive.

The newborn's weight, length, and head circumference should be measured shortly after birth and plotted on a standardized chart. Although the most common reason for a significant discrepancy between weight, height, and head circumference percentiles is an inaccurate measurement, a valid discrepancy warrants close clinical observation or testing. Glucose testing may be indicated for newborns found to be small or large for their GA. If the estimated GA of the newborn is inconsistent with the growth parameters, then a formal evaluation by a Dubowitz–Ballard GA assessment may be helpful (Ballard et al., 1979).

When a newborn is examined for the first time, the initial focus is directed toward an overall assessment of the child's health. Observation and auscultation of the chest allow detection of an irregular heart rate, murmur, or acute lung condition such as pneumothorax. The heart rate and respiratory rate can be measured. Normal values for heart and respiratory rate in a newborn are 100–160 beats per minute and 35–60 breaths per minute respectively. Evaluation of skin color may be useful for the identification of a neonate with cyanotic congenital heart disease or pulmonary conditions. If uncertainty exists about the presence of cyanosis, oxygen saturation can be quickly measured with a pulse oximeter. The newborn's tone, general posture, and movement should be assessed; abnormalities may be indicative of an acute or chronic central nervous system problem or sepsis.

Routine Testing

Glucose

The fetal blood glucose level is approximately 70% of that of the maternal level. Following birth and separation from its major energy supply, the newborn's glucose level falls, on average, by a factor of two. Over the next several hours, it gradually increases to a level approaching that of older newborns (Fig. 26.1). The critical factors involved in this normal adaptive process include transient inhibition of the newborn's insulin secretion and an increase in levels of the counterregulatory hormones: growth hormone, cortisol, catecholamines, and glucagon (Adamkin, 2015). The effect of this is to promote liver glycogen breakdown, gluconeogenesis, and tissue lipolysis. Clinical scenarios that might indicate the need for early glucose screening and possible therapeutic intervention include:

- Any newborn who demonstrates clinical signs of hypoglycemia (Box 26.1)
- Newborns of diabetic mothers/large for GA newborns
- Newborns demonstrating intrauterine growth retardation
- Premature newborns
- Newborns delivered after in utero and/or intrapartum distress
- Family history of congenital hyperinsulinism

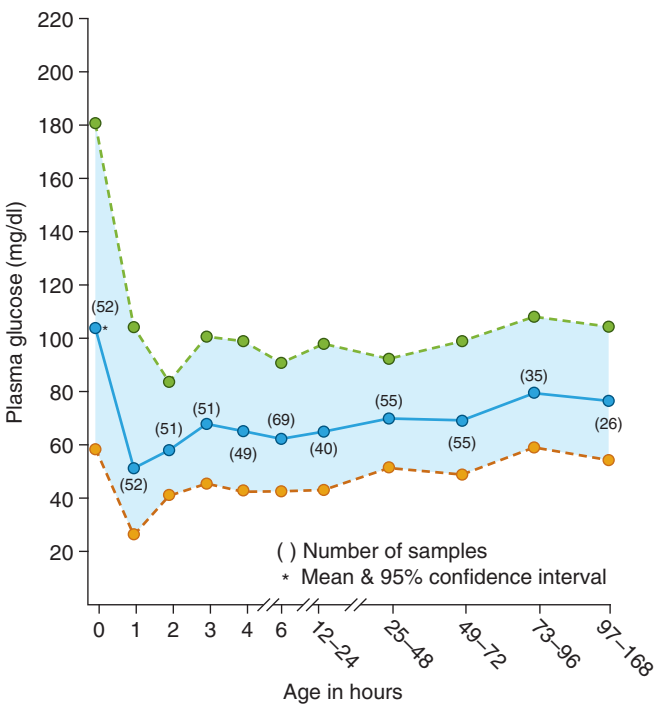
• BOX 26.1 Clinical Signs Compatible With Hypoglycemia

Poor feeding
Lethargy
Hypotonia
Irritability
Tremor
Seizure-like activity
Apnea

- Newborns with midline facial anomalies that might be markers for pituitary deficiency

The treatment approach to confirmed hypoglycemia depends on the glucose level and/or the presence of clinical signs. Newborns with symptomatic hypoglycemia require immediate intervention (Committee on Fetus and Newborn and Adamkin, 2011). However, while it is apparent that severe and symptomatic hypoglycemia result in brain injury leading to developmental and other issues, the effects of less severe and asymptomatic hypoglycemia on the neonatal brain are much less clear (Burns et al., 2008; Rozance and Hay, 2012). Thus there is considerable debate regarding the definition of *hypoglycemia* and an actionable glucose level in this early transition period in asymptomatic newborns. In an attempt to provide a rational and standardized approach, the American Academy of Pediatrics (AAP) published a guideline on neonatal hypoglycemia in 2011 (American Academy of Pediatrics. Committee on Fetus and Newborn and Adamkin, 2011). It is recommended that asymptomatic, at-risk term and late preterm newborns who have glucose levels below 25 mg/dL in the first 4 hours after birth or levels below 35 mg/dL at 4–24 hours of age should receive intravenous glucose. Early feeding and retesting are suggested for those with glucose levels between 25 and 45 mg/dL, depending on age. Whereas a "target" glucose level greater than 45 mg/dL before routine feeds is recommended, the guideline authors acknowledge that there is no clear evidence that this is the appropriate threshold for defining a normal glucose level in newborns (American Academy of Pediatrics. Committee of Fetus and Newborn and Adamkin, 2011).

Following publication of the guideline, two large studies on neonatal hypoglycemia have had somewhat contradictory results.



• Fig. 26.1 Predicted plasma glucose values during the first week of life in healthy term neonates with birthweight appropriate for their gestational age. Green and orange lines denote upper and lower limits of 95% confidence interval, respectively, around the mean values (blue line). (Modified from Srinivasan G, Pildes RS, Cattamanchi G, Voora S, Lilien LD. Plasma glucose values in normal neonates: a new look. *J Pediatr.* 1986:109:114–117.)

First, among a group of almost 1400 fourth grade children who had universal glucose screening during their birth hospitalizations, those with transient hypoglycemia, defined as a glucose level below 35 mg/dL, below 40 mg/dL, or below 45 mg/dL, were significantly more likely to score below grade level on standardized testing for literacy and mathematics proficiency than those without hypoglycemia. The odds ratios for lack of proficiency related to hypoglycemia ranged from 1.28–2.33, and there was some suggestion of a "dose effect" with severer hypoglycemia leading to worse outcomes (Kaiser et al., 2015). Conversely, in a prospective study of 528 newborns at risk of hypoglycemia, no association between hypoglycemia (defined as a glucose level <47 mg/dL) and developmental assessment at 2 years of age was found (McKinlay et al., 2015). In this study, newborns were managed with a goal of maintaining a glucose level greater than 47 mg/dL; neither the number of hypoglycemia episodes nor the lowest glucose concentration was associated with abnormal development. Further, study participants underwent continuous interstitial glucose monitoring, but the results of this monitoring were not available to the treating clinicians. Nearly 25% of study newborns had undiagnosed and untreated hypoglycemia identified with continuous monitoring, some for several hours. These episodes of unrecognized hypoglycemia were also not associated with developmental delays.

Taken in their entirety, the results of these two large studies suggest that it is "safe" to follow the AAP hypoglycemia guideline; screening and treatment protocols designed to maintain glucose levels greater than 45 mg/dL are associated with good developmental outcomes. It is much less clear if this is the "best" approach. The higher the threshold for defining hypoglycemia, the more testing and treatment there will be in asymptomatic newborns. It is possible that, in the absence of a clear benefit, more screening and more treatment will actually lead to more harm than good (McKinlay and Harding, 2015). In addition, although the rate of hypoglycemia is greater in newborns at risk, at any given time in a typical newborn nursery most newborns with hypoglycemia will be term newborns without any risk factors, simply because there are so many more of these neonates (Kaiser et al., 2015). Thus most hypoglycemia in a newborn nursery goes undiagnosed if screening is limited to those at risk.

Newborn Metabolic Screening

Newborn screening (NBS) for metabolic disorders began in 1962 when 29 states participated in a trial of testing for phenylketonuria (PKU). With the implementation of screening programs, criteria were proposed for determining which conditions should be included in screening programs. It was recommended that only disorders that were important health problems be included in screening programs. The condition should be detectable before the onset of significant symptoms. Importantly, a specific treatment to prevent adverse clinical consequences from the disorder should be available, and the screening program for the condition should be cost effective (Tarini, 2007). On the basis of these criteria, conditions such as congenital hypothyroidism and congenital adrenal hyperplasia were slowly added to NBS tests in many states, and subsequently conditions such as sickle cell disease were added. Although there is no specific treatment for sickle cell disease, there was evidence that the use of an NBS program to identify newborns with the disorder led to early initiation of penicillin treatment, which resulted in fewer deaths from sepsis than when newborns were identified at the onset of symptoms (Vichinsky et al., 1988). Given the demonstrable effectiveness of early identification, sickle cell disease met the criteria for newborn screening.

The advent of tandem mass spectrometry in the 1990s revolutionized newborn metabolic screening. With this technology it is possible to test for a multitude of conditions on a very small sample of blood. In 1995 the average number of conditions included in state-mandated screening programs was 8; by 2005 this had increased to 19, with some states testing for up to 46 conditions. Unfortunately, this increase in NBS has been controversial. Some of the conditions included do not meet the long-established criteria for screening in that there are no known effective treatments, and, in some cases, it is not known whether the targeted condition always leads to disease. In addition, with increasing numbers of tests come increasing numbers of false-positive results, leading to increased parental anxiety and potential for overuse of medical services (Tarini et al., 2006; Berry, 2015).

In an attempt to define a rational list of disorders for which NBS is appropriate, the American College of Medical Genetics used an iterative process to identify 29 "core conditions" that should be included in mandatory screening programs (Watson et al., 2006). Subsequently, federal legislation was passed to facilitate standardization of NBS across the United States. This legislation led to the development of the Recommended Universal Screening Panel, which initially included 29 core disorders. All US states currently provide testing for all of these disorders (Berry, 2015). The recommended screening panel has now been expanded to include 32 core disorders and 26 secondary disorders. In addition to newborn hearing screening and screening for critical congenital heart disease (CCHD), there are nine organic acid, five fatty acid oxidation, six amino acid, two endocrine, three hemoglobin, and four other conditions included in the list of core disorders. Information on the screening program in each state in the United States and on specific disorders can be found at http://www.babysfirsttest.org.

The most common disorders included on newborn metabolic screens in the United States are congenital hypothyroidism (1 case per 3000–4000 newborns) and sickle cell disease (Kaye et al., 2006; Hertzberg et al., 2011). The incidence of PKU is approximately 1:15,000 (Serving the family from birth to the medical home, 2000). For many of the core conditions for which screening is now recommended, the incidence rates are in the 1:100,000 to 1:200,000 range (Kaye et al., 2006). For some disorders, the incidence rate is unknown.

Hearing Screening

Newborn hearing screening has become universal in the United States, with more than 97% of newborns screened in 2013. Every state and territory in the United States has now established an early hearing detection and intervention program and is required to provide tracking data. Newborns who do not "pass" the hearing screen in the newborn nursery should be referred for more definitive testing in a timely manner. Ultimately, in 4.8%–10.3% of newborns who do not pass the hearing screen, permanent hearing loss is diagnosed; the current rate of hearing loss in the United States is approximately 1.5 per 1000 newborns screened (Williams et al., 2015; Summary of 2013 National CDC EHDI Data, 2016). Many other countries have adopted or are in the process of adopting universal hearing screening. Experts from the World Health Organization endorsed universal newborn hearing screening in 2009. It is reported that 80% of early childhood hearing loss is congenital and that most cases have genetic origins and/or are a result of cytomegalovirus infection (Declau et al., 2008; Lammens et al., 2013).

There is growing evidence that early intervention with amplification or cochlear implants can improve childhood reading, language,

and communication skills (Vohr et al., 2008; McCann et al., 2009; Ohmori et al., 2015; Stika et al., 2015). These treatments are effective when implemented by 6 months of age, preferably younger. This creates time urgency to verify an initial screen with a test and make referrals to specialists who can provide treatment. This process is particularly challenging in rural areas and in countries with limited access to these services (Bush et al., 2015).

A significant challenge is to avoid labeling a child as abnormal with this screening process. Of the newborns who fail to pass their newborn hearing screen, more than 80% will be found to have normal hearing on follow-up testing (Nelson et al., 2008). Given this false-positive rate, approximately 8–10 newborns with normal hearing will be referred for follow-up testing to identify newborns with hearing loss (Nelson et al., 2008). The risk of labeling a child as possibly abnormal can cause permanent alteration of the parent–child relationship, a condition dubbed *vulnerable child syndrome* (Pearson and Boyce, 2004).

To decrease the risk of false-positive tests and vulnerable child syndrome, it is recommended that the term *refer* be used instead of *fail* when the screen results are being discussed. Babies have an increased "refer" rate when born by cesarean delivery or screened during the first day of life, so it is best to wait until the third or fourth day to screen newborns whenever possible (Lupoli Lda et al., 2013; van Dyk et al., 2015; Xiao et al., 2015). Many nurseries have adopted a two-step process using an automated otoacoustic emissions (OAE) test for the first step followed by a brainstem auditory evoked potential test in those who do not pass the automated OAE test. This process has been shown to decrease the false-positive rate (Papacharalampous et al., 2011; Caluraud et al., 2015). All newborns who are at high risk of early hearing loss should be sent directly for auditory brainstem response (ABR) screening. High-risk factors include premature birth, family history of early childhood or infant hearing loss, craniofacial anomalies or abnormal ear examination findings (includes microtia but not tags), and exposure to aminoglycoside antibiotics.

False-negative screens are also a concern but the rate is low. A screen will be falsely negative in 0%–2% of newborns (Johnson et al., 2005; Cebulla et al., 2014). With use of ABR screening, the false negative rate is lower.

Screening for Critical Congenital Heart Disease

It has been estimated that approximately 25% of newborns with congenital heart disease have "critical" lesions, defined as a lesion requiring surgery and/or cardiac catheterization in the first year of life (Mahle et al., 2009). Overall, CCHD is diagnosed in less than half of newborns prenatally, and 25%–30% are not identified as having CCHD during the birth hospitalization (Peterson et al., 2014). Further, some neonates with lesions that are amenable to surgical intervention who are not identified as having CCHD before discharge from their birth hospitalization may die from their CCHD before a clinical diagnosis is made (Peterson et al., 2014). Because of this, it is now recommended that all newborns be screened with pulse oximetry for CCHD before discharge from their birth hospitalization (Mahle et al., 2012).

Pulse oximetry screening is based on the concept that most, but not all, CCHD lesions lead to hypoxemia in the affected newborn. To minimize false-positive results, pulse oximetry screening should be delayed until newborns are 24 hours or older, if possible. Conversely, since some newborns with CCHD have different oxygen saturation levels when measured preductally or postductally, false negatives results are reduced by screening newborns both in the right hand (preductal) and in a lower extremity (postductal). Newborns with a measured oxygen saturation level of less than 90% at either site are classified as having a positive screen and should be evaluated by a pediatric cardiologist on an urgent basis. Repeated screening is recommended for newborns with oxygen saturation levels of 90% or greater and less than 95% or with a difference of 3 or more percentage points between the right hand and the lower extremity; if either of these findings persists after three screenings, the screen is considered positive (Kemper et al., 2011).

There were initially concerns that wide-scale implementation of universal pulse oximetry screening would result in a high proportion of false-positive results, leading to unnecessary and expensive evaluations of normal newborns. Thankfully, these concerns have been largely unfounded, with observed false-positive rates of less than 0.5%. However, the sensitivity of pulse oximetry screening is only approximately 77% (Thangaratinam et al., 2012). Sophisticated models have indicated that the number of "true" positives might be approximately matched by the number of false-negative results (Ailes et al., 2015). Given this, a diagnosis of CCHD should be seriously considered in a young infant with signs or symptoms of one of the lesions that screening is designed to identify despite the presence of negative screening results during the birth hospitalization.

Prenatal Ultrasound Screening for Birth Defects

Ultrasound screening for fetal anomalies has become increasingly routine. Major fetal organ system abnormalities can, for the most part, be identified, and the mother can be referred for appropriate fetal and neonatal management. There are, however, a number of ultrasound findings that have a variable natural history, which may or may not be markers for serious conditions and do not always result in a definitive prenatal work-up. These findings often do not fit within the pediatric lexicon. They can present a challenge to the pediatrician when it comes to parent counseling and/or determining management in the neonatal period.

Central Nervous System Findings

Choroid plexus cysts are found in 2%–4% of second trimester fetal ultrasound examinations. They are transient, functionally benign in nature, and generally resolve spontaneously before term. If one or more choroid plexus cysts are found in isolation on prenatal ultrasound examination, no adverse effect on fetal growth and development has been noted. Thus without other risk factors, no further evaluation is needed in an infant with this isolated finding who has had a benign prenatal and a normal postnatal course (Ebrashy et al., 2016). Choroid plexus cysts are believed to be a "soft marker" for aneuploidy (particularly trisomy 18) when associated with other fetal anomalies or with maternal risk factors, such as advanced maternal age. In such situations current recommendations are to begin an appropriate prenatal evaluation, that is, karyotyping (DiPietro et al., 2006; Lopez and Reich, 2006; Sohaey, 2008a).

Agenesis of the corpus callosum is reported to occur in 0.3%–0.7% of unselected postnatal populations. Aneuploidies have been reported in 10%–20% of children with this prenatal ultrasound finding. Major organ system abnormalities are reported to occur in up to 60% of such fetuses. Notably, when absence of the corpus callosum is an isolated fetal ultrasound finding, the reported rate of a relatively normal developmental outcome ranges from 50% to 75%. However, well-conducted long-term follow-up studies are lacking. It is recommended that fetal magnetic resonance imaging be considered when one is confronted with this diagnosis since other abnormalities have been identified in more than 50% of such fetal patients. Postnatal management for infants with a

history of agenesis of the corpus callosum on prenatal ultrasound examination should include, at a minimum, close clinical assessment and indicated work-up (Fratelli et al., 2007; Chadie et al., 2008; Winter, 2008; Sotiriadis and Makrydimas, 2012).

Mild, isolated ventriculomegaly is a relatively uncommon fetal ultrasound finding that may be a soft marker for aneuploidy, fetal infection, or other central nervous system abnormalities. As such, it is recommended that serial imaging studies and, in some cases, more extensive work-up be undertaken. In the presence of a benign fetal assessment, most newborns appear to do reasonably well following delivery. It is important to consider close developmental follow-up and serial imaging studies (Leitner et al., 2009; Melchiorre et al., 2009; Devaseelan et al., 2010).

Cardiac Findings

Echogenic cardiac focus is an incidental ultrasound finding in 3%–4% of normal fetuses. Notably, there is an increased incidence (10%–30%) in Asian populations. It is said to be a soft marker for chromosomal abnormalities (trisomy 21 and trisomy 13) when associated with other screening abnormalities. Further work-up may be indicated in high-risk populations. If the physical examination findings for a newborn are normal and there are no other ultrasound findings, no further evaluation is suggested (Borgida et al., 2005; Koklanaris et al., 2005; Ouzounian et al., 2007; Sohaey, 2008b Rodriguez et al., 2013).

Gastrointestinal Findings

Echogenic bowel when noted to be present during a second trimester ultrasound examination and determined to be grade 0 or 1 (i.e., less echogenic than bone) is considered a normal variant with a good prognosis. No special prenatal or postnatal work-up is recommended. Anything of density equal to or greater than that of bone (grade 2 to 3) is abnormal and potentially a marker for cystic fibrosis, trisomy 21, gastrointestinal anomalies, in utero infection, bowel ischemia or bleeding, intrauterine growth restriction, and/or impending in utero demise. Appropriate work-up is indicated (Goetzinger et al., 2011; Ebrashy et al., 2016).

Cholelithiasis is an uncommon third trimester fetal ultrasound finding that needs to be differentiated from hepatic calcification. Cholelithiasis is considered a benign condition requiring no special evaluation or treatment but careful clinical follow-up. An imaging examination at 1 year of age for a child with this prenatal finding may be helpful in documenting expected resolution (Sohaey, 2008d; Triunfo et al., 2013).

Hepatic calcifications are uncommon fetal ultrasound findings. They are often isolated, single and, in a low-risk mother, of no significance. However, when numerous, hepatic calcifications may be markers for fetal aneuploidy, infection, meconium peritonitis, hepatic tumor, or vascular insult. A significant percentage are associated with some form of fetal disease. Neonatal management depends on the prenatal work-up and the clinical presentation in the newborn period (Simchen et al., 2002; Pata et al., 2012).

Urinary Tract Findings

Mild fetal pelviectasis is one of the more common abnormalities detected by second trimester ultrasound examination, with a reported incidence of 0.5%–5% in unselected pregnant populations. Diagnostic criteria differ but generally include a second trimester renal pelvis diameter of more then 4 mm and less than 10 mm and a third trimester renal pelvis diameter of more than 7 mm and less than 10 mm. Renal pelvis diameters of 10 mm or greater are always considered abnormal. Some experts consider mild fetal pelviectasis to be a soft marker for aneuploidy, especially trisomy 21. When mild, fetal pelviectasis is an isolated finding, the prognosis is good, and the condition often resolves either in utero or during early childhood. In a metaanalysis it was reported that only 11% of children with a history of mild fetal pelviectasis demonstrated postnatal disease. The authors of a prospective cohort follow-up study reported uropathy in 18% of their cases. Authorities thus recommend a postnatal follow-up renal ultrasound examination approximately 1 week after birth and, if necessary, at 1 month of life to document resolution (Lee et al., 2006; Coelho et al., 2007; Nguyen et al., 2010; Sohaey, 2008d; Ebrashy, et al., 2016).

Car Seats and the Newborn Car Seat Challenge

All states have laws that require the use of car seats for children. It is important that parents purchase only approved car seats, so bargain-hunting at used child equipment stores should be done with caution. Lists of approved seats are available online at websites such as https://www.healthychildren.org/English/safety-prevention/on-the-go/Pages/Car-Safety-Seats-Product-Listing.aspx.

The observation that preterm newborns had episodes of hypoxia when monitored in car seats led the AAP to recommend in 1991 that preterm newborns be observed and monitored for apnea, bradycardia, or oxygen desaturation in their car safety seat before hospital discharge—the so-called car seat challenge (American Academy of Pediatrics Committee on Injury and Poison Prevention and Committee on Fetus and Newborn 1991, 1996; American Academy of Pediatrics Committee on Injury and Poison Prevention, 1999). In the United States, the car seat challenge expanded to include late preterm newborns, most of whom did not have respiratory problems during their hospital stay. It has been reported that 25% of late preterm newborns do not fit securely into standard car safety seats, and 12% of healthy late preterm newborns have apneic or bradycardic events in their car seats (Merchant et al., 2001). The rate of failure (about 4%) has been found to be about the same in small for GA babies as those born late preterm.

The authors of a Cochrane systematic review questioned whether or not car seat trials actually prevent morbidity or death and if there might be adverse effects from not passing this "screen," such as prolonging the hospital stay or creating parental anxiety. Their review did not discover any randomized trials, and they concluded that "it is unclear whether undertaking a car seat challenge is beneficial or indeed whether it causes harm" (Pilley and McGuire, 2006). Since then, there has been one randomized trial in healthy term newborns comparing car seats with car beds, and no differences were found in the rates of oxygen desaturation or apnea events (Kinane et al., 2006). A study comparing a polysomnogram with the car seat challenge showed that the challenge has a low negative predictive value when compared with polysomnogram (Schutzman et al., 2013).

Routine and Common Medical Treatments

Prevention of Ophthalmia Neonatorum and Conjunctivitis

Approximately 15%–20% of babies will develop conjunctivitis in the first few weeks of life. Conjunctivitis can be caused by a sexually transmitted bacterium, normal skin or nasopharyngeal flora, or chemical irritation (Krohn et al., 1993). In addition, eye discharge

can be caused by obstruction of the nasolacrimal duct rather than from conjunctivitis. The most worrisome infection is that of *Neisseria gonorrhea*, which can invade the cornea in a matter of hours and lead to blindness. Despite effective preventive measures known since the 1880s, thousands of children are still blinded by this infection worldwide each year.

Most states in the United States have laws or regulations requiring administration of topical antibiotic ointment to the conjunctivae of babies within a few hours of birth. This practice has been effective in reducing the cases of blindness caused by gonococcal conjunctivitis. It is moderately effective in preventing conjunctivitis caused by chlamydia. The main risk of antibiotic ointment application is that it may cause a chemical conjunctivitis. Silver nitrate solution instilled into both eyes immediately after birth was the standard of care for many years, but it caused a high rate of chemical conjunctivitis.

Parents may question the need to expose their babies to eye medication, especially if the mother has been tested and found to be without gonorrhea or chlamydia. Some countries have stopped routine administration of eye prophylaxis. In those countries, an increase in infection, primarily caused by chlamydia, has been noted.

There has been an ongoing search for alternative prophylaxis that causes less chemical conjunctivitis and is not in an ointment base. A variety of prophylactic treatments have been recommended, including 1% nitrate solution, 1% tetracycline solution, 1% erythromycin solution, 2.5% povidone–iodine solution, fusidic acid, and freshly expressed breast milk. Among those, tetracycline has been reported as most effective (Zuppa et al., 2011). There is lay literature recommending the instillation of colostrum or breast milk into the eyes of babies to prevent or treat conjunctivitis. Although colostrum has antimicrobial action, its efficacy has not been adequately studied.

Povidone–iodine solution has been shown to be more effective and cause less irritation than erythromycin ointment. It is also less expensive but is not yet approved for this use by the US Food and Drug Administration (Ali et al., 2007). A major concern is that medical errors can occur if povidone–iodine soap is mistakenly substituted for the solution; it can cause eye damage. Fusidic acid has been used for preoperative prophylaxis for a number of surgical procedures in adults. However, data on its use in newborns are limited (Zuppa et al., 2011).

Vitamin K

Vitamin K is necessary for biologic activation of several human proteins, most notably coagulation factors II (prothrombin), VII, IX, and X. Since placental transfer is limited, umbilical cord blood levels of vitamin K_1 (phylloquinone) are 30-fold lower than maternal levels. Intestinal bacteria synthesize menaquinone (vitamin K_2), which has 60% of the activity of phylloquinone. However, neonates have a decreased number of bacteria in their gut that manufacture vitamin K_2; levels of this form of vitamin K are not found in the livers of infants until they are 2–3 months old. Thus newborns are deficient in vitamin K at birth and are at risk of significant bleeding. Fortunately, intramuscular (IM) vitamin K rapidly activates clotting factors, greatly decreasing this risk.

Three presentations of vitamin K–deficient bleeding (VKDB) have been described. "Early" VKDB presents in the first 24 hours after birth, is not prevented by postnatal administration of vitamin K, and usually occurs in newborns born to mothers who are taking medications that inhibit vitamin K. Common medications that inhibit vitamin K include many anticonvulsants, isoniazid, rifampin, warfarin, and some antibiotics, such as cephalosporins. Early VKDB is frequently serious because of intracranial and/or intraabdominal hemorrhage. It is estimated that in neonates at risk of early VKDB the incidence is as high as 12% (Van Winckel et al., 2009).

"Classic" VKDB occurs in newborns during the first week of life. Although the presentation is often mild, blood loss can be significant, and intracranial hemorrhages have been reported. Although estimates differ, the incidence of classic VKDB, in the absence of vitamin K supplementation, is 0.25%–1.7% (American Academy of Pediatrics Committee on Fetus and Newborn, 2003).

"Late" VKDB occurs between the ages of 2 and 12 weeks and is usually severe. The mortality rate from late VKDB is approximately 20%, and 50% of infants with this disorder develop intracranial hemorrhages. Late VKDB is associated with exclusive breastfeeding. Human milk contains only 1–4 μg of vitamin K per liter, while commercially available formula contains 50 μg/L or more. In exclusively breastfed neonates who do not receive supplemental vitamin K, the incidence of late VKDB is estimated at 4.4–7.2 per 100,000 (or 1 per 15,000 to 1 per 20,000) (Van Winckel et al., 2009).

Vitamin K administered shortly after birth is effective in preventing classic and late VKDB. Since 1961, the recommended dose of vitamin K for term newborns born in the United States has been 1 mg given intramuscularly. However, the results of a study suggesting an association between intramuscularly administered vitamin K given at birth and childhood cancer created controversy regarding this practice (Golding et al., 1990, 1992). The results of subsequent studies strongly suggest that there is no increased risk of solid tumors in children given vitamin K intramuscularly (Puckett and Offringa, 2000).

Because of those previous concerns regarding an increased risk of childhood cancers, a switch to orally administered vitamin K occurred in some countries but not in the United States. It is apparent that a single oral dose of vitamin K has efficacy similar to that of an IM dose in preventing classic VKDB but offers less protection against late VKDB. Repeated doses of an oral vitamin K preparation until an infant is 8–12 weeks old increases the efficacy of this route of administration. However, it is not clear that even multiple doses of an oral formulation of vitamin K are as effective as a single IM dose given at birth. In a multination review, the rates of late VKDB in infants receiving various regimens of orally administered vitamin K were mostly in the range of 1.2–1.8 per 100,000 compared with no cases in 325,000 children receiving an IM dose (Cornelissen et al., 1997). The oral regimens assessed included a birth dose of 1 mg. The reported rates of VKDB in newborns who received 2 mg orally at birth, with repeated doses subsequently, are lower but still somewhat higher than in neonates treated with intramuscularly administered vitamin K (Von Kries et al., 2003; Busfield et al., 2007). Early data from the Netherlands where infants received 1 mg orally at birth and 25 μg daily for up to 12 weeks suggested that this regimen was as efficacious as an IM dose (Cornelissen et al., 1997). However, in a subsequent study from the Netherlands, the rate of late VKDB was 3.2 per 100,000 in a group of infants with undiagnosed biliary atresia who had been treated with this dosing schedule (van Hasselt et al., 2008). Unrecognized cholestatic liver disease is a significant risk factor for VKDB. Finally, no cases of late VKDB were found among 396,000 Danish infants who received an oral dose of 2 mg of vitamin K at birth and 1 mg weekly until the age of 3 months (Hansen et al., 2003).

Highlighted by the reports of intracranial hemorrhages in four newborns from Tennessee who did not receive vitamin K at birth, there are concerns that the rate of parental refusal of vitamin K in the United States is increasing (Centers for Disease Control and Prevention, 2013; Schulte et al., 2014). Although there has been little widespread surveillance on the rates of vitamin K refusals, recent studies suggest that the rates in North America may be in the 0.3%–0.8% range; the rates are higher for newborns born at birthing centers rather than in a hospital (Sahni et al., 2014; Hamrick et al., 2016). Rather than being concerned about the reports linking vitamin K with childhood cancers, parents who refuse vitamin K treatment for the newborn are also more likely to refuse vaccines for their children at later ages and share many of the beliefs of other parents refusing vaccines for their children (Hamrick et al., 2016). In one study the most commonly cited reason for parents refusing vitamin K treatment for their newborns was "synthetic or toxic ingredients," followed by concerns about an "excessive dose" and side effects; only 7% of those surveyed were concerned about the risks of cancer (Hamrick et al., 2016).

The risks from intramuscularly administered vitamin K include pain at the injection site and the possibility of a serious medication error. The risks of a significant complication from the injection are probably negligible; in one study, zero significant complications were reported after 420,000 injections (Von Kries, 1992). In the United States, oral administration is complicated by the lack of an oral vitamin K preparation licensed for newborns. In some settings, infants have received the IM preparation orally. However, tolerability may be a problem, and the efficacy of this preparation when given orally may not be comparable with the oral formulations used in Europe. In addition, adherence with repeated doses of orally administered vitamin K in infants may be suboptimal. Finally, it is unknown whether the use of repeated administration of an oral vitamin K preparation in the dose range of 1–2 mg each week is associated with an increased risk of childhood cancers.

For parents who have questions regarding the best method to prevent classic and late VKDB, the clinician is advised to discuss the pros and cons of IM versus oral administration of vitamin K. If the parents choose oral administration, a dose of 2 mg of vitamin K should be given shortly after birth, with subsequent doses until the newborn is at least 4 weeks old if he or she is breastfed. In a policy statement, the AAP suggests that if an oral vitamin K formulation becomes licensed for use in the United States, a 2-mg dose may be given at birth and repeated at 1–2 weeks of age and at 4 weeks of age for neonates whose parents decline IM vitamin K treatment (American Academy of Pediatrics Vitamin K Ad Hoc Task Force, 1993).

Circumcision

Neonatal circumcision is a polarizing issue for both healthcare professionals and parents. Those who favor routine circumcision highlight health benefits such as decreased risk of urinary tract infections (UTIs), reduced risk of penile cancer, and possibly lower rates of sexually transmitted infections, including HIV (Schoen, 2008). Those who oppose the procedure point out that the number of circumcisions needed to be performed to prevent one of these outcomes (number needed to treat) is large, that the risks of the procedure balance out the benefits, that circumcision leads to loss of sexual sensation, and that subjecting a neonate to a painful procedure without clear benefits may be unethical (Andres, 2008). In 2012 the AAP published a policy statement concluding that the benefits of circumcision outweigh the risks of the procedure. However, these health benefits were not great enough to recommend routine circumcision in all male neonates (American Academy of Pediatrics Task Force on Circumcision, 2012a).

It is clear that circumcision reduces the risk of UTI by threefold to 10-fold (American Academy of Pediatrics Task Force on Circumcision, 2012b). However, given the low incidence of UTI in male newborns, 100 boys need to be circumcised to prevent one UTI. Similarly, although circumcision has been shown to prevent penile cancer, this is an extremely rare condition, and the number needed to treat is about 900 (Christakis et al., 2000). The results of studies in three African countries indicate that circumcision reduces the risk of HIV infection by 56% (Mills et al., 2008). In the United States, where HIV infection rates are lower, it has been estimated that circumcision might decrease the acquisition of HIV through heterosexual transmission by 16%; 298 boys would need to be circumcised to prevent one case of HIV infection (Sansom et al., 2010). There is limited evidence suggesting that circumcision might reduce the risk of other, selected, sexually transmitted infections, including syphilis and genital herpes. However, there is no compelling evidence that circumcision reduces the risk of chlamydia or gonorrhea (American Academy of Pediatrics Task Force on Circumcision, 2012b).

Circumcision is generally a safe procedure. Although some increased bleeding is reported after 1% of circumcisions, the rate of significant complications is about 0.2% (Gee and Ansell, 1976; Wiswell and Geschke, 1989; Christakis et al., 2000). Bleeding, sometimes requiring suturing of a vessel, is the most common significant complication, followed by penile injury and infection. Infection is more common following a circumcision using a Plastibell rather than a Gomco clamp; the incidence of hemorrhage is reportedly similar after either technique (Gee and Ansell, 1976).

Circumcision is an uncomfortable experience for the neonate. Small amounts of sucrose solutions can be offered to the baby for soothing. Pain from the actual surgery can be significantly decreased with the use of a dorsal penile nerve block or ring block (American Academy of Pediatrics Task Force on Circumcision, 2012b). In one study, 65% of newborns who had received a dorsal nerve block had no or minimal response to the initial clamping of the foreskin (Taeusch et al., 2002). However, the results of a randomized controlled trial suggest that ring block provides superior analgesia compared with dorsal penile nerve block (Lander et al., 1997). Although topical anesthesia may be better than no anesthesia, it provides inferior pain relief compared with dorsal penile nerve block (Brady-Fryer et al., 2004).

A poor cosmetic outcome can be caused by removal of too little foreskin. It has been estimated that 1%–9.5% of circumcisions are redone because of parental concern regarding the appearance. In a prospective study among boys younger than 3 years who had been circumcised with use of either a Plastibell clamp or a Mogen clamp, the glans was fully exposed in only 35.6%. However, in older circumcised boys, the glans was fully exposed in more than 90% (Van Howe, 1997). This suggests that parents of a circumcised infant should be counseled that the vast majority of properly done circumcisions will lead to an acceptable cosmetic appearance over time.

In the United States the Gomco clamp is the most commonly used apparatus for performing circumcisions, followed by the Plastibell clamp and the Mogen clamp (Stang and Snellman, 1998). The use of the Mogen clamp, which was designed by a Jewish mohel, leads to shorter procedures and, reportedly, less pain and bleeding than the other techniques (Reynolds, 1996; Kurtis et al., 1999; Taeusch et al., 2002). However, less foreskin is removed

with the use of the Mogen clamp than with the other two techniques (Alanis and Lucidi, 2004).

Hepatitis B Vaccine

The implementation of routine HBV immunization during infancy has been associated with a dramatic decrease in the incidence of this infection. Between 1990 (before routine vaccination of infants) and 2004 the overall incidence of acute HBV in the United States declined by 75% and by 94% among children and adolescents (Centers for Disease Control and Prevention, 2005). Both the Centers for Disease Control and Prevention and the AAP recommend that the initial dose of the three-dose HBV immunization series be given in the newborn nursery. However, this recommendation is not universally followed; the rate of receipt of a birth dose of HBV vaccine in United States was estimated at 72.4% in 2014. The rates differ substantially across the United States, ranging from 88.4% among newborns born in North Dakota to 48.4% among those born in Vermont (Hill et al., 2015).

There are at least two advantages of providing the first dose of HBV vaccine during the newborn nursery stay. First, newborns who receive a birth dose are more likely to complete their HBV immunization series on time than those who receive a first dose later (Yusuf et al., 2000). Secondly, since a dose of HBV vaccine given within 12 hours of birth can prevent vertical transmission of HBV infections in 75%–90% of cases, early provision of immunization serves as a "safety net" in cases where there has been an error in identifying a mother who is HBV surface antigen positive (Centers for Disease Control and Prevention, 2005).

The main disadvantage of providing a dose of HBV vaccine during the nursery stay is that it may complicate documentation of HBV immunization status in a child by increasing the number of vaccination providers. There is no evidence that administration of a birth dose of HBV vaccine leads to more evaluations for sepsis because of adverse events related to the immunization.

Ongoing Care

Umbilical Cords

Umbilical Cord Variants

At the time of delivery a description of the umbilical cord should be documented in the medical record as there may be long-term implications for care of the newborn if there are cord abnormalities. A great deal has been written about cords with a single umbilical artery, but other variations are also important.

Short cords are associated with decreased fetal movement and may indicate an underlying neuromuscular disorder or genetic syndrome. This decreased fetal movement may also cause a decrease in bone density in the newborn (Krakowiak et al., 2004; Wright and Chan, 2009).

Long cords are associated with large and active babies and more often are found in males. They are associated with an increased risk of cord compression, entrapment, knotting, and nuchal cords (Sornes, 2000). True knots may cause problems for the fetus during pregnancy and may also compress at the time of delivery, causing additional compromise. In the presence of chronic cord compression, neonates have an increased risk of brain imaging abnormalities (Baergen et al., 2001). Velamentous insertions of the umbilical cord are associated with an increase in obstetric complications such as vasa previa and cord rupture (Hasegawa et al., 2006).

A single umbilical artery is detected in about 4 in 1000 births and is associated with a number of congenital anomalies, including renal or genitourinary malformations, cardiac malformations, and chromosomal anomalies, including Down syndrome, but most newborns with a single umbilical artery are normal. In this era of near universal prenatal fetal ultrasonography, many of the associated anatomic abnormalities are discovered before delivery (Johnson and Tennenbaum, 2003; Deshpande et al., 2009). Unless there are additional problems noted on physical examination of the newborn, there is no need to repeat diagnostic ultrasound examinations after the birth of a newborn with a single umbilical artery.

Prevention of Omphalitis

The recommendations for umbilical cord care may range from "dry cord care" to use of dyes and/or cleansing with alcohol, soap and water, or antiseptics. Concerns over the possible toxic effects of dye and antiseptics led many hospitals in the United States to adopt the "dry cord care" method of cord care. Unfortunately, this may be causing an increase in the risk of omphalitis (Janssen et al., 2003; Simon and Simon, 2004). In one review a 50% reduction in omphalitis and a 12% reduction in neonatal mortality was found when chlorhexidine was used versus standard dry cord care methods (Sinha et al., 2015). This was the same conclusion reached in a review of home births in developing countries, but no clear difference was found in developed countries (Imdad et al., 2013). If the dry cord method is used, parents and healthcare providers should watch for redness around the umbilical cord stump.

Tetanus neonatorum, with the infection occurring via the umbilical cord, continues to be reported in more than 20 developing countries, resulting in 58,000 neonatal deaths per year. The condition is related to low vaccination rates in women of childbearing age, home deliveries, and certain cultural care practices. Public health efforts focusing on effective vaccination programs and use of "clean bed" deliveries are needed to eliminate the disease (Thwaites et al., 2015).

Delayed Cord Clamping

The results of several studies suggest a benefit to delaying clamping of the umbilical cord at birth. This practice has been shown to benefit term as well as preterm newborns. The babies are more hemodynamically stable, have greater red cell mass and iron stores during infancy, and have improved neurodevelopmental outcome during childhood. These findings have led to the endorsement of policies to delay cord clamping by both the AAP and the American College of Obstetrics and Gynecology (McAdams, 2014). With delayed cord clamping, there is an increase in the risk of mild polycythemia and an increase in risk of jaundice but not increased treatment for these conditions.

While current guidelines call for a 30–60-second delay before clamping, it seems beneficial to wait for the baby to show physiologic readiness. Babies who cry vigorously may be ready for clamping sooner than quiet babies. An ultrasound study of blood flow through the umbilicus showed arterial and venous flow may not stop for 3 minutes (Boere et al., 2015).

Umbilical Cord Blood Banking

The practice of banking umbilical cord blood is increasing worldwide. This service is offered by both public and privately supported entities; however, the quality of service is better regulated in public blood banks. While there are controversies, the potential for use of stem cells is growing, and there will likely be an increased demand for this service (Yoder, 2014). One of the greatest barriers

to more consistent collection of umbilical cord blood is that current hospital practices generally do not support this service (Broder et al., 2013).

Breastfeeding

Benefits of Breastfeeding

There is voluminous evidence that the optimal nutrition for normal neonates is human milk provided via the mother's breast. Growing evidence supports the role of human milk in prevention of early onset of allergies, prevention of adult obesity, reduction in severity and frequency of infections (including those leading to hospitalization in developed countries and those leading to death in developing countries), and increased intellectual functioning (Section on Breastfeeding, 2012). It is a public health imperative and incumbent on our society to provide systems that support breastfeeding (Christakis, 2013).

Support of Breastfeeding

Breastfeeding is not always the "easy and natural" undertaking it is touted to be. Primiparous mothers report more difficulties than multiparous mothers. Breastfeeding support begins with encouragement and education at prenatal visits. After birth, in-person lactation support is helpful in promoting both initiation and persistence of nursing (Renfrew et al., 2012). Places of employment should provide support by having adequate maternity care leave policies, improving facilities, and having policies allowing time and space for nursing and pumping for lactating women at the workplace (Sattari et al., 2013). Fathers and grandparents should provide a supportive social network by performing homecare tasks to facilitate rest for lactating mothers (Alvarez et al., 2015). Problems with nursing should trigger additional intervention with lactation specialist evaluation and advice.

In 1991 the World Health Organization and the United Nations Children's Fund developed a program to promote breastfeeding called the Baby-Friendly Hospital Initiative (BFHI). As a comprehensive program, implementation of the 10 steps of the BFHI (Box 26.2) has been shown to significantly increase the rates of breastfeeding (Kramer et al., 2001). In addition, there is evidence of a "dose–response" relationship between the number of BFHI steps that women are exposed to and improved breastfeeding outcomes (Perez-Escamilla et al., 2016).

• BOX 26.2 Baby-Friendly Hospital Initiative: Ten Steps to Successful Breastfeeding

1. Maintain a written breastfeeding policy that is routinely communicated to all healthcare staff.
2. Train all healthcare staff in the skills necessary to implement this policy.
3. Inform all pregnant women about the benefits and management of breastfeeding.
4. Help mothers initiate breastfeeding within 1 hour of birth.
5. Show mothers how to breastfeed and how to maintain lactation, even if they are separated from their newborns.
6. Give newborns no food or drink other than breast milk unless medically indicated.
7. Practice "rooming-in"—allow mothers and newborns to remain together 24 h a day.
8. Encourage unrestricted breastfeeding (breastfeeding on demand).
9. Give no pacifiers or artificial nipples to breastfeeding newborns.
10. Foster the establishment of breastfeeding support groups, and refer mothers to them on their discharge from the hospital or clinic.

For some of the individual steps of the BFHI, such as excluding the use of pacifiers, the evidence is contradictory (Cramton et al., 2009; O'Connor et al., 2009). There are a number of epidemiologic studies showing cessation of breastfeeding is associated with pacifier use, but the few randomized prospective trials done give different results. The authors of a review concluded that among mothers who were motivated to breastfeed, pacifier use did not significantly affect the prevalence or duration of breastfeeding (Jaafar et al., 2012). Sucking is a primitive brain self-soothing process. Babies with certain temperaments may benefit more than others by using sucking to self-soothe. Pacifier use has been shown in some studies since the 1970s to decrease the risk of sudden infant death syndrome (SIDS), and in premature infants, nonnutritive sucking actually enhances weight gain. The AAP developed a policy statement supporting pacifier use but recommended waiting until approximately 1 month of age (Section on Breastfeeding, 2012). The important issue is whether or not the use of a pacifier is replacing feedings, so if a mother is motivated to breastfeed and maintains a frequency of 8–12 feedings per day, the use of a pacifier between meals seems reasonable.

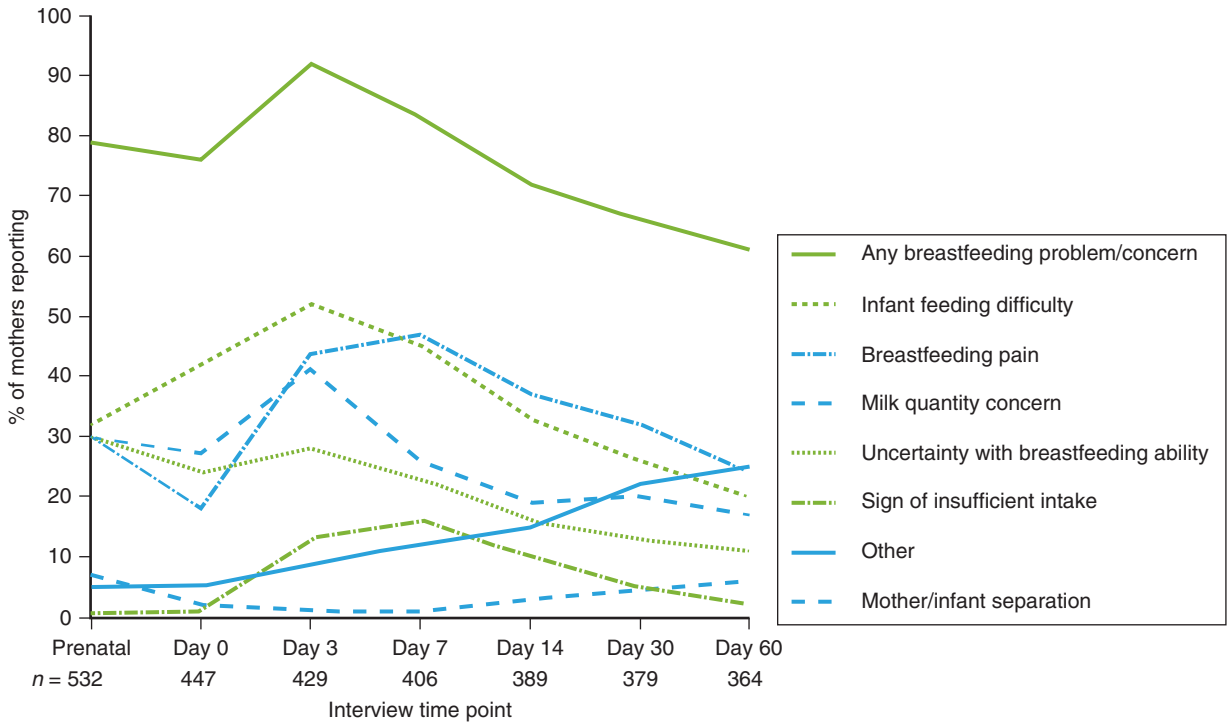
Another contentious issue is the use of supplemental formula during the initial newborn period. The results of a randomized prospective trial indicated that use of limited supplemental formula was associated with increased breastfeeding rates at 3 months of age (Flaherman et al., 2013). That seems contradictory to earlier studies showing a decline in nursing when formula samples or discharge packages were given to families. One key difference is that in the trial, formula use was limited to 10 mL after feedings, administered via a syringe, and supplement was discontinued once mature milk was produced. More research is needed to determine which mother–infant dyads will benefit from supplement while avoiding sabotage of breastfeeding.

From a practical standpoint there are several evidence-based interventions during the newborn nursery stay that increase the rate and/or duration of breastfeeding. These include the use of frequent demand feedings as opposed to a rigid feeding schedule, early skin-to-skin contact between the mother and the newborn, professional advice on breastfeeding techniques, and exclusion of commercial formula from discharge packs (Donnelly et al., 2000; Renfrew et al., 2000; Anderson et al., 2003; Britton et al., 2007).

In an era of early hospital discharge for healthy newborns, it is particularly important to have in-home or clinic follow-up at age 3–4 days. This is when the newborn's weight reaches its nadir, jaundice peaks, lactogenesis II is starting (see later), and mothers are sleep deprived because of dealing with the around-the-clock needs of the newborn. Breastfeeding mothers may need extra encouragement during this time and continued vigilance to ensure that breastfeeding is established.

Breastfeeding Problems

Breast milk development is divided into two or three phases: lactogenesis I occurs during pregnancy with breast enlargement due to proliferation of ducts and lobules and later in pregnancy with colostrum production. Lactogenesis II occurs usually about 56–72 hours after birth; gonadotropin and progesterone levels decline and prolactin level increases (Dewey et al., 2003). This phase is characterized by the rapid increase in milk volume—sometimes this is exuberant to the point of engorgement. Lactogenesis III occurs generally after 1 month of nursing when the milk composition and volume are responsive to the reciprocal relationship between the mother and her baby—a demand and



• **Fig. 26.2** Prevalence of reported breastfeeding concerns by mothers by newborn age. (Modified from Wagner EA, Chantry CJ, Dewey KG, Nommsen-Rivers LA. Breastfeeding concerns at 3 and 7 days postpartum and feeding status at 2 months. *Pediatrics*. 2013;132:e865–e875.)

supply feedback loop. Some experts combine lactogenesis II and lactogenesis III into one phase.

Delays in lactogenesis II have been shown to occur after cesarean birth, in poorly controlled diabetic mothers, when there is stress during delivery, when there are retained placental fragments, and when there is pituitary failure. There are some situations when no milk production occurs, leading to frustration and feelings of failure in mothers. The timing of lactogenesis II is a biologic clock that cannot be accelerated by pumping or frequent nursing (Chapman et al., 2001; Flaherman et al., 2012a).

More than 90% of mothers report concern and difficulty with nursing during the first 10 days after delivery (Fig. 26.2) (Wagner et al., 2013). Combined with hormonal changes and sleep deprivation, this can compound the risk of postpartum depression and early cessation of nursing. Postpartum depression should be screened for at health supervision visits until the infant is 6–12 months of age (McLearn et al., 2006).

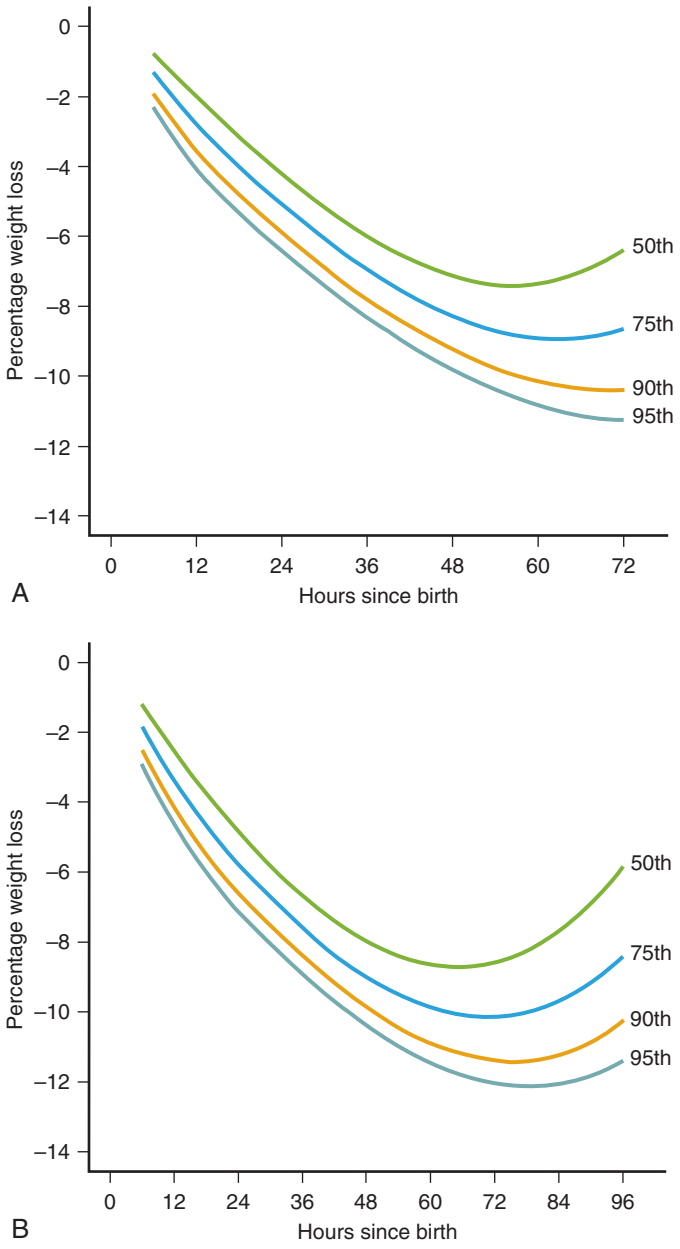
Common issues that may lead to early cessation of nursing include nipple pain, newborn jaundice, excessive weight loss or poor weight gain, concern about maternal medications, and lack of social support. There are also conditions associated with low milk volume production, including maternal factors (lack of social support, prenatal confidence and expectations about breastfeeding, timing of return to work, inadequate frequency of nursing, inadequate breast tissue, flat or inverted nipples, or very large breasts) and baby factors (hypotonia, drug withdrawal, asymmetric jaw, high arch palate, poor tongue motor abilities, and temperamental issues).

For nipple pain there is no treatment that is clearly advantageous (e.g., hydrogel, lanolin, breast milk, shields), but education on latch position is helpful. For most, the pain decreases within the first 7 days regardless of the treatment selected (Dennis et al., 2012). In a review of nipple shields, McKechnie and Eglash (2010) found a lack of randomized trials but expressed concern about shields interfering with milk transfer.

There has been a recent increase in the use of frenotomy to alleviate pain with nursing, presumably due to a tight lingual frenulum (tongue-tie or ankyloglossia). With use of objective rating scales, the rate of tongue-tie in newborns is about 1%–4%, but more infants are undergoing frenotomy, and there are concerns that this may be more due to anecdotal reports rather than more rigorous study (Power and Murphy, 2015). Sometimes frenotomy is done to alleviate the frustrations of mothers (and lactation specialists) who are dealing with breastfeeding problems of unknown origin. There are only a few prospective studies on frenotomy, and the results are contradictory (Power and Murphy, 2015). It may be prudent to wait until the physiologic process of lactogenesis II and early nipple pain have passed before frenotomy is considered. Although the procedure is simple and relatively free of side effects, unnecessary interventions or labeling of a newborn as abnormal should be avoided in newborn care whenever possible. Frenotomy for posterior tongue-tie has received extra scrutiny because evidence is lacking that supports the diagnosis and outcome from treatment, and the procedure is more invasive (Douglas, 2013).

Jaundice has become more prevalent with the resurgence of breastfeeding. Along with more visible jaundice, there has been an increase in concern and anxiety about the risks associated with jaundice. Most jaundice is physiologic and resolves with onset of lactogenesis II. It is important for providers who care for newborns not to overestimate the risks, while maintaining vigilance for the exceptionally rare case when there is true risk. The bilirubin level should serve as a call for action to emphasize lactation support rather than lead to a separation of the newborn from the mother and artificial feeding to lower the bilirubin level.

The normal newborn is born with a surplus of extracellular free water, and in cesarean delivery births, mothers are often given



• **Fig. 26.3** Nomograms of weight loss in exclusively breastfed newborns born vaginally (A) or by cesarean delivery (B). (Modified from Flaherman VJ, Schaefer EW, Kuzniewicz MW, et al. Early weight loss nomograms for exclusively breastfed newborns. *Pediatrics*. 2015;135:e16–e23.)

additional boluses of fluids that may further hydrate the newborn (Chantry et al., 2011). It is normal, expected, and perhaps preferable that babies will lose this free water in the first 72 hours of life. This free water is protective of the newborn's fluid balance while the mother's milk is awaited (Mulder and Gardner, 2015). In cases of extra hydration, extra weight loss may be expected. The average term newborn loses about 7% of birthweight, with 12% of newborns born vaginally losing more than 10% of birthweight (Fig. 26.3) (Flaherman et al., 2015). The loss during the first 24 hours of life can predict those who will lose more. This is not a state of dehydration but is a normal physiologic adaption to extrauterine life, so healthcare providers should not alarm parents or suggest that there is something wrong with their baby.

With the onset of copious production of mature milk, neonates begin to gain weight and their serum sodium levels fall (Marchini and Stock, 1997). Newborns fed human milk regain their birthweight, on average, by the age of 8.3 days; 97.5% have regained their birthweight by 21 days (Macdonald et al., 2003). In newborns who lose substantially more than 10% of their birthweight because of breastfeeding difficulties, there is the potential for significant hypernatremia (Oddie et al., 2013).

Supplementation of Breastfeeding

It is usually unnecessary to provide any nutrition or fluid to term breastfed newborns beyond human milk. Dextrose water or commercial formula may be needed in neonates with hypoglycemia who are not responsive to breastfeeding. Supplementation may also be indicated in newborns who have lost more than 10% of their birthweight and/or have decreased urine and stool output or in the presence of significant hyperbilirubinemia. Supplementation should be considered a temporary intervention, and its provision should not interfere with the onset of successful breastfeeding.

Temporary supplemental formula or expressed breast milk when available can be provided via a supplemental nursing system, finger feeding, or a bottle. Of greatest importance is close monitoring of the change in weight of the baby and continued lactation support. The use of banked or donor milk is increasing, but there has also been increased concern about the use of the unregulated milk that may be available. Some milk has been diluted with formula and may contain infectious diseases. Publicly supported milk banks that follow the recommendations of the World Health Organization use pasteurization and quality control to provide safer milk (Kair et al., 2014; Steele et al., 2015).

Contraindications to Breastfeeding

The few, absolute contraindications to breastfeeding include maternal HIV infection, untreated tuberculosis in the mother, evidence of current cocaine use,[158] use of antimetabolite drugs, and galactosemia in the neonate (Gartner et al., 2005; Field, 2008). There are a myriad of drugs for which concern exists regarding long-term neurodevelopmental outcomes in the infant. Selective serotonin reuptake inhibitors are commonly used to treat depression and anxiety in young women. Among drugs in this category, sertraline and paroxetine are thought to be the safest for use in breastfeeding mothers, while fluoxetine and citalopram are felt to have the most potential for toxicity in the neonate (Field, 2008). Overall, few adverse effects have been noted with use of any of these drugs, and generally the potential risks associated with these medications are thought to be outweighed by the benefits of breastfeeding (Field, 2008). Similarly, although methadone is detectable in the breast milk of women receiving this medication, serum levels in neonates are quite low and unlikely to have a significant effect (Jansson et al., 2008). Online references are available that have the current status of the effects of toxins and medications in breast milk: http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm.

Hepatitis C virus RNA has been found in the milk of mothers infected with this virus. Despite this, transmission of infection via breastfeeding has not been documented. Maternal hepatitis C is not considered a contraindication to breastfeeding (Gartner et al., 2005).

Bottle feeding

Commercial formula that provides adequate nutrition, vitamins, and minerals is available for infants of mothers who do not wish

to breastfeed their infants or in those rare instances when breastfeeding is contraindicated or impossible. There are three major categories of formula used in neonates: cow's milk–based, soy, and hydrolyzed formula. Of these, cow's milk–based formula is the most commonly used. The main carbohydrate in cow's milk–based formula is lactose. Soy formulas were developed for infants with suspected cow's milk allergy. Because the main carbohydrate in soy formulas is sucrose or corn syrup, soy formula can be used in neonates with suspected galactosemia. Protein hydrolyzate formulas were initially developed for use in infants who are highly intolerant to cow's milk protein (Kleinman, 2009b). They are purported to lead to fewer allergies in babies and children than cow's milk–based formula, but the evidence for this is limited (Osborn and Sinn, 2006). All extensively hydrolyzed formulas are lactose free (Kleinman, 2009b). Extensively hydrolyzed formulas are indicated in infants with definitive evidence of cow's milk protein allergy because 10%–14% of such children also have soy allergy (Bhatia and Greer, 2008).

Traditionally, standard preparations of formulas available for use in healthy term neonates provide 0.67 kcal/mL. This caloric density was based on the calories in human milk. However, the results of some studies indicate that the average caloric density of human milk may be closer to 0.64–0.65 kcal/mL. Because of this, some infant formulas have been modified to provide 0.643 kcal/mL (19 kcal/oz) (Marriage et al., 2015). Most formulas are fortified with iron at a concentration of 10–12 mg/L. Vitamin D at a concentration of approximately 400 IU/L is provided in all of the commercially available formulas (Kleinman, 2009a).

Mothers who elect to bottlefeed their babies report feeling unsupported in their decision by healthcare professionals, and up to 50% feel pressured to breastfeed (Lakshman et al., 2009). Although the benefits of breastfeeding should be provided to mothers who have not decided how to feed their babies, the role of healthcare providers is also to support the decision of those who have elected to bottlefeed their babies. It is also important to provide practical education about bottlefeeding to these parents; this is frequently not done in many newborn nurseries (Lakshman et al., 2009).

Newborns who are bottlefed can feed ad lib beginning shortly after birth. The average formula intake in term newborns during the first day of life is 15–20 mL/kg and is 40–45 mL/kg during the second day (Dollberg et al., 2001). Term newborns who are formula fed during their birth hospitalization typically lose less weight than breastfed infants (Flaherman et al., 2015; Miller et al., 2015). The median weight loss in formula-fed term newborns at 48 hours of life has been reported to be 2.9% of birthweight for those born vaginally and 3.7% among those born by cesarean delivery; weight loss of 7% or more during a typical newborn nursery stay in formula-fed infants is uncommon (Miller et al., 2015).

Anticipatory Guidance

A primary duty of newborn care providers is to ensure that the newborn's caregivers (usually the parent or parents) have the knowledge and skills to provide for their baby's normal growth and development. Parents who are well informed about normal newborn development and behavior have more realistic expectations about the work involved and look on their child with more fondness. Conversely, it is important to assess the parents' ability to provide a safe and nurturing environment for the neonate before discharge from the newborn nursery. Parents showing concerning behaviors, possibly leading to abuse or neglect, should have supervision and interventions to help them, or their parental rights should be terminated (Wattenberg et al., 2001; Davidson-Arad et al., 2003).

There are several major challenges faced by parents of normal newborns: sleep deprivation, learning how to calm a crying newborn, dealing with significant life changes, and the new worries that come with being responsible for a totally dependent being. Postpartum depression is more common and of longer duration than previously thought and is present in at least 10% of mothers. Depression also occurs in about 10% of fathers during early infancy and is related to maternal depression. This condition is related to sleep deprivation and has a major and long-lasting impact on infant homeostasis and development (Chaudron, 2003). Depression screening of parents should occur at all well-child visits during the first 6–12 months of life.

Anticipatory guidance should be given to help prepare new parents for the common tasks of newborn care and to educate them about the many normal variations in newborn behavior. Learning how to soothe a baby is one of the earliest needed parenting tasks; providers can help give suggestions both to reduce crying and to better cope with those newborns who are more sensitive and harder to soothe (Barr et al., 2009).

Most parents have questions about feeding, elimination, bathing, cord care, genital care, jaundice, and common rashes. There are numerous checklists of educational topics that can be overwhelming to new parents and providers. In addition, learning styles differ, with some preferring written materials and others preferring audiovisual materials or hands-on demonstration. Ideally, education should be targeted toward the topics of interest and with the appropriate materials for the learning style (Dusing et al., 2008).

Mothers are often not in a good learning state in the immediate postpartum period because of pain, postpartum hormonal changes, and the stress of being in a hospital. However, this is also a period of heightened receptivity to change, so attempts to teach or make lifestyle changes (e.g., smoking cessation) may be more effective. There is some evidence that providing parental education using tools such as interactive videos and computers may be superior to traditional teaching (Trepka et al., 2008; Snowdon et al., 2009). Also, DVDs provided in the nursery or along with well-child visits have been shown to be helpful. A randomized controlled trial of a 15-minute anticipatory guidance DVD linked to a well-child visit led to more parents in the DVD group feeling prepared to care for their baby after the visit, having high confidence in bathing their baby, and having high confidence in recognizing congestion when compared with the control group. Those in the DVD group also had fewer additional office visits between birth and 2 months (Paradis et al., 2011). Another effective teaching method is to perform home visits for education of parents. A metaanalysis comparing 60 home visit programs revealed improvement in parenting behaviors, faster parental return to work or school, and lower rates of child abuse (Sweet and Appelbaum, 2004).

Given the obstacles to providing meaningful education during the nursery stay, it is probably better for practitioners to focus on a few key points of anticipatory guidance rather than reciting a long litany of instructions. There is also a philosophical choice in deciding whether to emphasize the overall health of a newborn or to concentrate on prevention or identification of illness. There is little evidence about the efficacy of most anticipatory guidance provided to parents during the newborn nursery stay. A notable exception is the successful Back to Sleep campaign to reduce the risk of SIDS, discussed in the next section.

There is also emerging evidence that education regarding the normality of inconsolable crying in newborns helps parents deal with this stressful situation and may reduce the risk of shaken baby syndrome (Barr et al., 2009). A DVD entitled "Period of

Purple Crying" is provided at some newborn nurseries to parents to help prevent shaken baby syndrome by teaching calming and coping techniques. Early evaluations of the DVD indicate that it may lead to better parental knowledge about newborn crying; however, in one population-based study, provision of the DVD in newborn nurseries was not associated with a decrease in the incidence of abusive head trauma in infants (Zolotor et al., 2015).

Sleep Position

With the exception of immunizations, no child health intervention in the past 3 decades has resulted in a larger decrease in postneonatal infant mortality than the Back to Sleep campaign. The remarkable change in the predominant sleep position of infants from prone to supine has led to a 30%–50% reduction in the rate of SIDS in the United States (American Academy of Pediatrics Task Force on Sudden Infant Death Syndrome, 2005). A multipronged effort including brochures, public service announcements, and education provided by healthcare professionals was used to affect the change in sleep position (Willinger et al., 2000). Obviously, education provided to parents during the newborn nursery stay is a crucial determinant of the sleep position of an infant. In addition to providing education, there is evidence that parents model sleep position for their babies after how they saw nurses and physicians place their neonate in his/her bassinet in the newborn nursery (Colson and Joslin, 2002; American Academy of Pediatrics Task Force on Sudden Infant Death Syndrome, 2005). There is no evidence that placing newborns on their side during the first few hours after birth decreases the risk of aspiration (American Academy of Pediatrics Task Force on Sudden Infant Death Syndrome and Moon, 2011). Therefore it is crucial that neonates are placed on their backs to sleep in the newborn nursery. In addition, there is an additive effect from both physicians and nurses recommending and demonstrating the supine sleep position (Willinger et al., 2000).

In addition to the supine position, there are other factors related to the sleep environment that may impact the risk of SIDS. It is recommended that infants sleep on firm surfaces and without excessive bedding such as pillows. Although a controversial topic, the results of a metaanalysis strongly indicate that cosleeping increases the risk of SIDS by nearly threefold. The risk of cosleeping is highest in infants of mothers who smoke (Vennemann et al., 2012). In addition, although use of a pacifier has been found to reduce the risk of SIDS, there is a reluctance to recommend these devices because of concerns about reducing breastfeeding (American Academy of Pediatrics Task Force on Sudden Infant Death Syndrome, 2005; American Academy of Pediatrics Task Force on Sudden Infant Death Syndrome and Moon, 2011).

Discharge and Follow-Up

The average length of the initial hospital stay for US newborns born at 35 weeks' gestation or later is 48–52 hours (Datar and Sood, 2006; Paul et al., 2006; Kuzniewicz et al., 2009). Since approximately 50% of newborns delivered vaginally are discharged before 48 hours after birth and up to 40% of those born by cesarean delivery are discharged before 72 hours after birth, a large proportion of newborns are discharged before 3–4 days after birth, which is when bilirubin levels typically peak and breastfeeding is well established (Paul et al., 2006). It is recommended that newborns discharged before 48 hours after birth have a follow-up appointment with a provider within 48 hours (American Academy of Pediatrics Committee on Fetus and Newborn, 2004). This follow-up can be accomplished either by a visit to a healthcare provider or by a home nursing visit.

The risk factors for readmission following an initial hospital stay of less than 48–72 hours include GA of less than 39 weeks (and especially <37 weeks), primiparous mother, and Asian race (presumably because of an increased risk of hyperbilirubinemia) (Liu et al., 1997; Grupp-Phelan et al., 1999; Paul et al., 2006; Burgos et al., 2008). Consideration of a longer nursery stay is suggested for newborns with one or more of these risk factors. In addition, early discharge is not recommended for term newborns who have not voided, passed at least one stool, or demonstrated adequate breastfeeding (American Academy of Pediatrics Committee on Fetus and Newborn, 2004). However, there is little evidence to support these recommendations.

Common Problems During the Nursery Stay

Hypothermia and Hyperthermia

Being too cold or too hot causes metabolic stress to the newborn, so efforts to maintain a steady and neutral thermal environment should be made. The best practice is to dry the baby immediately after delivery and place the newborn skin-to-skin with the mother. Although the AAP and the American College of Obstetricians and Gynecologists jointly recommend keeping newborns' core temperatures within the narrow range of 36.5°C to 37°C, in one study of healthy term newborns the average temperature was 36.5°C, with a normal range from 36.0°C to 37.9°C (Takayama et al., 2000). Thin babies tend to have lower body temperatures, and heavier babies tend to have higher body temperatures. Bathing a newborn often causes hypothermia. This is less likely when bathing is performed from trunk to head or when a bath is used versus washing with a cloth.

Standard practice at most nurseries is to measure axillary temperatures, probably because of reports in the 1960s and 1970s of rare perforations caused by rectal thermometers; however, axillary temperatures may not always accurately reflect core temperature (Hutton et al., 2009). Importantly, axillary temperatures are not the standard used in studies of sepsis in infants younger than 2–3 months of age.

Hypothermia

On leaving the womb a newborn is immediately challenged with maintaining a normal body temperature. If a neonate is not quickly dried at birth, he or she may lose up to 1°C body temperature per minute. Healthy term babies are able to increase heat production through glycogenolysis and nonshivering thermogenesis for minutes to a few hours, depending on environmental conditions (Aylott, 2006). Babies typically experience a decline in body temperature during the first hour after birth, with a gradual increase during the following 12 hours (Li et al., 2004). By the second day the newborn's body temperature becomes more stable, but heat loss can occur again with bathing or other stresses (Takayama et al., 2000).

Many nurseries worldwide have adopted policies to delay bathing to avoid hypothermia, to allow time for initial bonding, and to promote breastfeeding. Early skin-to-skin contact between the newborn and the mother is useful both to prevent and to treat early temperature loss, but attention to positioning and frequent checks by nursing staff are required (George et al., 2015). Hypothermia should be managed by the baby being placed skin-to-skin with a parent or under a radiant warmer.

Hyperthermia

An elevated body temperature at birth generally reflects the intrauterine temperature and is not usually a sign of sepsis (Baumgart, 2008). Isolated hyperthermia during labor is associated with neonatal encephalopathy, occurring in approximately 1 in 2000 births (Blume et al., 2008). After the first 3–4 days of life, increased temperatures are most likely caused by dehydration from suboptimal breast milk supply (Maayan-Metzger et al., 2003). A single increased temperature in an otherwise normally behaving newborn is not a strong predictor of infection but has been reported as a sign of intracranial hemorrhage (Fang et al., 2008).

Elimination

Urination

Approximately 15% of healthy newborns void at the time of delivery, and 95% void by 24 hours of age. Delayed voiding is likely a consequence of stress on the newborn during labor and delivery, which is a protective mechanism for the baby (Vuohelainen et al., 2007, 2008). Normally, no intervention is needed once homeostatic adaption to extrauterine life has been established.

The differential diagnosis of delayed voiding (defined as no urine output by 24–48 hours of age) includes renal and postrenal causes. With the frequent use of prenatal ultrasound examination, it is unusual for a significant renal anomaly to be unknown before birth. Most newborns with bilateral renal agenesis have other findings, such as oligohydramnios or Potter sequence. Unilateral renal agenesis does not usually give signs of decreased urine output. Renal vascular thrombosis can cause anuria, and babies with this condition are usually ill. Severe cystic kidney disease can involve urinary outflow obstruction. The diagnosis of cystic kidneys is usually made after the newborn period or is found incidental to evaluation of other anomalies and not because of delayed voiding.

Postrenal causes of delayed voiding include neuropathic bladder dysfunction and anatomic obstruction of urinary flow by anomalies in ureters, the bladder, or the urethra. Persistent or recurrent bladder distention after catheterization is found with occult lower spinal cord anomalies. Presacral teratoma or other tumors can cause compression and urinary blockage as well. In male newborns, there is the possibility of posterior urethral valves. Congenital lower urinary tract obstruction occurs in 1 in 3000 births, with two-thirds of these due to posterior urethral valves. Physical findings of loose abdominal skin or musculature and a distended bladder suggest this diagnosis (Malin et al., 2012).

In a healthy-appearing newborn who has a normal physical examination and a history of a normal prenatal ultrasound, allowing up to 72 hours for a spontaneous first void will avoid excessive testing. In fussy neonates and neonates with other genitourinary abnormalities, enlarged kidneys, or a distended bladder, testing should begin immediately. Ultrasound examination of the bladder, kidneys, and posterior urethra is often diagnostic.

Normal newborns have decreased renal concentrating ability and excessive extracellular free water at birth. As a result, they will continue to void despite low intake of fluids. This process is normal. Newborns maintain normal hydration despite weight loss. Conversely, delayed voiding is not indicative of dehydration in the first 72 hours after birth. When mothers undergo cesarean section, the fluid boluses given to prevent hypotension may result in additional free water in their newborn. This can lead to greater than 7% birthweight loss with extra voiding (i.e., a physiologic diuresis) (Mulder et al., 2010). Hearing about weight loss in their newborn creates stress, guilt, and anxiety in parents, which may be counterproductive to breastfeeding success. It is important for providers to emphasize the normalcy of weight loss (Flaherman et al., 2012b).

Defecation

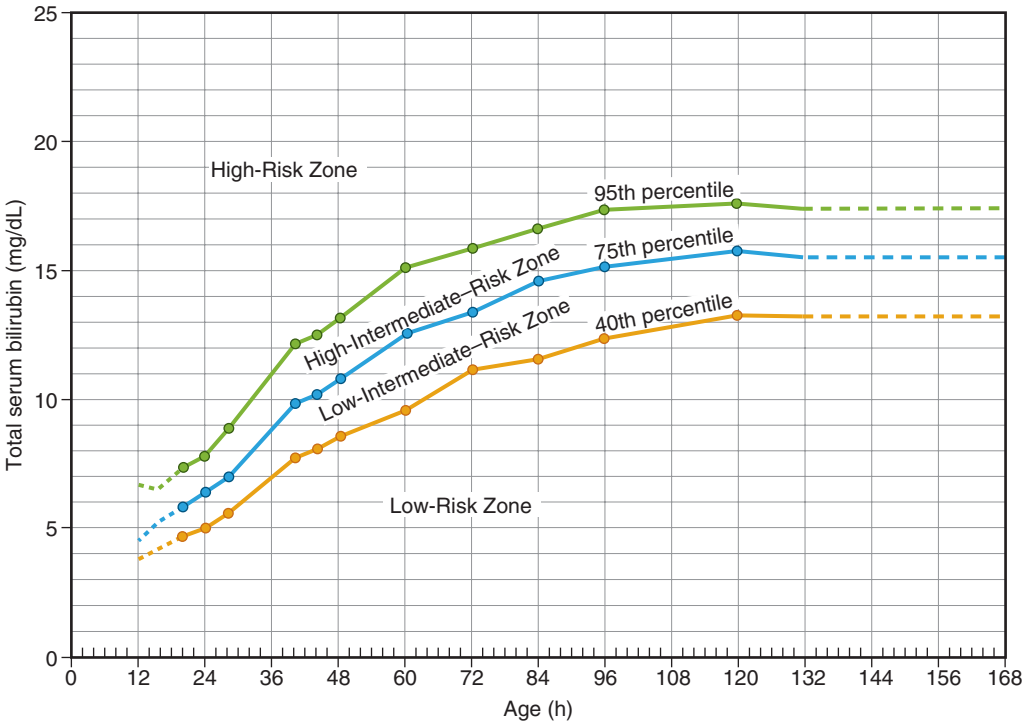
Similarly to the first void, the first passage of meconium occurs by an average of 7 hours of age. One-third of newborns pass meconium before their first feeding. Late preterm newborns tend to pass meconium later than term newborns, and 32% of preterm newborns do not pass meconium within 48 hours after birth. Although intake is not well correlated with meconium output, the number of wet and soiled diapers does reflect adequacy of breast milk production by day 4. Fewer than four soiled diapers on day 4 correlates with inadequate milk production (Nommsen-Rivers et al., 2008). By 2 weeks of age, breastfed newborns pass feces more frequently than bottlefed newborns; they also have larger variability in the time between bowel movements (Sievers et al., 1993; den Hertog et al., 2012). After the first month, breastfed and formula-fed infants have about the same rate of defecation.

Because 99.7% of healthy newborns pass meconium by 34 hours of age, those whose passing of meconium is delayed beyond that time deserve extra vigilance during examination to avoid obstructions being missed, such as an imperforate anus (Metaj et al., 2003). A baby with abdominal distention or vomiting and delayed stooling deserves evaluation for a possible gastrointestinal tract obstruction.

Jaundice

As many as 60%–84% of newborns develop visual jaundice in the first few days after birth (Bhutani et al., 2013a; National Institute for Health and Clinical Excellence, 2016). Despite this almost ubiquitous nature, there are few conditions in newborns that create as much controversy and clinician and parental angst as hyperbilirubinemia. Since the discovery of phototherapy in 1956 and its integration into medical care in the 1970s, the standard management of neonatal jaundice in the United States has gone through three distinct phases. Until the early 1990s, clinicians visually monitored term neonates during their 2–5-day newborn nursery stay and obtained serum bilirubin levels on those with significant jaundice. Phototherapy was initiated when the total serum bilirubin (TSB) level reached 15 mg/dL, and an exchange transfusion was indicated if the level rose to 20 mg/dL (Watchko and Oski, 1983). The wisdom of this approach was challenged by reviews of data on jaundice in term newborns without hemolytic disease indicating that the risk of kernicterus in such newborns was extraordinarily low (Watchko and Oski, 1983; Newman and Maisels, 1992).

On the basis of this evidence a "kinder and gentler" approach to the management of hyperbilirubinemia in term newborns was advocated, leading to the AAP practice parameter in 1994 (Provisional Committee for Quality Improvement and Subcommittee on Hyperbilirubinemia, 1994). Under this guideline, phototherapy for a healthy, 72-hour-old term newborn was not definitively recommended unless the TSB level was 20 mg/dL or greater. Unfortunately, publication of this guideline coincided with a shortening of the nursery stay by term newborns to as little as 24 hours. Thus newborns were discharged home before their bilirubin levels "peaked" at 3–4 days, and there were numerous reports of newborns with extremely high bilirubin levels and a general



• **Fig. 26.4** "Bhutani nomogram" for total serum bilirubin levels in newborns born at 36 weeks' gestation or later. (Modified 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;103:6–14.)

impression that the incidence of kernicterus was increasing as well. In retrospect, it does not appear that the incidence of kernicterus did increase, but case reports and anecdotal evidence led to significant consternation by clinicians, parents, and quality assurance organizations (Burke et al., 2009; Brooks et al., 2011).

Since newborns are usually discharged well before their bilirubin levels reach their peak, it was clear that predictive models were needed to assess risk in newborns who are discharged early. Bhutani et al. (1999) developed a nomogram based on data from neonates in whom serum bilirubin levels were measured multiple times (Fig. 26.4). Those newborns who had initial bilirubin levels above the 95th percentile at any time point (in hours) were more likely to have "significant hyperbilirubinemia" when the levels were measured subsequently than those with lower levels initially. These data were used in the development of the 2004 AAP practice guideline (American Academy of Pediatrics Subcommittee on Hyperbilirubinemia, 2004). With this iteration of the guideline, clinicians are provided hour-by-hour guidance on TSB levels for which phototherapy or exchange transfusion is indicated. Separate curves for "low-risk," "medium-risk," and "high-risk" neonates have been developed on the basis of the presence of factors (e.g., GA less than 38 weeks, hemolytic disease, serum albumin level less than 3.0 g/dL, glucose 6-phosphate dehydrogenase deficiency, sepsis, and acidosis) that might increase the risk of brain damage in an neonate who has an extremely high TSB level (Maisels et al., 2009). Internet-based tools are available in which the appropriate management for a newborn with a specific bilirubin level at a specific hour after birth is provided.

There are numerous neonatal conditions that increase the risk of hyperbilirubinemia (Dennery et al., 2001). Chief among these is hemolysis secondary to maternal antibodies to red blood cell antigens. Although hemolysis secondary to antibodies to Rh factor is now quite rare in the United States and other high-income countries because of proper management of Rh-negative mothers, it has been estimated that as many as 114,000 newborns die each year in locations in the world where resources are not adequate to prevent Rh sensitization (Bhutani et al., 2013b). A common cause of hemolysis in newborns is an ABO incompatibility. Since there is no way to prevent hemolysis from an ABO incompatibility, it may be useful to test umbilical cord blood from neonates born to mothers with blood type O for blood type and the presence of antibodies on their red cells (i.e., Coombs test) at birth. The increase in bilirubin level secondary to ABO compatibility, even with a positive direct Coombs test, is highly variable. Some newborns will have an early and dramatic rise in serum bilirubin level and evidence of hemolysis, while in others no effect can be detected clinically. In addition to ABO incompatibility, some women will have antibodies to "minor" red cell antigens that can usually be diagnosed prenatally. In most instances the increases in bilirubin level associated with antibodies against minor antigens are mild.

Other neonatal conditions that are risk factors for hyperbilirubinemia include bruising secondary to birth trauma and polycythemia. Decreased intake of breast milk may lead to decreased passage of stool. Because intestinal bacteria break down conjugated bilirubin to the unconjugated form, a decrease in stool frequency may lead to increased reabsorption of this unconjugated bilirubin (enterohepatic circulation). Breastfeeding is a significant risk factor for hyperbilirubinemia particularly when intake is limited. The propensity for developing significant jaundice is variable in different racial groups. Asian and Native American newborns are at the highest risk of significant hyperbilirubinemia (Dennery et al., 2001).

Finally, late preterm newborns are at significantly increased risk of both significant hyperbilirubinemia and kernicterus.

Traditionally, visual assessment has been used to judge whether or not a newborn has significant jaundice. Unfortunately, visual assessment is only relatively accurate; reported correlations between estimated bilirubin levels and TSB levels are in the range of 0.36–0.75, and clinicians tend to underestimate the severity of newborn jaundice (National Institute for Health and Clinical Excellence, 2016). Because of this, it is recommended that all newborns be screened for jaundice before discharge from the birth hospitalization with a TSB level or a transcutaneous bilirubin (TcB) measurement using a transcutaneous bilirubinometer, a noninvasive method for estimating bilirubin levels (Maisels et al., 2009).

Although TcB level offers a reasonable approximation of the gold standard TSB level, with published correlations ranging from 0.77 to 0.93, it is designed to be used only as a screening tool (Maisels et al., 2009; National Institute for Health and Clinical Excellence, 2016). If the TcB level is above a certain threshold, it is recommended that blood be obtained for a TSB measurement to be used for clinical decision making. Several decision rules have been recommended for use in newborns during their birth hospitalization. These include:

1. Plot TcB level results on the Bhutani nomogram. If the TcB level is in the high-intermediate or high-risk zone, the screen is "positive."
2. Determine the phototherapy threshold with use of the AAP hyperbilirubinemia guideline. If the TcB level is within 70% of this threshold, the screen is positive.
3. Determine the phototherapy threshold. If the TcB level is within 3 mg/dL of this threshold, the screen is positive (Maisels, 2006; Maisels et al., 2009).

With each of these rules it is recommended that a TSB level be obtained in a newborn with a positive TcB screen. The utility of these three decision rules has been evaluated in a large multisite study (Taylor et al., 2016). The main outcome was accurate identification of a newborn with a TSB level at or above the phototherapy threshold. The false-negative rates with each of the rules was less than 10%, but no rule correctly identified all neonates with a TSB level requiring phototherapy. These results indicate that use of TcB level for screening is not foolproof; a blood draw for a TSB level may be needed if clinical evaluation suggests that the level of jaundice in a neonate is more severe than that indicated by TcB measurement.

Unless levels are high enough to require an exchange transfusion, phototherapy is effective for treatment of a newborn with significant hyperbilirubinemia. Although repeated measurements of direct bilirubin level are not cost-effective, one assessment is helpful before, or just after, initiation of phototherapy to rule out direct hyperbilirubinemia (Newman et al., 1991). An assessment of the potential for hemolysis as the cause of the elevated bilirubin level, possibly including a review of maternal and infant blood type, direct Coombs test result, hematocrit, reticulocyte count, and red cell morphology, may also be useful.

There is no conclusive evidence as to whether continuous phototherapy leads to more rapid reduction in serum bilirubin levels than intermittent treatment (Lau and Fung, 1984; American Academy of Pediatrics Subcommittee on Hyperbilirubinemia, 2004; Sachdeva et al., 2015). Unless bilirubin levels are approaching exchange transfusion levels, it is probably reasonable to discontinue treatment for several minutes to 1 hour at frequent intervals to allow parents to feed and hold their baby. Serial bilirubin measurements are needed to determine the adequacy of therapy and to determine when phototherapy can be discontinued. A "rebound" bilirubin level obtained 24 hours after discontinuation of phototherapy may be helpful in some clinical situations.

Respiratory Complications

The term or late preterm fetus accomplishes transition from dependency on the placenta to the newborn cardiorespiratory system, for the most part, without incident. After birth, pulmonary blood flow increases, fetal shunts reverse and begin to close, spontaneous breathing effort is initiated, and fetal lung fluid is cleared. Effective cardiorespiratory function, as represented by an absence of respiratory distress (nasal flaring, grunting, chest wall retractions, a respiratory rate of greater than 60 per minute) and an oxygen saturation in the mid-90s, is established by several hours of age (Levesque et al., 2000; O'Brien et al., 2000).

This normal sequence of events fails to occur in 2%–8% of newborns born at 34 weeks' gestation or later (Hansen et al., 2008; Yoder et al., 2008; Farchi et al., 2009). It is important to keep in mind that the initial presenting symptoms are relatively nonspecific. Agrawal et al. (2003) studied a large number of consecutively born neonates in an attempt to determine the frequency and nature of different early-onset respiratory disorders, and found that more than half of the cases did not meet specific diagnostic criteria. When confronted with early-onset respiratory symptoms, the most important diagnostic considerations to consider include:

- Complex structural cardiac system anomalies; incidence estimated to be between 0.11% and 0.17%; often, but not always, identified by in utero imaging studies (Oster et al., 2013)
- Diaphragmatic hernia; incidence estimated to be between 0.04% and 0.08%; commonly identified by second trimester ultrasound examination (de Buys Roessingh and Dinh-Xuan, 2009)
- Respiratory distress syndrome (RDS); incidence estimated to range between 0.45% and 2.4% depending on the population studied; risk is increased in late preterm newborns and newborns born by cesarean delivery particularly if this happens before labor (Bertin et al., 1996; Yoder et al., 2008; Jain et al., 2009)
- Persistent pulmonary hypertension of the newborn; incidence between 0.1% and 0.3%; often occurs in association with other acute respiratory conditions; a recent large study suggests a slightly increased risk with maternal selective serotonin reuptake inhibitor treatment (Konduri and Kim, 2009; Huybrechts et al., 2015)
- Meconium aspiration syndrome; incidence reported to range between 2% and 9% among newborns delivered through meconium-stained amniotic fluid (7%–20% of all deliveries); risk is increased in newborns delivered after 40 weeks' gestation and/or with intrapartum distress (routine tracheal intubation to facilitate suction is no longer recommended) (Liu and Harrington, 2002; Bhutani, 2008; Perlman et al., 2015)
- Spontaneous pneumothorax; incidence between 0.1% and 0.8%; newborns born by cesarean delivery may be at increased risk (Zanardo et al., 2007; Benterud et al., 2009)
- Transient tachypnea of the newborn (TTNB); incidence ranges between 0.3% and 3.9%; risk factors include late prematurity and cesarean delivery; initial diagnosis is sometimes difficult to differentiate from pneumonia and early respiratory distress (Guglani et al., 2008; Yoder et al., 2008; Jain et al., 2009; Tita et al., 2009)
- Pneumonia; incidence difficult to determine, one recent retrospective report estimated it to be 0.3%; risk factors include maternal chorioamnionitis and prolonged rupture of membranes;

sometimes it is difficult to differentiate it from RDS and/or TTNB (Yoder et al., 2008)

Review of the maternal history, particularly pregnancy, labor, and delivery, may provide useful diagnostic information. For example, the results of a second trimester ultrasound examination could reveal the possibility of a cardiac defect or diaphragmatic hernia. A positive maternal GBS test result without adequate treatment, prolonged rupture of amniotic membranes, and/or evidence of chorioamnionitis suggests the possibility of pneumonia. For newborns with respiratory distress born by cesarean delivery before the onset of labor a diagnosis of RDS should be considered and GA should be estimated. Finally, TTNB is a diagnosis of exclusion; it is prudent to rule out other causes before this is considered to be the cause of respiratory distress in a term neonate.

In most cases, minimum initial diagnostic efforts for a term newborn with unsuspected respiratory distress should include a chest X-ray and assessment of the arterial oxygen saturation. The results of these studies, in combination with the maternal history, should provide information helpful to (1) establish the initial management, such as the need for supplemental oxygen and/or continuous monitoring, (2) determine the need for further work-up or treatment, possibly including an echocardiogram, laboratory testing, and treatment for possible sepsis, or (3) in severe cases, refer the newborn for further specialty consultation and/or intensive care.

Cardiovascular Issues

Congenital heart disease is a relatively common condition in newborns, with an estimated incidence of 81 cases per 10,000 live births (Reller et al., 2008). Ventricular septal defect (VSD) is, by far, the most common defect, accounting for more than 30% of all cases. The increasing accuracy of prenatal ultrasound examinations has greatly improved the early diagnosis of complex congenital heart disease (CHD). The results of population-based reviews indicate that the sensitivity of routine prenatal ultrasound examinations in identifying selected congenital defects is as high as 70% and is as high as 85% for hypoplastic left-sided heart syndrome (Rasiah et al., 2006; Chew et al., 2007). For mothers at high risk of delivering a newborn with CHD, the use of fetal echocardiography is helpful for delineating the anatomy and significance of specific lesions. However, many of the most common defects, particularly VSD, are not typically detected prenatally.

In the absence of a prenatal diagnosis, detection of CHD is via physical examination and oxygen saturation screening (see the section entitled "Screening for Critical Congenital Heart Disease"). Even if the oxygen saturation screen is normal, it is important to continue to consider the possibility of CCHD since some lesions, particularly coarctation of the aorta, may not be detected with screening (Lannering et al., 2015).

At birth, many babies have loud murmurs that are thought to be from either a closing ductus arteriosus or tricuspid regurgitation (Silberbach and Hannon, 2007). These murmurs are transient and not indicative of disease. Conversely, murmurs associated with VSDs may not be heard for several days, when the pulmonary vascular resistance has dropped enough to permit a significant shunting of blood from left to right. Although the ratio of pathologic to benign murmurs is higher in newborns than in older children, most of the murmurs heard during the newborn nursery stay in a healthy neonate are not clinically significant. Characteristics that increase the likelihood that a murmur signifies the presence of CHD include an intensity of 0.5 or more, a harsh quality, occurrence during all of systole or into diastole, and being heard best at the lower sternal border or right upper border (Mackie et al., 2009). In a healthy newborn the most common presentation of CHD is a somewhat harsh systolic murmur that is heard best at the lower left sternal border in an asymptomatic newborn, indicative of a VSD.

In addition to auscultation, it is helpful to assess a newborn with a murmur for dysmorphic features and/or other anomalies as these findings increase the likelihood that the murmur is indicative of CHD. It is important to evaluate the adequacy of femoral pulses to rule out coarctation of the aorta. Femoral pulses may be hard to feel in a neonate; if there is uncertainty, upper and lower extremity blood pressures can be measured. Chest radiographs and electrocardiograms are usually of limited value in evaluating healthy newborns with murmurs (Oeppen et al., 2002; Mackie et al., 2009).

Term neonates frequently have alterations in cardiac rhythm and rate. Heart rates in term newborns may be as high as 200 beats per minute (particularly when agitated) or as low as 80 beats per minute (particularly when asleep). These values are usually indicative of normal variation and are not clinically meaningful unless there are other signs of illness and/or if there is a lack of variability in rate with stimulation or attempts at calming the newborn. Arrhythmias are also not uncommon, occurring in approximately 1% of newborns (Southall et al., 1981). By far the most common arrhythmia in a well-appearing term newborn is from premature atrial contractions (PACs) (O'Brien et al., 2000; Larmay and Strasburger, 2004). These are almost always benign and usually transient. If there is concern about an irregular rhythm in a newborn, an electrocardiogram can be obtained. With PACs the irregular beat is initiated by a P wave. Although the QRS complex may be widened, it is always preceded by the P wave. In most cases no further work-up is needed. Cardiology consultation may be warranted if PACs are persistent or if widened QRS complexes are seen on the electrocardiogram.

Possible Neonatal Sepsis

Although early-onset sepsis (EOS) is a distinctly rare occurrence in term neonates, early identification of a newborn with EOS is a central focus of newborn care and a source of considerable anxiety for clinicians. This anxiety is driven by two unique features of EOS. First, the phenomenon of an apparently healthy newborn becoming moribund from overwhelming sepsis in a matter of hours is well described. Secondly, the earliest signs of infection are frequently subtle and nonspecific. Fortunately, with the advent of screening mothers for GBS colonization prenatally and providing intrapartum antibiotics for those colonized, the rates of EOS have fallen substantially in the past 25 years. In the 1980s and 1990s the rates of neonatal sepsis in the United States were estimated at 2.0–2.5 cases per 1000 live births. By 2008 the overall rate was estimated at 0.8–1.0 cases per 1000 live births (Isaacs et al., 1995; Cordero et al., 2004; Stoll et al., 2011; Weston et al., 2011).

The rate of EOS is lower among term newborns. In one large surveillance study, conducted in the era of nearly universal screening for maternal GBS infection, the rate of sepsis in newborns with birthweights greater than 2500 g was 0.57 cases per 1000 live births (Stoll et al., 2011). However, even with the reduction of GBS cases, this bacterium accounted for most cases of EOS in newborns with birthweights of 2500 g or greater, with a rate of 0.37 cases per 1000 live births. The rate of EOS caused by *Escherichia coli* among newborns with birthweights greater than 2500 g was 0.07 cases per 1000 live births, with the remainder of cases caused

by a variety of other bacteria. Of note, in this study, among a group of almost 400,000 newborns, only two cases of EOS caused by *Listeria monocytogenes* were identified.

Given the current rates of EOS and distribution of pathogens, the decision of whether to initiate empiric antibiotic therapy for possible EOS in a term newborn is dependent on a few key variables. The easiest of these variables to quantify are the maternal GBS screening results, the drugs used, and the timing of intrapartum antibiotic therapy provided to mothers who screen positive. In addition to GBS status, other "risk factors" related to labor and delivery can be used to develop a numeric estimate of a newborn's risk of EOS at birth (Puopolo et al., 2011; Escobar et al., 2014). In some cases the estimated risk of EOS is sufficiently high at birth such that empiric antibiotic therapy for possible sepsis is begun regardless of the appearance of a neonate. In newborns who are not initially treated with antibiotics, clinicians use vital sign, physical examination, and laboratory test findings in combination with the newborn's estimated risk at birth to determine when to begin empiric antibiotic therapy for EOS. Unfortunately, although the overall appearance of a newborn is said to be the best predictor of EOS, there are only a handful of specific, objective, and evidence-based vital sign and physical examination findings that are useful, and laboratory test results are, disappointingly, of only moderate help. The utility and limitations of these variables are discussed in the following sections

Group B Streptococcus Screening and Intrapartum Antibiotic Prophylaxis

Since the 1970s GBS has been a major cause of neonatal sepsis (Schuchat, 1998). The implementation of intrapartum antibiotic prophylaxis (IAP) to prevent early-onset GBS disease in neonates has been associated with a more than 80% decrease in the rate of infection (Phares et al., 2008; Centers for Disease Control and Prevention, 2016). Recent surveillance data from the United States suggest that the overall rate of EOS caused by GBS is now in the range of 0.25 cases per 1000 live births. Unfortunately, the rates of GBS disease are more than twice as high among African-American neonates in the United States than in newborns of other races (Centers for Disease Control and Prevention, 2016).

The currently recommended strategy to prevent GBS disease is to obtain rectovaginal cultures on all pregnant women at 35–37 weeks' gestation and to administer IAP with penicillin or ampicillin during labor to those colonized with the bacteria. In situations where the mother's GBS status is unknown before the onset of labor, IAP is advised for those with certain risk factors for neonatal infection. IAP is not needed in women who undergo cesarean delivery before the onset of labor with intact amniotic membranes (Verani et al., 2010).

The effectiveness of IAP in preventing early-onset GBS disease in neonates born to colonized mothers is dependent on the drugs used and the timing of administration. Penicillin or ampicillin, with at least one dose given more than 4 hours before delivery, is the most effective treatment. It is estimated that the efficacy of this regimen in preventing GBS disease in term newborns is 91% (95% confidence interval 63%–98%). Although ampicillin or penicillin administered less than 4 hours before delivery has been shown to be effective in reducing vertical transmission, in one surveillance study the effectiveness of ampicillin or penicillin administered less than 2 hours before delivery in preventing early-onset GBS disease was only 47%, and the effectiveness of a dose administered more than 2 hours but less than 4 hours before delivery was estimated at 38%. The effectiveness of clindamycin, administered to women who had a history of penicillin allergy, was estimated at 22%, although antimicrobial susceptibility testing was infrequently performed on the GBS strains cultured from the mothers in this study (Fairlie et al., 2013). It is recommended that clindamycin be used only for IAP in mothers who are colonized by a strain of GBS that is documented to be sensitive to this antibiotic (Verani et al., 2010). Although there are fewer data on the effectiveness of cefazolin for IAP, on the basis of its pharmacologic profile it is likely to have an effectiveness similar to that of penicillin in preventing GBS disease.

Overall, about 75% of women who are screened for GBS are classified as GBS negative (Van Dyke et al., 2009). However, approximately 10% of these classifications are false negatives. Ironically, because of this false-negative rate, and since mothers with negative GBS screening results do not commonly receive IAP, more than 60% of newborns in the United States who develop early-onset GBS disease are born to women classified as GBS negative (Van Dyke et al., 2009). Thus although the risk of EOS from GBS is very low, clinicians should consider this possibility in term newborns born to "GBS-negative" mothers who are displaying signs and symptoms of the disease.

Term newborns whose mothers have received IAP for a positive GBS screen at least 4 hours before delivery (termed *adequate* IAP) can be safely discharged at 24 hours of age if there are no signs or symptoms of infection (Verani et al., 2010). One area of consternation is how long to observe term newborns when the only doses of antibiotics were administered less than 4 hours before delivery ("inadequate" IAP). Most newborns with sepsis present early in life–many at birth, and nearly all by 12 hours of age (Escobar et al., 2000). Among a group of 172 term newborns with documented early-onset GBS infection, 95% had presenting symptoms within 24 hours after delivery (Bromberger et al., 2000). There is the theoretical concern that newborns whose mothers receive some but inadequate IAP to prevent early-onset GBS disease will have a delayed or muted initial presentation because of the antibiotics received. Perhaps because of this concern, in current guidelines it is recommended that such newborns be monitored in the hospital for at least 48 hours after birth (Verani et al., 2010). However, evidence to date suggests that newborns who develop GBS disease despite IAP, either inadequate or adequate, continue to present within the first 24 hours of life and have the same presentation as those with EOS caused by GBS whose mothers did not receive IAP (Bromberger et al., 2000). These data suggest, but do not definitively indicate, that some term newborns born to GBS-positive mothers who received IAP less than 4 hours before delivery may be discharged at less than 48 hours of age. This decision is best made on an individual basis considering all risk factors, examination of the baby, vital sign stability, the results of any available laboratory tests, and parental wishes.

Evaluation of Perinatal Risk Factors

Because the initial signs and symptoms of EOS can be difficult to distinguish from normal newborn variation, the estimate of a newborn's risk of sepsis at birth is crucial for determining appropriate monitoring, laboratory testing, and/or treatment. Several prenatal and perinatal conditions are known to substantially increase the chance that a newborn will develop EOS, including preterm birth, prolonged rupture of amniotic membranes, maternal GBS infection and IAP, maternal fever, chorioamnionitis, and history of a sibling with EOS (Verani et al., 2010, Wortham et al., 2016). In particular, the clinical diagnosis of chorioamnionitis may increase the risk of EOS by twofold to sixfold (Benitz et al., 1999; Escobar et al.,

2000). Because of this, both the Centers for Disease Control and Prevention and the AAP recommend blood cultures be obtained and *all* newborns born to mothers with diagnosed chorioamnionitis be treated with empiric intravenous antibiotics pending the results of the blood cultures.

However, guideline recommendations to initiate treatment with intravenous antibiotics on all *term* newborns born to women with chorioamnionitis remain controversial. Many of the large studies that documented the increased risk of EOS in the setting of chorioamnionitis were conducted before universal GBS screening and IAP (Taylor and Opel, 2012). Although exact figures are elusive, it is estimated that chorioamnionitis complicates approximately 3% of births in the United States (Verani et al., 2010). Given the low current rate of EOS, it has been estimated that 80–210 newborns born to mothers with chorioamnionitis would require empiric antibiotic treatment in order to "catch" one neonate with EOS (i.e., the number needed to treat is 80–210). For term newborns who appear well, the estimated number needed to treat is 450 (Wortham et al., 2016).

Investigators from Boston and northern California have adopted a different approach for estimating the risk of EOS at birth in newborns born at 34 weeks' gestation or later. Using data from more than 600,000 deliveries, they developed a model for assigning a numeric risk of EOS in a newborn based on the following criteria: GA, maximal maternal temperature during labor, hours of rupture of membranes, GBS screening results in the mother, and use and timing of IAP (Puopolo et al., 2011). Of note, the specific presence or absence of chorioamnionitis is not a variable considered in the model. Using a website (http://www.newbornsepsiscalculator.org), clinicians can enter the appropriate data for these variables, and a numeric estimate of sepsis at birth in a particular newborn is provided. The risk of sepsis is further refined on the basis of the clinical appearance of the newborn (well-appearing, equivocal presentation, or evidence of clinical illness). Specific criteria for these classifications are provided. The estimated risk for newborns in each of these categories is provided. The clinician can then consider this risk estimate and determine the appropriate management for the baby. Alternatively, the originators have recommended that empiric antibiotic therapy be initiated if the estimated risk of EOS is 1.54 or more cases per 1000 live births (Escobar et al., 2014). However, there is no rationale for this threshold other than the opinion of the investigators.

Clinical and Laboratory Evaluation

Early identification of a newborn with EOS based on clinical and laboratory findings is difficult. A number of signs and symptoms have been reported to be present in neonates with EOS, including fever, hypothermia, temperature instability, hypotension, lethargy, irritability, pale or mottled skin, cyanosis, apnea, hypoglycemia, acidosis, tachycardia, tachypnea, grunting respirations, nasal flaring, and inspiratory retractions (Escobar et al., 2014; Wortham et al., 2016). Unfortunately, with a few exceptions there has been little investigation on how frequently these signs and symptoms are present early in the course of EOS in term newborns, and it is unclear whether the presence of each of these signs and symptoms is more common in those with EOS versus noninfected babies. Thus the utility of most of these signs and symptoms in helping to diagnose EOS is unknown.

It is apparent that most newborns with EOS have clinical signs of illness and that the rate of EOS is significantly lower in well-appearing neonates who are at risk of infection because of maternal and/or perinatal risk factors. In a compilation of studies the rate of EOS among well-appearing term and preterm newborns was 0.04 per 1000 "at-risk" infants versus 2.9% in symptomatic term and late preterm neonates (Benitz et al., 2015). In another study, of 2785 newborns with birthweights greater than 2000 g who underwent a laboratory evaluation for sepsis, the absence of clinical signs of sepsis reduced the risk of EOS by almost fourfold (Escobar et al., 2000).

The developers of the newborn sepsis calculator (described in the previous section) identified four specific and objective clinical signs of sepsis: temperature of 38.0°C or greater or less than 36.4°C; heart rate of 160 or more beats per minute; respiratory rate of 60 or more breaths per minute; and respiratory distress (grunting, flaring, and retractions) (Escobar et al., 2014). Importantly, for one of these signs to be "present" it needs to be identified at least twice, with the two instances separated by more than 2 hours. If one or more of these signs are present in a newborn previously thought to be "well-appearing," the newborn is not categorized as having "equivocal" examination findings for EOS. This classification system is useful; the sepsis calculator provides different numeric estimations for the risk of sepsis in a newborn with a given risk at birth based on whether the examination findings are normal or equivocal.

Several laboratory test findings, including a low absolute neutrophil count, a high ratio of immature to total neutrophil counts, a high ratio of immature to total neutrophil counts divided by total neutrophil count, and an elevated C-reactive protein level, are statistically associated with an increased risk of EOS (Benitz et al., 1998; Escobar et al., 2000; Newman et al., 2010; Newman et al., 2014). Unfortunately, many, if not most, newborns with EOS have normal laboratory screening test results (Benitz et al., 1998; Escobar et al., 2000; Newman et al., 2010). Further, the negative predictive values of these tests are very high, but since the prevalence of EOS in term newborns, even those with risk factors for sepsis, is low, a normal laboratory test finding, in isolation, is of limited help in aiding clinical decision making.

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