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Cloherty and Stark's Manual of Neonatal Care

NINTH EDITION

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Anne R. Hansen
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Wolters Kluwer

CLOHERTY AND STARK'S MANUAL OF NEONATAL CARE

Ninth Edition

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We dedicate this edition

to former editor and inspiration for the Manual:
John P. Cloherty

to our spouses: Caryn, Jonathan, Brad, and Peter

to our children: Zachary, Taylor, Connor, Emily,
Laura, Jonah, Gregory, Kristen, Linnea, Kathryn, Oliver,
Julian, and Nathalie

to our grandchildren: Abe and Sascha

and to the many babies and parents we have cared for.

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Preface

This edition of *Cloherty and Stark's Manual of Neonatal Care* has been updated and revised to reflect the many changes in fetal, perinatal, and neonatal care that have occurred since the eighth edition.

In the *Manual*, we describe our current and practical approaches to evaluation and management of conditions encountered in the fetus and the newborn, as practiced in high-volume clinical services that include contemporary prenatal and postnatal care of infants with routine as well as complex medical and surgical problems. Although we base our practice on the best available evidence, we recognize that many areas of controversy exist, that there is often more than one approach to a problem, and that our knowledge continues to grow. Our commitment to values, including clinical excellence, multidisciplinary collaboration, teamwork, and family-centered care, is evident throughout the book. Support of families is reflected in our chapters on breastfeeding, developmental care, bereavement, and decision making and ethical dilemmas. To help guide our readers, we have a section of key points at the start of each chapter.

Many individuals around the world contributed to advance the care of newborns. We especially recognize our teachers, colleagues, and trainees at Harvard, where the four editors trained in newborn medicine and practiced in the neonatal intensive care units (NICUs). We are grateful to Clement Smith, Nicholas M. Nelson, and Mary Ellen Avery for their pioneering insights into newborn physiology and to all the former and current leaders and members of the Newborn Medicine Program at Harvard.

This would have been an impossible task without the administrative assistance of Isabelle Smith. We also thank Wolters Kluwer.

We dedicate this book to William D. Cochran for his commitment to the care of newborns in the Harvard teaching hospitals and to the personal support and advice he provided to so many, including the editors. We also acknowledge the contribution of our founding editor, Dr. John P. Cloherty, whose collaboration with current editor Dr. Ann R. Stark led to the first edition more than four decades ago and is acknowledged in the title of this edition. Finally, we gratefully acknowledge the nurses, residents, fellows, parents, and babies who provide the inspiration for and measure the usefulness of the information contained in this volume.

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Contents

General Newborn Condition

Respiratory Disorders

Cardiovascular Disorders

Hematologic Disorders

Infectious Diseases

1 Fetal Assessment and Prenatal Diagnosis

Rebecca M. Reimers, Stephanie Dukhovny, and Louise E. Wilkins-Haug

KEY POINTS

- Several different methods for prenatal diagnosis of fetal disease are currently available to the clinician.
- Fetal size and growth rate abnormalities may have significant implications for perinatal prognosis and care.
- Methods to assess fetal well-being prenatally are central to obstetrical practice.

I. GESTATIONAL AGE ASSESSMENT is important to both the obstetrician and pediatrician and must be made with a reasonable degree of precision. Elective obstetric interventions such as chorionic villus sampling (CVS) and amniocentesis must be timed appropriately. When premature delivery is inevitable, gestational age is important with regard to prognosis, the management of labor and delivery, and the initial neonatal treatment plan.

A. The clinical estimate of gestational age is usually made on the basis of the first day of the last menstrual period (LMP). Accompanied by physical examination, auscultation of fetal heart sounds and maternal perception of fetal movement can also be helpful.

B. Ultrasound is the most accurate method for estimating gestational age early in gestation, but as gestation advances, dating based on ultrasound alone may introduce error if there is fetal growth restriction (FGR). Once established based on clinical and ultrasound criteria, the due date should not be changed later in gestation. During the first trimester, fetal crown-rump length (CRL) can be an accurate predictor of gestational age. After 14 weeks, measurements of the biparietal diameter (BPD), the head circumference (HC), abdominal circumference (AC), and the fetal femur length are used to estimate gestational age. Strict criteria for measuring the cross-sectional images through the fetal head ensure accuracy. If the due date by LMP differs from the due date estimated by ultrasound, there are established criteria for changing the due date. Table 1.1 lists the criteria for changing the due date based on the difference between the due date estimated by LMP and ultrasound.

Table 1.1. Estimating Due Date by Last Menstrual Period (LMP) and Ultrasound Measurements

Gestational Age Range by LMP	Redate by Ultrasound for Discrepancy of	Method of Ultrasound Measurement
<8 6/7 weeks	>5 days	CRL
9 0/7–13 6/7 weeks	>7 days	CRL
14 0/7–15 6/7 weeks	>7 days	BPD, HC, AC, FL
16 0/7–21 6/7 weeks	>10 days	BPD, HC, AC, FL
22 0/7–27 6/7 weeks	>14 days	BPD, HC, AC, FL
28 0/7 weeks and beyond	>21 days	BPD, HC, AC, FL

CRL, crown-rump length; BPD, biparietal diameter; HC, head circumference; AC, abdominal circumference; FL, femur length.

Source: Based on American College of Obstetricians and Gynecologists. ACOG Committee Opinion No. 700: methods for estimating due date. *Obstet Gynecol* 2017;129(5):e150–e154.

II. PRENATAL DIAGNOSIS OF FETAL DISEASE continues to improve. The genetic and developmental basis for many disorders is emerging, along with increased test accuracy. Two types of tests are available: screening tests and diagnostic tests. Screening tests, such as a sample of the mother's blood or an ultrasound finding, are noninvasive but relatively nonspecific. A positive screening test, concerning family history, or an ultrasonic examination that suggests anomalies or aneuploidy may lead patient and physician to consider a diagnostic procedure. Diagnostic procedures, which necessitate obtaining a sample of fetal or placental tissue, pose a small risk to both mother and fetus but can confirm or rule out the disorder in question.

A. Cell-free DNA (cfDNA) screening for aneuploidy. Sequencing technology allows analysis of cfDNA from maternal serum to detect trisomies 13, 18, and 21 and sex chromosomal aneuploidies. Additionally, some platforms will also test for microdeletions and microduplications and single-gene disorders. The fetal DNA detected in maternal blood is placental in origin, can be detected as early as 9 weeks, and can be tested throughout the entire pregnancy. The cfDNA in maternal blood originates from apoptosis (or programmed cell death), and the fetal fraction ranges from 3% to 13%. Gestational age, fetal, and maternal characteristics can lead to a low fetal fraction which can lead to a "no-call" result due to insufficient information. A number of laboratories have commercially available tests; all of which report a high detection rate and low false-positive rate. The most recent meta-analysis detection rate for trisomy 21 was 99.7%; for trisomy 18, the detection rate was 97.9%; and 99% for trisomy 13. The combined false-positive rate was 0.13%, although these figures do not account for no call results. cfDNA screening is the most accurate screening test available and can also be offered to women

who are low risk or who are carrying twins. For younger women as a group, the positive predictive value (PPV) is lower secondary to the lower prevalence of aneuploidy in this population. For example, for trisomy 21, the PPV is 33% for women younger than 25 years, in comparison to 87% for women older than 40 years. Similarly for twins, the detection rate is lower and false-positive rate higher. However, for twins, cfDNA screening is still the most accurate screening test available and can be offered with appropriate genetic counseling. It is important to note that routinely offered cell-free fetal DNA screening targets specific aneuploidies and may miss abnormalities in other chromosomes, mosaicism, and many copy number variants (CNVs). One study estimates up to 17% of fetuses with an ultrasound anomaly had a significant chromosome abnormalities that may go undetected with the use of cell-free fetal DNA screening alone. cfDNA is considered a screening test, and any positive cell-free fetal DNA result should be followed up with a diagnostic test (CVS or amniocentesis) for confirmation of the diagnosis. Additionally, the recommended test after finding a fetal structural anomaly on ultrasound is a diagnostic test rather than a screening test. cfDNA is also known as noninvasive prenatal testing (NIPT), and as mentioned earlier, aspects of screening as opposed to diagnosis should be remembered.

B. Single-gene cfDNA screening is available commercially for multiple purposes. Identification of fetal Rh status for women at risk for isoimmunization can be done with >99% accuracy, although this test is not currently widely used in clinical applications. Additionally, commercially available multigene panels based on sequencing of maternal DNA, paternal DNA, and cfDNA are available to detect many single-gene conditions such as achondroplasia, Noonan syndrome, osteogenesis imperfecta, and CHARGE syndrome (syndrome of coloboma, heart defects, atresia choanae, growth restriction, genital and ear abnormalities) among others. The use of single-gene cfDNA screening for these Mendelian disorders is not yet recommended by national organizations, and the utility and screening parameters are still active areas of investigation.

C. Screening by maternal serum analysis during pregnancy individualizes a woman's risk of carrying a fetus with a neural tube defect (NTD) or an aneuploidy such as trisomy 21 (Down syndrome) or trisomy 18 (Edward syndrome).

1. **Maternal serum α-fetoprotein (MSAFP)** measurement between 15 and 22 weeks' gestation screens for NTDs. MSAFP elevated above 2.5 multiples of the median for gestation age occurs in 70% to 85% of fetuses with open spina bifida and 95% of fetuses with anencephaly. In half of the women with elevated levels, ultrasonic examination reveals another cause, most commonly an error in gestational age estimate. Ultrasonography that incorporates cranial or intracranial signs such as changes in head shape (lemon sign) or deformation of the cerebellum (banana sign) that are secondary to the NTD increases the sensitivity of ultrasound for the visual detection of open spinal defects.
2. **Second-trimester aneuploidy screening: MSAFP/quad panel.** Low levels of MSAFP are associated with chromosomal abnormalities. Altered levels of human chorionic gonadotropin (hCG), unconjugated estriol (uE3), and inhibin are also associated with fetal chromosomal abnormalities.

On average, in a pregnancy with a fetus with trisomy 21, hCG and inhibin levels are higher than expected and uE3 levels are decreased. A serum panel in combination with maternal age can estimate the risk of trisomy 21 for an individual woman. For women younger than 35 years, 5% will have a positive serum screen, but the majority (98%) will not have a fetus with aneuploidy. Only 80% of fetuses with trisomy 21 will have a "positive" quad screen (MSAFP, hCG, uE3, inhibin). Trisomy 18 is typically signaled by low levels of all markers.

3. **First-trimester serum screening.** Maternal levels of two analytes, pregnancy-associated plasma protein-A (PAPP-A) and hCG (either free or total), are altered in pregnancies with an aneuploid conception, especially trisomy 21. Similar to second-trimester serum screening, these values can individualize a woman's risk of pregnancy complicated by aneuploidy. However, these tests need to be drawn early in pregnancy (optimally at 9 to 10 weeks) and, even if abnormal, detect less than half of the fetuses with trisomy 21.
4. **First-trimester nuchal lucency screening.** Ultrasonographic assessment of the fluid collected at the nape of the fetal neck is a sensitive marker for aneuploidy. With attention to optimization of image and quality control, studies indicate a 70% to 80% detection of aneuploidy in pregnancies with an enlarged nuchal lucency on ultrasonography. In addition, some fetuses with structural abnormalities such as cardiac defects and genetic disorders such as Noonan syndrome and other RASopathies will also have an enlarged nuchal lucency.
5. **Combined first-trimester screening.** Combining the two first-trimester maternal serum markers (PAPP-A and β-hCG) and the nuchal lucency measurements in addition to the maternal age detects 80% of trisomy 21 fetuses with a low screen positive rate (5% in women younger than 35 years). This combined first-trimester screening provides women with a more sensitive risk assessment in the first trimester.
6. **Combined first- and second-trimester screening for trisomy 21.** Various approaches have been developed to further increase the sensitivity of screening for trisomy 21 while retaining a low screen positive rate. These approaches differ primarily by whether they disclose the results of their first trimester results.

   a. Integrated screening. This is a nondisclosure approach that achieves the highest detection of trisomy 21 (97%) at a low screen positive rate (2%). It involves a first-trimester ultrasound and maternal serum screening in both the first and second trimester before the results are released.

   b. Sequential screening. Two types of sequential screening tools exist. Both are disclosure tests, which means that they release those results indicating a high risk of trisomy 21 in the first trimester but then go on to either further screen the entire remaining population in the second trimester (stepwise sequential) or only a subgroup of women felt to be in a medium-risk zone (contingent sequential). With contingent sequential screening, patients can be classified as high risk, medium risk, or low risk for Down syndrome in the first trimester. Low-risk patients do not return for further screening as their risk of a fetus with Down syndrome

is low. When the two types of sequential tests are compared, they have similar overall screen positive rates of 2% to 3%, and both have sensitivities of >90% for trisomy 21 (stepwise, 95%; contingent, 93%).

7. **Use of ultrasound following serum screening for aneuploidy**

a. Second-trimester ultrasound targeted for the detection of aneuploidy has also been successful as a screening tool. Application of second-trimester ultrasound that is targeted to screen for aneuploidy can decrease the *a priori* maternal age risk of Down syndrome by 50% to 60% as well as the risk conveyed by serum screening. Second-trimester ultrasound following first-trimester screening for aneuploidy has likewise been shown to have value in decreasing the risk assessment for trisomy 21.

D. In women with a **positive family history of genetic disease**, a positive screening test, or at-risk ultrasonographic features, diagnostic tests are recommended. When a diagnostic test is performed for a structural abnormality detected on ultrasound, a chromosomal microarray is indicated, which will detect aneuploidy as well as smaller chromosomal CNVs, also called microdeletions or duplications. Pathogenic CNVs are present in 0.4% of pregnancies among women pursuing testing due to advanced maternal age or maternal anxiety. Moreover, the distribution of pathogenic CNVs did not differ by maternal age, and women younger than 35 years have a higher incidence of a syndromic CNV than a fetus with Down syndrome. A microarray will not detect balanced translocations or structural rearrangements, and some platforms will miss triploidy. However, in fetuses with ultrasound anomalies and a normal karyotype, microarray will be abnormal in an additional 6% of cases. If an invasive diagnostic test is performed secondary to a positive screening test, a chromosomal microarray and/or a karyotype can be offered. When a significant malformation or a genetic disease is diagnosed prenatally, the information gives the obstetrician and pediatrician time to educate parents, discuss reproductive options, and establish an initial neonatal treatment plan before the infant is delivered. In some cases, treatment may be initiated *in utero*.

1. **CVS.** Under ultrasonic guidance, a sample of placental tissue is obtained through a catheter placed either transcervically or transabdominally. Performed at or after 10 weeks' gestation, CVS provides the earliest possible detection of a genetically abnormal fetus through analysis of trophoblast cells. Transabdominal CVS can also be used as late as the third trimester when amniotic fluid is not available or fetal blood sampling cannot be performed.
2. **Technical improvements** in ultrasonographic imaging and in the CVS procedure have brought the procedure-related pregnancy loss rate very close to the loss rate after second-trimester amniocentesis at 0.2%. The possible complications of amniocentesis and CVS are similar. CVS, if performed before 10 weeks of gestation, can be associated with an increased risk of fetal limb-reduction defects and oromandibular malformations.

a. Direct preparations of rapidly dividing cytotrophoblasts can be prepared, making a full karyotype analysis available in 2 days. Although direct preparations minimize maternal cell contamination, most centers

also analyze cultured trophoblast cells, which are embryologically more similar to the fetus. Analysis based on cell culture takes an additional 8 to 12 days.

b. In approximately 2% of CVS samples, two or more karyotypically distinct populations of cells may be present, termed mosaicism. Because CVS-acquired cells reflect placental constitution, in these cases, amniocentesis is offered as a follow-up study to analyze fetal cells. Approximately one-third of CVS mosaicisms are confirmed in the fetus through amniocentesis.

3. **Amniocentesis.** Amniotic fluid is removed from around the fetus through a needle guided by ultrasound. The removed amniotic fluid (20 to 30 mL) is replaced by the fetus within 24 hours. Amniocentesis can technically be performed as early as 10 to 14 weeks' gestation, although early amniocentesis (<13 weeks) is associated with a pregnancy loss rate of 1% to 2% and an increased incidence of clubfoot. Procedure-related loss of the pregnancy due to ultrasonography-guided second-trimester amniocentesis (16 to 20 weeks) occurs in 0.3% of cases and pregnancy loss overall is 0.9%. Rupture of membranes can occur in 1% of cases with the majority reaccumulating normal amounts of amniotic fluid within 3 weeks and proceed to a normal delivery.

a. Amniotic fluid can be analyzed for a number of compounds, including α-fetoprotein (AFP), acetylcholinesterase (AChE), and bilirubin. Increased levels of AFP along with the presence of AChE identify NTDs with >98% sensitivity when the fluid sample is not contaminated by fetal blood. AFP levels are also elevated when the fetus has abdominal wall defects, congenital nephrosis, or intestinal atresias.

b. Fetal cells can be extracted from the fluid sample and analyzed for chromosomal and genetic makeup.

i. Among second-trimester amniocenteses, 73% of clinically significant karyotype abnormalities relate to one of five chromosomes: 13, 18, 21, X, or Y. These can be rapidly detected using fluorescent *in situ* hybridization (FISH), with sensitivities in the 90% range.

ii. **DNA analysis** is diagnostic for an increasing number of diseases.

a) Rapid advances in molecular technologies have provided many new opportunities for genetic diagnosis, which are now applicable to prenatal diagnosis. Sequencing of fetal DNA can be diagnostic specifically when paired with parental DNA samples for analysis. If the pattern of fetal anomalies or family history is clear, single-gene sequencing and/or deletion/duplication testing can be offered. Alternatively, for less specific fetal presentations, offering a panel of genes or exome sequencing (looking at the protein-encoding exons of over 20,000 genes) can be performed. Studies determining the yield and utility of exome sequencing in prenatal cohorts are rapidly emerging. In studies where exome sequencing was applied in the setting of ultrasound anomalies, a diagnosis was made in 8% to 10% of fetuses. In a study of fetuses with hydrops, 29% of fetuses had a diagnosis made through exome sequencing. Exome sequencing

analysis differs between laboratories which can contribute to a higher percentage of variants of unknown significance, a challenge for prenatal counseling but also an opportunity for exploring developmental biology. A specific diagnosis allows for tailored treatment, planning for delivery location, and family preparation and can inform the family of recurrence risk if an X-linked or autosomal recessive disease is diagnosed. Additionally, an *in utero* therapy trial is ongoing for α-thalassemia, and other disorders may have tailored *in utero* treatment opportunities in the near future.

4. **Percutaneous umbilical blood sampling (PUBS)** is performed under ultrasonic guidance from the second trimester until term. PUBS can provide diagnostic samples for cytogenetic, hematologic, immunologic, or DNA studies; it can also provide access for treatment *in utero*. An anterior placenta facilitates obtaining a sample close to the cord insertion site at the placenta. Fetal sedation is usually not needed. PUBS has a 1% to 2% risk of fetal loss along with complications that can lead to a preterm delivery in another 5%.
5. **Preimplantation biopsy or preimplantation genetic testing (PGT).** During an *in vitro* fertilization process, early in gestation (at day 5 of embryonic development), prior to transfer, cells can be removed without known harm to the embryo. PGT is used to detect aneuploidy (PGT-A), structural rearrangements (PGT-SR) in families with known chromosomal translocations, and monogenic disease (PGT-M) for a wide range of autosomal recessive, dominant, and X-linked molecular diagnoses. For couples at risk, testing allows for identification of embryos that would likely be affected by the disorder in question, and transfer of unaffected embryos can occur. In women who are at risk for X-linked recessive disorders, determination of XX-containing embryos can enable transfer of female embryos. An alternative approach is analysis of the second polar body, which contains the same genetic material as the ovum. The clinical benefit of PGT-A on pregnancy outcomes is an area of controversy and ongoing investigation. Recent trials in women younger than 35 years showed no benefit to PGT-A on live birth rate. Prior studies in women of advanced maternal age showed PGT-A may increase the live birth rate and decrease time to pregnancy. Currently, there is insufficient evidence to recommend PGT-A for routine care.

III. FETAL SIZE AND GROWTH-RATE ABNORMALITIES

may have significant implications for perinatal prognosis and care (see Chapter 7). Appropriate fetal assessment is important in establishing a diagnosis and a perinatal treatment plan.

A. FGR may be due to conditions in the fetal environment (e.g., chronic deficiencies in oxygen or nutrients or both) or to problems intrinsic to the fetus. It is important to identify constitutionally normal fetuses whose growth is impaired so that close antenatal testing can begin as soon as possible. Because their risk of mortality is increased severalfold in the antenatal period and during labor, fetuses with FGR may benefit from preterm delivery to avoid stillbirth. Once delivered, these newborns are at increased risk for

immediate complications including hypoglycemia and pulmonary hemorrhage, so they should be delivered at an appropriately equipped facility.

Intrinsic causes of FGR include genetic abnormalities (such as aneuploidy, microdeletions, or microduplications, or single gene disorders), congenital malformations, and congenital infections (e.g., cytomegalovirus, toxoplasmosis, varicella, or rubella). Prenatal diagnosis of anomalous or infected fetuses is important so that appropriate interventions can be made. Prenatal assessment with a detailed anatomic ultrasound and diagnostic testing with microarray should be considered if FGR is diagnosed before 32 weeks. Also, genetic testing is of relevance in a fetus with an ultrasound anomaly or polyhydramnios as up to 20% of these fetuses have a chromosomal abnormality. Prior knowledge that the FGR fetus has a genetic abnormality (e.g., trisomy 18) that limits life allows the parents to be counseled before birth of the child and may influence the management of labor and delivery.

1. **Definition of FGR.** A fetus that does not reach his or her intrauterine growth potential is included. Fetuses with an ultrasound estimate of fetal weight or AC <10th percentile for gestational age are classified as FGR; however, many of these fetuses are at the lower end of the growth spectrum but meeting their genetic potential (i.e., "constitutionally small").
2. **Diagnosis of FGR.** Maternal clinical exam detects about two-thirds of cases and incorrectly diagnoses it about 50% of the time. Ultrasonography improves the sensitivity and specificity to >80%. FGR may be diagnosed with a single scan when a fetus <10th percentile demonstrates corroborative signs of a compromised intrauterine environment such as oligohydramnios, an elevated head–abdomen ratio in the absence of central nervous system pathology or abnormal Doppler velocimetry in the umbilical cord. Serial scans documenting absent or poor intrauterine growth regardless of the weight percentile could also indicate FGR. The greatest risk for morbidity/mortality is among fetuses below the 3rd percentile for estimated fetal weight with abnormal umbilical Doppler perfusion and delayed serial growth trajectory. The use of composite growth profiles derived from a variety of ultrasound measurements and repeated serially to identify individual restriction of fetal growth potential remains controversial.

B. Macrosomia. Macrosomic fetuses (>4,000 g) are at increased risk for shoulder dystocia and traumatic birth injury. Conditions such as maternal diabetes, postterm pregnancy, genetic overgrowth syndromes, and maternal obesity are associated with an increased incidence of macrosomia. Unfortunately, efforts to use a variety of measurements and formulas have met with only modest success in predicting the condition.

IV. FUNCTIONAL MATURITY OF THE LUNGS

is a critical variable in determining neonatal survival in the otherwise normal fetus. A number of tests can be performed on amniotic fluid specifically to determine pulmonary maturity (see Chapter 33). Currently, however, assessment of fetal maturity is not recommended to guide timing of delivery as nonmedically indicated delivery before

39 weeks is not advised. Even with documentation of functional maturity of the lungs, morbidity of neonates in the early term is increased relative to neonates delivered after 39 weeks. In pregnancies complicated by maternal medical illness, hypertensive disorders, diabetes, or fetal anomalies, the risk of stillbirth must be weighed against the risk of neonatal morbidity due to preterm or early term delivery.

V. ASSESSMENT OF FETAL WELL-BEING.

Acute compromise is detected by studies that assess fetal function. Some are used antepartum, whereas others are used to monitor the fetus during labor.

A. Antepartum tests generally rely on biophysical studies, which require a certain degree of fetal neurophysiologic maturity. The following tests are not used until the third trimester; fetuses may not respond appropriately earlier in gestation.

1. Fetal movement monitoring is the simplest method of fetal assessment. Fetuses normally have a sleep–wake cycle, and mothers generally perceive a diurnal variation in fetal activity. Active periods average 30 to 40 minutes. Periods of inactivity >1 hour are unusual in a healthy fetus and should alert the physician and patient to the possibility of fetal compromise. A "count to 10" method by the mother is the only approach to fetal movement which has been validated and then evaluated as a screening test. The same time of day is chosen, fetal movements are noted with the expectation of 10 fetal movements achieved within 2 hours. The average time to 10 movements is 20 minutes (±18). Lack of attaining 10 movements should prompt evaluation. However, although a mother's perception of decreased fetal movement should always elicit further surveillance, the specifics of fetal movement quantification remain to be further established.

2. The **nonstress test (NST)** is a reliable means of fetal evaluation. It is simple to perform, relatively quick, and noninvasive, with neither discomfort nor risk to mother or fetus.

The NST is based on the principle that fetal activity results in a reflex acceleration in heart rate. The required fetal maturity is typically reached by approximately 32 weeks of gestation. Absence of these accelerations in a fetus who previously demonstrated them may indicate that hypoxia has sufficiently depressed the central nervous system to inactivate the cardiac reflex. Testing reflexes the current fetal state and cannot predict future events or precisely the neonatal outcome.

The test is performed by monitoring fetal heart rate (FHR) either through a Doppler ultrasonographic device or through skin-surface electrodes on the maternal abdomen. Uterine activity is simultaneously recorded through a tocodynamometer, palpation by trained test personnel, or the patient's report. The test result may be reactive, nonreactive, or inadequate. The criteria for a reactive test are as follows: (i) heart rate between 110 and 160 bpm, (ii) moderate beat-to-beat variability (5 to 25 bpm), and (iii) two accelerations of at least 15 bpm lasting for at least 15 seconds each within a 20-minute period. A nonreactive test is defined as less than two accelerations in 40 minutes. If an adequate fetal

heart tracing cannot be obtained for any reason, the test is considered inadequate.

A reactive result is reassuring, with the risk of fetal demise within the week following the test at approximately 3 in 1,000. Negative predictive values for stillbirth within 1 week of reactive NSTs are 99.8%. A nonreactive test is generally repeated later the same day or is followed by another test of fetal well-being. The frequency with which NST should be performed is not established. The NST is commonly obtained on a weekly basis, although increased testing (two times per week to daily testing) is recommended for high-risk conditions.

3. The **contraction stress test (CST)** may be used as a backup or confirmatory test when the NST is nonreactive or inadequate, although with multiple other modalities for fetal surveillance, CST is now rarely used.

   The CST is based on the idea that uterine contractions can compromise an unhealthy fetus. A healthy fetoplacental unit has sufficient reserve to tolerate the short reduction in oxygen supply associated with contractions. Under hypoxic conditions, the FHR slows in a characteristic way following the contraction. This characteristic heart rate pattern is known as a *late deceleration* because of its relationship to the uterine contraction.

   If no spontaneous contractions are present, they can be induced with intravenous oxytocin, in which case the test is called an *oxytocin challenge* test.

   A CST is negative if at least three contractions of at least 40 seconds each occur within a 10-minute period without associated late decelerations. A CST is suspicious if there are occasional or inconsistent late decelerations. A negative CST is even more reassuring than a reactive NST, with the chance of fetal demise within a week of a negative CST being approximately 0.4 per 1,000. If a positive CST, with late decelerations occurring consistently after contractions, follows a nonreactive NST, the risk of stillbirth is 88 per 1,000, and the risk of neonatal mortality is also 88 per 1,000. Statistically, about one-third of patients with a positive CST will require cesarean section for persistent late decelerations in labor.

4. The **biophysical profile** (BPP) assesses four parameters determined by real-time ultrasonic examination. A score of 0 or 2 is assigned for the absence or presence of each of the following: adequate amniotic fluid volume (vertical fluid pocket >2 cm), fetal breathing movements for 30 seconds, fetal activity, and normal fetal musculoskeletal tone. An NST, if reactive, will add 2 additional points. A modified BPP can assess both acute (NST) and chronic stress (amniotic fluid volumes). The total score determines the course of action. Reassuring tests (8 to 10) are repeated at weekly intervals, whereas less reassuring results (4 to 6) are repeated later the same day. Very low scores (0 to 2) generally prompt delivery. The likelihood that a fetus will die *in utero* within 1 week of a reassuring test is approximately the same as that for a negative CST, which is approximately 0.6 to 0.7 per 1,000. Similarly, the negative predictive value for a stillbirth within 1 week of a reassuring BPP, modified BPP, and negative CST is >99.9%.

5. Doppler ultrasonography of **fetal umbilical artery blood flow** is a noninvasive technique to assess placental resistance. Placentas with extensive vasospasm or infarction have an increased resistance to blood

flow that is particularly noticeable in fetal diastole. Umbilical artery Doppler flow velocimetry is the primary surveillance tool for pregnancies with FGR and uses the peak systolic frequency shift (S) and the end-diastolic frequency shift (D). Multiple studies have established the association of increased morbidity and mortality occurring primarily among FGR fetuses with abnormal umbilical Doppler studies (pulsatility index >95th percentile or absent/reversed end-diastolic flow). Analyses of placental histology with abnormal umbilical Doppler flow have suggested loss of 70% function is reflected with absent/reversed umbilical Doppler readings. The two commonly used indices of flow are the systolic:diastolic ratio (S/D) and the resistance index (S-D/S). Umbilical artery Doppler velocimetry measurements have been shown to improve perinatal outcome only in pregnancies with a presumptive diagnosis of FGR and should not be used as a screening test in the general obstetric population. The use of umbilical artery Doppler velocimetry measurements, in conjunction with other tests of fetal well-being, can reduce the perinatal mortality in FGR by almost 40%. Doppler measurements of the middle cerebral artery can also be used in the assessment of the fetus that is at risk for either FGR or anemia. Further evidence of the progression of uteroplacental insufficiency can be revealed by ultrasound assessment of the ductus venosus. Absent or even reversal of the normally forward end-diastolic flow through this vessel is considered a terminal finding. Modern high-quality prospective data using ductus venosus Doppler is lacking, but retrospective studies support the use of electronic fetal monitoring (EFM), BPPs, and late ductus venosus Doppler changes in determining timing of delivery in order to avoid stillbirth and cerebral palsy.

6. **Indications for fetal surveillance.** Pregnancies with ongoing increased risk for stillbirth (chronic hypertension, pregestational diabetes, poorly controlled gestational diabetes, growth restriction, advanced maternal age, maternal obesity, or vascular disease) or new risk (decreased fetal movement, abdominal trauma, vaginal bleeding) are candidates for fetal surveillance. Most fetal surveillance methods are begun at 32 weeks, although in the setting of FGR, in particular, initiation prior to 32 weeks is often undertaken. The frequency of monitoring is typically weekly to twice weekly, although in high-risk conditions or those in which the mother's condition is changing, more frequent monitoring may be needed.

B. Intrapartum assessment of fetal well-being is important in the management of labor.

1. **Intrapartum events** are associated with 25% to 35% of cases of cerebral palsy. Continuous EFM is widely used and has been associated with reduced neonatal seizures. However, the role of EFM in reducing perinatal mortality has been questioned, and it does not lower rates of neurologic injury relative to auscultation by trained personnel. EFM has, however, increased the incidence of operative delivery. When used, the monitors simultaneously record FHR and uterine activity for ongoing evaluation. Either continuous or intermittent monitoring is acceptable for low-risk patients.

   a. The **FHR** can be monitored in one of three ways. The noninvasive methods are ultrasonic monitoring and surface-electrode monitoring from

the maternal abdomen. The most accurate but invasive method is to place a small electrode into the skin of the fetal presenting part to record the fetal electrocardiogram directly. Placement requires rupture of the fetal membranes. When the electrode is properly placed, it is associated with a very low risk of fetal injury. Approximately 4% of monitored babies develop a mild infection at the electrode site, and most respond to local cleansing.

b. Uterine activity can also be recorded either indirectly or directly. A tocodynamometer can be strapped to the maternal abdomen to record the timing and duration of contractions as well as crude relative intensity. When a more precise evaluation is needed, an intrauterine pressure catheter can be inserted following rupture of the fetal membranes to quantitatively record contraction pressure. Invasive monitoring is associated with an increased incidence of chorioamnionitis and postpartum maternal infection.

c. Parameters of the fetal monitoring that are evaluated include the following:

i. **Baseline heart rate** is normally between 110 and 160 bpm. The baseline must be apparent for a minimum of 2 minutes in any 10-minute segment. Baseline fetal bradycardia, defined as an FHR <110 bpm, may result from congenital heart block associated with congenital heart malformation, or fetal heart block from maternal rheumatologic disease. Baseline tachycardia, defined as an FHR >160 bpm, may result from a maternal fever, infection, stimulant medications or drugs, and hyperthyroidism. Fetal dysrhythmias are typically associated with FHR >200 bpm. In isolation, tachycardia is poorly predictive of fetal hypoxemia or acidosis unless accompanied by reduced beat-to-beat variability or recurrent decelerations.

ii. **Beat-to-beat variability** in an awake term fetus constantly varies the heart rate from beat to beat by approximately 5 to 25 bpm because of the autonomic nervous system. Reduced beat-to-beat variability may result from depression of the fetal central nervous system due to fetal immaturity, hypoxia, fetal sleep, or specific maternal medications such as narcotics, sedatives, β-blockers, and intravenous magnesium sulfate.

iii. **Accelerations** of the FHR are associated with lack of fetal hypoxemia, as with an NST.

iv. **Decelerations** of the FHR may be benign or indicative of fetal compromise depending on their characteristic shape and timing in relation to uterine contractions.

a) Early decelerations are symmetric in shape and closely mirror uterine contractions in time of onset, duration, and termination. They are benign and usually accompany good beat-to-beat variability. These decelerations are more commonly seen in active labor when the fetal head is compressed in the pelvis, resulting in a parasympathetic effect.

b) Late decelerations are visually apparent decreases in the FHR in association with uterine contractions. The onset, nadir, and recovery of the deceleration occur after the beginning, peak, and end of the contraction, respectively. Late decelerations are the result of uteroplacental insufficiency and possible fetal hypoxia. Repetitive late decelerations demand action.

c) Variable decelerations vary in their shape and in their timing relative to contractions. Usually, they result from fetal umbilical cord compression. Variable decelerations are a cause for concern if they are severe, associated with poor beat-to-beat variability, or mixed with late decelerations. Umbilical cord compression secondary to a low amniotic fluid volume (oligohydramnios) may be alleviated by amnioinfusion of saline into the uterine cavity during labor.

2. National Institute of Child Health and Human Development. classification of intrapartum FHR monitoring

a. Endorsed by the American College of Obstetricians and Gynecologists, a three-tiered classification of intrapartum monitoring was introduced in 2008 to promote a systematic interpretation and response to the subjective nature of fetal monitor interpretations. Category I tracings are considered reflexive of a fetus with a normal acid–base status but require repeated review. Category III tracings require prompt intervention and, if unresolved quickly, then delivery. For category II tracings, various precipitating factors may be addressed, and if unsuccessful, then delivery is recommended (Table 1.2).

Table 1.2. Classification of Intrapartum Monitoring

Category I	Tracings meeting these criteria are predictive of normal fetal acid–base balance at the time of observation.	All of the criteria must be present: ■ Baseline rate: 110–160 bpm ■ Moderate baseline FHR variability ■ No late or variable decelerations ■ Early decelerations may be present or absent. ■ Accelerations may be present or absent.
Category II	FHR tracing does not meet criteria for either category I or III and is considered indeterminate.	
Category III	■ Category III tracings are predictive of abnormal fetal acid–base status at the time of observation. ■ Prompt evaluation is indicated and intervention indicated.	Either 1 or 2 is present: **1.** Absent baseline FHR variability and any of the following: ■ Recurrent late decelerations ■ Recurrent variable decelerations ■ Bradycardia **2.** Sinusoidal pattern

FHR, fetal heart rate.

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2 Maternal Diabetes Mellitus

Cara D. Dolin

KEY POINTS

- With appropriate management of pregnant women with diabetes, those with good glycemic control and minimal microvascular disease can expect pregnancy outcomes comparable to the general population.
- Women with pregestational diabetes are at significantly increased risk for hypertensive disorders of pregnancy, such as preeclampsia, which is potentially deleterious to both maternal and fetal well-being.
- Timing and route of delivery of a fetus affected by maternal diabetes is determined by ultrasonography-estimated fetal weight, maternal and fetal conditions, and previous obstetric history.
- Preconception glucose control for women with pregestational diabetes can reduce the risk of congenital anomalies to near that of the general population.
- Strict glycemic control can reduce fetal macrosomia in both pregestational and gestational diabetes. Targeting postmeal glycemia is more effective than solely premeal measurement to reduce fetal overgrowth.
- Women with pregestational diabetes and microvascular disease are at risk for medically indicated preterm delivery due to worsening maternal or fetal status.
- Women with pregestational diabetes may have reduced insulin requirements postpartum, especially if breastfeeding.
- Women with gestational diabetes have an increased lifetime risk of developing diabetes.

I. CLASSIFICATION OF DIABETES IN PREGNANCY

A. Gestational diabetes. Gestational diabetes mellitus (GDM) is defined as glucose intolerance of variable severity first diagnosed during pregnancy. In the United States, most women are screened for GDM between 24 and 28 weeks' gestation by a 50-g, 1-hour glucose challenge. A positive result of a blood glucose ≥130 to 140 mg/dL is followed by a diagnostic 100-g, 3-hour oral glucose tolerance test (GTT). A positive test is defined as two or more elevated values on the GTT. Outside of the United States, a single diagnostic test consisting of a 75-g, 2-hour GTT is used to diagnose GDM.

B. Pregestational diabetes. Preexisting diabetes includes both type 1 and type 2 diabetes. Type 1 diabetes is characterized by an absolute insulin deficiency caused by autoimmune destruction of pancreatic beta cells leading to little or no insulin production. Type 2 diabetes is characterized by a relative insulin deficiency, caused by decreased insulin secretion by the pancreas and insulin resistance.

II. EPIDEMIOLOGY

A. Gestational diabetes. GDM affects 6% to 8% of pregnancies in the United States. Approximately 3% to 5% of patients with GDM actually have underlying pregestational diabetes, but pregnancy is the first opportunity for testing. Risk factors for GDM include obesity, advanced maternal age, hypertension, multifetal gestation, and strong family history of diabetes.

B. Pregestational diabetes. Approximately 1% to 2% of pregnancies are complicated by pregestational diabetes. Pregestational diabetes accounts for 10% to 14% of diabetes in pregnancy with the reminder due to GDM.

III. COMPLICATIONS.

Improved management of diabetes mellitus and advances in obstetrics have reduced the incidence of adverse perinatal outcome in pregnancies complicated by diabetes mellitus. With appropriate management, women with good glycemic control and minimal microvascular disease can expect pregnancy outcomes comparable to the general population. Women with advanced microvascular disease, such as hypertension, nephropathy, and retinopathy, have a 25% risk of preterm delivery because of worsening maternal condition or preeclampsia. Pregnancy does not have a significant impact on the progression of diabetes. In women who begin pregnancy with microvascular disease, diabetes often worsens, but in most, the disease returns to baseline. Preconception glucose control may reduce the rate of complications to as low as that seen in the general population.

A. Maternal complications

1. **Hypertensive disorders of pregnancy.** Women with diabetes are at increased risk for hypertensive disorders, such as preeclampsia, which can lead to significant maternal and neonatal morbidity. Women at risk for preeclampsia, including those with pregestational diabetes should begin low-dose aspirin in the second trimester, ideally before 16 weeks.
2. **Diabetic ketoacidosis (DKA).** In those with pregestational diabetes, DKA occurs in 5% to 10% of pregnancies and carries a 50% risk of fetal death, especially if it occurs before the third trimester. Importantly, DKA can be present in the setting of even mild hyperglycemia (200 mg/dL) and should be excluded in every patient with type 1 diabetes who present with hyperglycemia and symptoms such as nausea, vomiting, or abdominal pain.

B. Fetal and neonatal complications

1. **Congenital malformations.** One of the most important complications is diabetic embryopathy resulting in congenital malformations. Congenital malformations are associated with 50% of perinatal deaths

among women with diabetes compared to 25% among women without diabetes. The risk of congenital malformations is related to the glycemic profile at the time of conception. A glycosylated hemoglobin (HbA1c) of 7% to 10% is associated with a 3% to 7% risk of congenital malformations, whereas ≥11% is associated with a 10% to 20% risk. The most common types of malformations include cardiac malformations and neural tube defects.

2. **Fetal overgrowth.** Uncontrolled diabetes during pregnancy can lead to fetal macrosomia and large for gestational age neonates. The risk of macrosomia is 30% in pregnancies complicated by GDM and 40% in those complicated by pregestational diabetes. Maternal hyperglycemia leads to increased glucose transfer across the placenta and fetal hyperglycemia. In response, the fetus increases insulin secretion leading to higher levels of insulin-like growth factor and growth hormone, which contribute to increased fetal fat deposition and fetal overgrowth. This increased fat deposition confers an additional risk of shoulder dystocia, even without macrosomia, with subsequent risk of fetal birth injury, including brachial plexus injuries and even death. There is also an increased risk of operative (vacuum, forceps) and cesarean delivery.
3. **Polyhydramnios.** Excessive amniotic fluid is not an uncommon finding in pregnancies complicated by diabetes. It may be secondary to osmotic diuresis from fetal hyperglycemia. Careful ultrasonographic examination is required to rule out structural anomalies, such as esophageal atresia, as an etiology, when polyhydramnios is present.
4. **Stillbirth.** Fetal demise is an uncommon complication of diabetes in pregnancy. It is most often associated with poor glycemic control, fetal anomalies, severe vasculopathy, fetal growth restriction, and preeclampsia.
5. **Neonatal hypoglycemia.** Fetal hyperglycemia may lead to fetal pancreatic hyperplasia increasing the risk of neonatal hypoglycemia. Strict glycemic control both antepartum and intrapartum can decrease the risk of neonatal hypoglycemia.
6. **Neonatal morbidities.** Neonates born to women with diabetes are at increased risk for hyperbilirubinemia, polycythemia, respiratory distress, and cardiomyopathy.

IV. PRECONCEPTION MANAGEMENT. Management of pregestational diabetes during pregnancy begins before conception. Tight glucose control is paramount during the periconceptional period and throughout pregnancy. Optimal glucose control requires coordinated care between endocrinologists, maternal–fetal medicine specialists, diabetes nurse educators, and nutritionists. Preconception glycemic control has been shown to decrease the risk of congenital anomalies to close to that of the general population. However, almost half of pregnancies are unplanned. Providers caring for women of reproductive age with diabetes should ask patients about pregnancy intention at each visit. This allows the opportunity to optimize glycemic control, ensure current medications are safe for pregnancy, and address complications of diabetes if pregnancy is planned, or recommend contraception if pregnancy is not planned.

V. ANTEPARTUM MANAGEMENT

A. Baseline assessment. In addition to routine prenatal care, women with pregestational diabetes should have a baseline assessment for complications of diabetes.

1. **HbA1c.** In the first trimester, HbA1c can give a risk assessment for congenital anomalies by reflecting ambient glucose concentrations during the period of organogenesis.
2. **Ophthalmologic examination.** Retinopathy may progress during pregnancy because of the rapid normalization of glucose concentration in the first trimester. Women with retinopathy need periodic examinations throughout pregnancy and are candidates for laser photocoagulation as indicated.
3. **Renal function.** Assessment for diabetic nephropathy can be performed through a spot protein/creatinine ratio or spot urine microalbumin, followed by a 24-hour urine collection for protein excretion and creatinine clearance if abnormal. Serum creatinine should also be assessed. Because the incidence of preeclampsia is significantly elevated in women with diabetes, identification of baseline proteinuria can impact the diagnosis of preeclampsia later in pregnancy.
4. **Thyroid function.** Women with pregestational diabetes, especially type 1 diabetes, are at risk for autoimmune thyroid dysfunction. Hypothyroidism can be treated with levothyroxine.

B. Glucose monitoring. For women with pregestational diabetes, during the first half of pregnancy, as a result of nausea and vomiting, hypoglycemia can be as much of a problem as hyperglycemia. Hypoglycemia, followed by hyperglycemia from counter-regulatory hormones, may complicate glucose control. Gastroparesis from long-standing diabetes may be a factor as well. There does not appear to be a direct relationship between hypoglycemia alone and adverse perinatal outcome. Throughout pregnancy, insulin requirements increase because of the increasing production of placental hormones that antagonize the action of insulin. This is most prominent in the mid-third trimester and requires intensive blood glucose monitoring and frequent adjustment of medications to control blood glucose.

During pregnancy, glycemic targets are a fasting glucose concentration <95 mg/dL and 1- or 2-hour postprandial values of <140 mg/dL or <120 mg/dL, respectively. Women with type 1 diabetes who use a continuous glucose monitor (CGM), time in range can be used to assess glycemic control with the following goals: time in range 63 to 140 mg/dL, goal $>70\%$; time below range <63 mg/dL, goal $<4\%$, with goal $<1\%$ of the time <54 mg/dL; and time above range >140 mg/dL, goal $<25\%$.

C. Treatment

1. **Nutrition therapy.** Diet is the mainstay of treatment for diabetes in pregnancy. A personalized nutrition plan should be developed which includes adequate calories and complex carbohydrates for normal fetal growth and development while meeting glycemic targets. Focus should be on consuming a variety of vegetables, whole grains, legumes, and healthy whole-food sources of fat.

2. **Pharmacologic therapy.** Insulin therapy has the longest record of accomplishment of perinatal safety and is first line for treatment of diabetes in pregnancy. It has been demonstrated that human insulin analogs do not cross the placenta. Oral hypoglycemic agents such as glyburide and metformin do cross the placenta with possible long-term safety concerns; further, they have not proven to be as effective as insulin. They are considered second line for the treatment of diabetes in pregnancy.

D. Fetal surveillance

1. **Early fetal ultrasound.** An early ultrasound is important to both ensure fetal viability and accurately date the pregnancy.
2. **Anatomic survey.** All patients undergo a thorough ultrasonographic anatomic survey for structural anomalies. Fetal echocardiography is recommended for women with type 1 diabetes or poorly controlled type 2 diabetes or if there is a concern for a congenital cardiac anomaly on anatomy ultrasound.
3. **Fetal growth ultrasound.** During the third trimester, at least one ultrasound for assessment of fetal growth is recommended.
4. **Antepartum surveillance.** Weekly or twice-weekly fetal surveillance using nonstress testing or biophysical profiles are implemented between 28 and 32 weeks' gestation, depending on glycemic control and other complications.

VI. INTRAPARTUM AND POSTPARTUM MANAGEMENT

A. Route and timing of delivery

1. **Preterm birth.** The risk of spontaneous preterm labor is not increased in patients with diabetes, although the risk of medically indicated preterm delivery is increased for patients with microvascular disease as a result of fetal growth restriction, nonreassuring fetal testing, and maternal hypertension. Antenatal corticosteroids for induction of fetal lung maturity should be employed for the usual obstetric indications. Corticosteroids can cause temporary hyperglycemia; therefore, patients may need to be managed with additional insulin or continuous intravenous (IV) insulin infusions until the effect of the steroids wear off.
2. **Timing of delivery.** For GDM controlled with diet and exercise, delivery should be planned for 39 to 40 weeks. Those with GDM controlled on medication, delivery should be planned for 39 weeks. Women with well-controlled pregestational diabetes should be delivered at 39 weeks. If women have complications of diabetes and/or poor glycemic control, earlier delivery can be considered.
3. **Route of delivery.** Mode of delivery is determined by estimated fetal weight (EFW), maternal and fetal conditions, and previous obstetric history. The ultrasonography-determined EFW at which an elective cesarean delivery is recommended is a controversial issue. The American College of Obstetricians and Gynecologists recommend discussion of cesarean delivery at an EFW of >4,500 g due to the increased risk of shoulder dystocia. Otherwise, cesarean delivery is performed for usual

obstetric indications; however, the risk of cesarean delivery is as high as 50% for women with diabetes. Those with pregestational diabetes and advanced microvascular disease are at increased risk for cesarean delivery because of the increased incidence of fetal growth restriction, preeclampsia, and nonreassuring fetal status. A history of retinopathy that has been treated in the past is not necessarily an indication for cesarean delivery. Patients with active proliferative retinopathy that is unstable or active hemorrhage may benefit from elective cesarean delivery.

B. Glycemic management during delivery. Blood glucose concentration is tightly controlled during labor and delivery. If an induction of labor is planned, patients are instructed to take one-half of their usual basal insulin on the morning of induction. During spontaneous or induced labor, blood glucose concentration is measured every 1 to 2 hours. Blood glucose concentration higher than 120 to 140 mg/dL is treated with an infusion of IV short-acting insulin. IV insulin is very short acting, allowing for quick response to changes in glucose concentration. Active labor may also be associated with hypoglycemia because the contracting uterus uses circulating metabolic fuels. Continuous fetal monitoring is mandatory during labor.

C. Postpartum

1. **Postpartum.** During the immediate postpartum period, patients are at increased risk for hypoglycemia, especially in the postoperative setting with minimal oral intake. Patients with pregestational diabetes may also experience a "honeymoon" period immediately after delivery, with greatly reduced insulin requirements that can last up to several days. Lactation is also associated with significant glucose utilization and potential hypoglycemia. For women with pregestational diabetes, the use of metformin and glyburide are compatible with breastfeeding.
2. **Long-term follow-up.** Women diagnosed with GDM have a 60% lifetime risk of developing overt type 2 diabetes. It is important for women diagnosed with GDM to have GTT 4 to 12 weeks postpartum and then routine screening for diabetes every 1 to 3 years. Risk of developing overt diabetes can be minimized by achieving a normal body weight, eating a healthy diet, and exercise.

Suggested Readings

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3 Preeclampsia and Related Hypertensive Conditions of Pregnancy

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KEY POINTS

- Hypertensive disorders in pregnancy are a major cause of maternal morbidity and mortality, accounting for 15% to 20% of maternal deaths worldwide.
- The definitive treatment for preeclampsia is delivery. However, the gestational age at diagnosis, maternal severity of disease, parity and cervical exam (dilation/effacement), and pulmonary maturity of the fetus all influence obstetric management.
- Because of the risks of worsening disease with adverse maternal and neonatal outcomes, patients with preeclampsia with severe features should be hospitalized after diagnosis until delivery at a center with adequate maternal and neonatal resources as well as readily available staff to provide close monitoring and care.
- Hypertensive disorders of pregnancy are associated with an increased risk of developing cardiovascular disease later in life.

I. CATEGORIES OF PREGNANCY-ASSOCIATED HYPERTENSIVE DISORDERS

A. Chronic hypertension. Hypertension preceding pregnancy or first diagnosed before 20 weeks' gestation

B. Chronic hypertension with superimposed preeclampsia. Worsening hypertension and new-onset or increase in proteinuria, in addition to possible concurrent thrombocytopenia, or transaminase or creatinine elevation after the 20th week of pregnancy in a woman with known chronic hypertension. It can be further subdivided into with or without severe features.

C. Gestational hypertension. Hypertension without proteinuria and without symptoms or abnormal laboratory tests after 20 weeks' gestation and returns to normal by 12 weeks postpartum (Table 3.1)

Table 3.1. Diagnosis of Preeclampsia versus Gestational Hypertension

	Gestational Hypertension	Preeclampsia without Severe Features	Preeclampsia with Severe Features
HTN >20 weeks	Yes	Yes	Yes
Previously normotensive	Yes	Yes	Yes
SBP	140–159 mm Hg	140–159 mm Hg	≥160 mm Hg
DBP	90–109 mm Hg	90–109 mm Hg	≥110 mm Hg
Persistent for 4 hours	Yes	Yes	Yes (but can diagnosis sooner to expediate IV treatment)
Presence of symptoms	No	No	Yes
Normal blood tests	Yes	Yes	No
Proteinuria: ≥300 mg/24 hours Protein/creatinine ratio ≥0.3 Urine dip stick ≥1+	No	Yes	Yes (but can have severe HTN without proteinuria)

HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; IV, intravenous.

D. Preeclampsia. Blood pressures >140 mm Hg systolic or 90 mm Hg diastolic with proteinuria after 20 weeks' gestation. It can be further subdivided into with or without severe features. Preeclampsia can be diagnosed in the absence of proteinuria in the setting of laboratory abnormalities, pulmonary edema, or persistent headache.

E. Eclampsia. New-onset, generalized tonic–clonic seizure activity in a pregnant or newly postpartum woman with no prior history of a seizure disorder and no other causative condition. This is usually, but not always, associated with hypertension and/or proteinuria at time of seizure.

F. Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. Clinical findings consistent with hemolysis, elevated liver function tests, and thrombocytopenia

II. INCIDENCE AND EPIDEMIOLOGY. Hypertensive disorders in pregnancy are a major cause of maternal morbidity and mortality, accounting for 15% to 20% of maternal deaths worldwide. The contribution of hypertensive disorders to pregnancy-related deaths has declined to about 7% in the United States; although previously the second leading cause of maternal mortality in the United States, after thrombotic/hemorrhagic complications, hypertensive disorders now rank below cardiovascular conditions, infection/sepsis, cardiomyopathy, hemorrhage, and thrombotic complications. Nevertheless, they remain an important contributor to adverse maternal and neonatal outcomes. Preeclampsia and associated hypertensive disorders contribute to 10% of all preterm births, majority of which are medically indicated for maternal benefit.

Beyond 20 weeks' gestation, preeclampsia complicates 5% to 8% of pregnancies, and preeclampsia with severe features complicates <1% of pregnancies. Eclampsia itself is much less frequent, occurring in 0.1% of pregnancies overall, 2.9% of patients with preeclampsia, and 3.2% of patients with severe features.

Racial disparities are particularly evident in incidence and outcomes of hypertensive disorders of pregnancy. Not only are Black women more likely to develop preeclampsia, they are 3 times more likely to experience mortality related to preeclampsia and experience higher morbidity, such as rates of cardiac arrest and heart failure.

Several risk factors have been identified, as outlined in Table 3.2. However, most cases occur in women without obvious risk factors. **Low-dose aspirin** has been shown to reduce the risk of developing preeclampsia in patients with specific risk factors, such as women with a medical history of preeclampsia, especially when <34 weeks, accompanied by an adverse outcome, or preeclampsia in more than one previous pregnancy. Low-dose aspirin is also recommended for patients with other high-level risk factors (multifetal gestation, preexisting hypertension or diabetes, renal disease, or autoimmune disease) and can also be considered if the patient has more than one moderate risk factor (nulliparity, obesity, family history in mother or sister, low socioeconomic status, age 35 years or older). The recommended dose is 81 mg/day, and it should be started after 12 weeks of gestation (and ideally before 16 weeks).

Despite being a leading cause of maternal and fetal morbidity worldwide, the etiology remains unknown. Many theories have been proposed, including chronic uteroplacental ischemia related to abnormal trophoblastic invasion of the maternal spiral arteries and an abnormal maternal immune response. This likely ultimately results in an imbalance in angiogenic factors. Increase in thromboxane A2 compared to prostacyclin may lead to an intense systemic vasospasm state with resulting hypertension, proteinuria, and edema.

III. DIAGNOSIS. Preeclampsia classically presents as hypertension and proteinuria after 20 weeks' gestation. However, the presence of proteinuria is not required in the setting of severe hypertension (>160 mm Hg systolic or 110 mm Hg diastolic). The clinical spectrum of preeclampsia ranges from mild to severe. Most patients have a nonsevere form of the disease that develops late in the third trimester. The amount of proteinuria does not predict perinatal outcome and does not impact severity of disease or influence management. Some patients will also have nondependent edema (swelling in

Table 3.2. Risk Factors for Hypertensive Disorders

Risk Factors
Nulliparity
Multifetal gestations
Preeclampsia in previous pregnancy
Preexisting chronic hypertension
Pregestational and gestational diabetes
Thrombophilia
Systemic lupus erythematosus
Prepregnancy body mass index >30
Antiphospholipid antibody syndrome
Maternal age 35 years or older
Kidney disease
Assisted reproductive technology
Obstructive sleep apnea

Source: Reprinted with permission from American College of Obstetricians and Gynecologists. Gestational hypertension and preeclampsia. *Obstet Gynecol* 2020;135(6):1492–1495.

their hands and face), but this is no longer a part of the diagnostic criteria for preeclampsia.

A. Criteria for the diagnosis of preeclampsia without severe features

1. **Hypertension** is defined as a blood pressure elevation to 140 mm Hg systolic or 90 mm Hg diastolic over two measurements at least 4 hours apart. Measurements should be taken in the sitting position at the level of the heart, and the proper cuff size needs to be ensured.
2. **Proteinuria** defined as at least 300 mg of protein in a 24-hour period, a protein-to-creatinine ratio ≥0.3, or a urine dipstick of 2+.

B. Criteria for the diagnosis of preeclampsia with severe features *Of note, not every criteria listed here is needed to make a diagnosis.*

1. **Blood pressure** >160 mm Hg systolic or 110 mm Hg diastolic with the diagnostic readings taken twice at least 4 hours apart. Severe hypertension can be verified prior to 4 hours if persistent to aid in timely administration of antihypertensive therapy.
2. **Symptoms suggestive of end-organ dysfunction.** New visual disturbances such as scotomata, diplopia, blindness, or persistent severe headache. Other symptoms such as severe persistent right upper quadrant pain

or severe epigastric pain not responsive to medications and not attributed to another medical cause are suggestive of distention of the liver capsule or hepatic necrosis and considered severe features of preeclampsia.

3. **Pulmonary edema**
4. **Renal insufficiency** is defined as serum creatinine >1.1 mg/dL.
5. **Thrombocytopenia** is defined as a platelet count of <100,000.
6. **Hepatocellular dysfunction.** Elevated transaminases (more than twice upper limit of normal concentration, aspartate aminotransferase [AST] usually elevated to greater extent than alanine aminotransferase [ALT])

Note: Fetal growth restriction is no longer an indicator of severe disease or an indication for delivery. However, given chronic uteroplacental ischemia, fetal growth restriction and oligohydramnios are commonly seen in pregnancies complicated by preeclampsia. This may affect obstetrical management.

C. HELLP syndrome. It represents an alternative, severe presentation of preeclampsia and reflects systemic end-organ damage. HELLP syndrome may appear without either hypertension or proteinuria (15%). The diagnosis does not require that all the laboratory abnormalities be present (partial HELLP).

IV. COMPLICATIONS.

Complications of preeclampsia result in a maternal mortality rate of about 3 per 100,000 live births in the United States. Higher rates are seen in centers with limited resources. Maternal morbidity may include central nervous system complications (e.g., seizures, intracerebral hemorrhage, and blindness), disseminated intravascular coagulation (DIC), hepatic failure or rupture, pulmonary edema, and *abruptio placentae* leading to maternal hemorrhage and/or acute renal failure. Fetal mortality markedly increases severity of disease process. Fetal morbidity may include fetal demise, intrauterine fetal growth restriction, fetal acidemia, and complications from prematurity.

V. CONSIDERATIONS IN MANAGEMENT

A. The definitive treatment for preeclampsia is delivery. However, the severity of disease, maternal obstetrical history and cervical exam, gestational age at diagnosis and delivery, and pulmonary maturity of the fetus all influence obstetric management. Delivery is usually indicated if there is nonreassuring fetal testing in a viable fetus or if the maternal status deteriorates regardless of either gestational age or fetal maturity.

B. Delivery should be considered for all patients at ≥37 weeks with any degree of gestational hypertension or preeclampsia.

C. Pregnancies may continue for patients with **preterm gestation and preeclampsia without severe features/gestational hypertension**, with close observation as outlined in section VI until 37 weeks' gestation. Delivery prior to 37 weeks is indicated with progression to preeclampsia with severe features (25% to 50%), nonreassuring fetal testing, or maternal instability.

D. If the patient has preeclampsia with severe features, treatment varies based on the severity of the patient's disease and the gestational age,

balancing maternal risk of worsening disease with fetal benefit of prolonged gestation. If the patient is >34 weeks, the recommendation by the American College of Obstetricians and Gynecologists (ACOG) is delivery. Prior to 34 weeks, three management options include delivery immediately, betamethasone then delivery, and expectant management. The timing of delivery is discussed in further detail in section VII.

E. Expectant management entails hospitalization and frequent maternal and fetal surveillance. This should only be undertaken in carefully selected patients after an initial period of observation to ensure stability of the pregnant woman. Monitoring of these patients includes daily maternal–fetal testing, routine vital signs, and monitoring for symptoms of preeclampsia. Patients may even be given oral antihypertensive medication to control their blood pressure. Women with uncontrolled hypertension despite maximum doses of two antihypertensive medications, eclampsia, stroke, thrombocytopenia, hepatocellular dysfunction, pulmonary edema, compromised renal function, or persistent neurologic symptoms are not candidates for expectant management. Given maternal risk with goal of prolonging gestation, expectant management is not recommended in the setting of fetal death, lethal anomaly, or previable gestational age.

F. The mode of delivery does not need to be a cesarean section. A number of factors have to be assessed including the fetal position, maternal status, gestational age, obstetrical history and cervical status, and fetal condition. At earlier gestational ages, a trial of labor induction is not contraindicated in patients with preeclampsia with severe features; however, the success rate is low. The managing team must balance the risks of progression of the disease against the time required to induce labor and anticipate fetal tolerance of labor.

VI. CLINICAL MANAGEMENT OF GESTATIONAL HYPERTENSION AND PREECLAMPSIA WITHOUT SEVERE FEATURES

A. Antepartum management. Management of gestational hypertension and preeclampsia without severe features is the same. Conservative management of gestational hypertension and preeclampsia without severe features generally consists of maternal daily assessment for symptoms and fetal movement; biweekly blood pressure checks; and weekly assessment of platelet counts, liver enzymes, and creatinine. Strict bed rest and salt restriction are not recommended.

1. Maternal evaluation

a. Women should be **evaluated for signs and symptoms** of preeclampsia with severe features.

b. Initial laboratory evaluation includes platelet count, transaminases, hemoglobin/hematocrit, creatinine, and urine protein-to-creatinine ratio.

c. If criteria for preeclampsia with severe features are not met, laboratory studies should be performed at weekly intervals to assess for worsening disease.

d. Maternal indications for delivery include a gestational age ≥37 weeks; thrombocytopenia (<100,000); progressive deterioration in hepatic or renal function; placental abruption; pulmonary edema; and persistent severe headaches, visual changes, or epigastric pain.

e. Antihypertensive agents are not routinely given because they have not been shown to improve the outcome in cases of preeclampsia without severe features.

f. When early delivery is indicated, cesarean delivery should be reserved for usual obstetrical indications, with vaginal delivery preferred when appropriate. Cesarean delivery should be reserved for cases with nonreassuring fetal testing, when further fetal evaluation is not possible, or when a rapidly deteriorating maternal condition mandates expeditious delivery (e.g., HELLP syndrome with decreasing platelet counts, abruption, refractory hypertension remote from delivery).

2. **Fetal evaluation**

a. An initial ultrasound should be performed at the time of diagnosis to rule out intrauterine fetal growth restriction and/or oligohydramnios. A nonstress test (NST) or biophysical profile may also be performed as indicated.

b. Ultrasonography every 3 weeks for growth is recommended. Twice-weekly NSTs with amniotic fluid index measurements are recommended. The frequency of these tests can be changed based on the findings noted during the evaluations.

c. Any **change in maternal status** should prompt evaluation of fetal status.

d. Fetal indications for delivery include nonreassuring fetal testing. If severe growth restriction and/or oligohydramnios is noted, then further assessment of the fetus is recommended with umbilical artery Doppler studies.

B. Intrapartum management of preeclampsia

1. **Magnesium sulfate** is not routinely recommended for women with preeclampsia without severe features or gestational hypertension unless symptoms of worsening disease/severe features develop (severe hypertension: systolic blood pressure >160 mm Hg, diastolic blood pressure >110 mm Hg; maternal symptoms; laboratory abnormalities).
2. **Antihypertensive therapy** is not recommended unless the systolic blood pressure is >160 mm Hg or the diastolic blood pressure is >110 mm Hg.
3. **Continuous electronic fetal monitoring** is recommended given the potential for placental dysfunction in the preeclamptic setting. Monitoring should be established during the initial evaluation, induction of labor, and labor itself. Continuous monitoring is not recommended during intervals of prolonged expectant management. Patterns that suggest fetal compromise include persistent tachycardia, minimal or absent fetal heart rate variability, and recurrent late decelerations not responsive to standard resuscitative measures.
4. In general, patients may be safely administered **epidural anesthesia** if the platelet count is >70,000 and there is no evidence of DIC. Regional anesthesia is preferred given potential for airway edema and failed intubation. Consideration should be given for early epidural catheter placement when the platelet count is reasonable and there is concern that it may decrease. Any anesthesia should be administered by properly trained personnel experienced in the care of women with preeclampsia given the hemodynamic changes associated with the

condition. Adequate preload should be ensured to minimize the risk of acute hypotension.

5. Aggressive fluid therapy is not recommended given risk pulmonary edema due to capillary leak. **Invasive central monitoring** of the mother is rarely indicated, even in the setting of preeclampsia with severe features.

C. Postpartum management. The mother's condition may worsen immediately after delivery. However, signs and symptoms usually begin to resolve within 24 to 48 hours postpartum, and in most women, it usually resolves within 1 or 2 weeks. Blood pressure may worsen in the first week after delivery and should be checked 7 to 10 days after delivery, either through in-person evaluation or home monitoring. If the patient develops symptoms of preeclampsia in the interim, he or she should be assessed in the office or hospital sooner.

VII. MANAGEMENT OF PREECLAMPSIA WITH SEVERE FEATURES (Fig. 3.1)

A. Timing of delivery

1. If previable or **>34 weeks' gestation**, delivery is indicated. Delivery should not be delayed for administration of steroids in the late preterm period.
2. Prior to 34 weeks, **expectant management** can be attempted unless there is evidence of eclampsia, pulmonary edema, DIC, stroke, uncontrollable severe hypertension, nonviable fetus, abnormal fetal test results, placental abruption, or intrapartum fetal demise. In those situations, the goal is to stabilize the mother and then deliver (see Fig. 3.1). If the patient has evidence of persistent symptoms, HELLP, partial HELLP, fetal growth restriction with severe oligohydramnios (largest vertical pocket <2 cm) or reversed end-diastolic flow on umbilical artery Doppler studies, labor, preterm premature rupture of membranes, or significant renal dysfunction, the goal is to administer betamethasone for fetal lung maturity and plan on delivery after 48 hours. If the patient does not meet any of the criteria for delivery, antenatal corticosteroid administration and expectant management is recommended until 34 weeks. Oral antihypertensive therapy (labetalol or nifedipine) can be used to control hypertension in this setting. Delivery can be performed sooner than 34 weeks if the patient develops evidence of worsening disease. Two randomized trials performed in the United States compared immediate delivery versus expectant management in mothers with preeclampsia with severe features. These trials showed that expectant management led to prolongation of pregnancy by about 7 days with a significant reduction in total neonatal complications from 75% to 33%. The disadvantage of expectant management is that preeclampsia with severe features can lead to acute and long-term complications for the patient including the progressive deterioration of the maternal and fetal condition.
3. Because of the risks of rapid deterioration, patients with preeclampsia with severe features should be hospitalized after diagnosis at a center with adequate maternal and neonatal resources as well as readily available staff to provide close monitoring and care.
4. Inpatient monitoring should include frequent vital sign and symptoms assessment, daily fetal assessment (NSTs), and serial laboratory evaluation, the frequency of which depends on maternal stability.

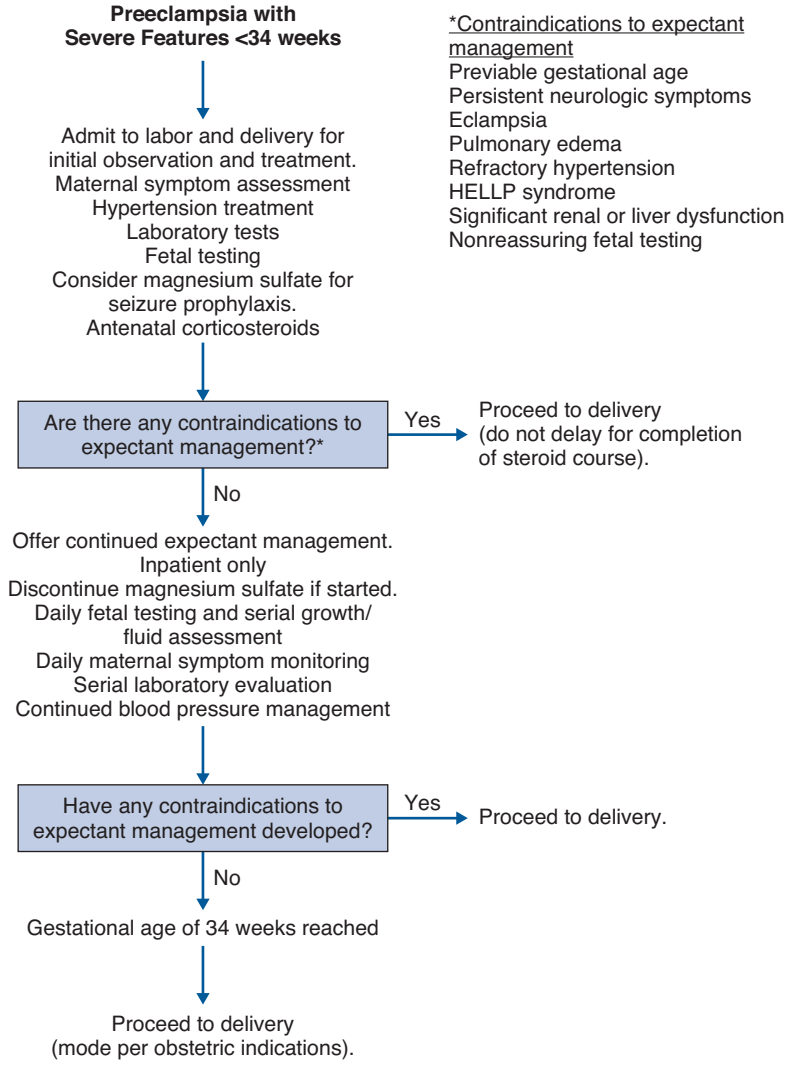

Figure 3.1. Management of preterm preeclampsia with severe features.

B. Intrapartum management. Intrapartum management should focus on treatment of severe hypertension to prevent stroke and prevention of seizures.

1. Magnesium sulfate (typically 6 g intravenous [IV] load followed by 2 g/hour infusion) is used as seizure prophylaxis in patients with preeclampsia with severe features. Four grams IV bolus or 1 g/hour continuous infusions are acceptable alternatives. Because magnesium

sulfate is excreted from the kidneys, patients with renal compromise may need alternative dosing (e.g., if the patient has evidence of reduced kidney function, i.e., serum creatinine >1.1 mg/dL, magnesium sulfate maintenance dose can be started at 1 g/hour after the initial bolus; if the patient's creatinine is >2.5 mg/dL, a maintenance dose may not be necessary). There is suggestion that patients with a high body mass index (BMI) may need higher dosages. Intramuscular injection (10-g loading dose followed by 5 g every 4 hours) can be used in patients without venous access. Magnesium sulfate is started when the decision to proceed with delivery is made and is continued for at least 24 hours postpartum. Magnesium sulfate should be continued during a cesarean delivery. Magnesium sulfate has been shown to be the agent of choice for seizure prophylaxis in randomized double-blind comparisons against both placebo and conventional antiepileptics. In patients with myasthenia gravis or hypocalcemia, magnesium sulfate is contraindicated and should not be given. Urine output should be carefully monitored. A serum magnesium level should be considered if reduced renal function is suspected while magnesium sulfate is being administered. Signs and symptoms of maternal toxicity include loss of deep tendon reflexes, somnolence, respiratory depression, cardiac arrhythmia, and, in extreme cases, cardiovascular collapse. Serum magnesium levels or discontinuation of the infusion may be indicated in the presence of renal dysfunction or concern for toxicity. Calcium gluconate (10 mL of 10% solution) can be used to reverse signs of overdose.

2. **Severe hypertension** may be controlled with agents including IV hydralazine (5- to 10-mg doses every 20 minutes for two doses), IV labetalol (contraindicated with severe asthma or some cardiac disease, 20 to 40 mg IV every 15 minutes as needed), or oral nifedipine (10 to 20 mg every 20 minutes). Treatment should be given within 30 to 60 minutes of persistent severe hypertension. Calcium channel blockers and magnesium sulfate can be safely used together with close monitoring of maternal vital signs. Sodium nitroprusside should be avoided before delivery because of potential fetal cyanide toxicity. It is important to avoid large or abrupt reductions in blood pressure because decreased intravascular volume and poor uteroplacental perfusion can lead to acute placental insufficiency and a resulting loss of reassurance regarding fetal well-being.
3. **Careful monitoring of fluid balance** is critical because preeclampsia is associated with endothelial dysfunction leading to decreased intravascular volume, pulmonary edema, and oliguria. Urine output should be carefully monitored, especially in patients with underlying renal dysfunction. Diuretics are indicated when pulmonary edema is present.
4. **Lab evaluation.** Serial evaluation for worsening thrombocytopenia, renal or hepatic dysfunction, or HELLP syndrome may be necessary. If there is concern for DIC, coagulation parameters should be assessed and appropriate blood products should be available if necessary.
5. **Continuous fetal heart rate monitoring is recommended.** Reduced fetal heart rate variability may also result from maternal administration of magnesium sulfate.

C. Postpartum management

1. Because postpartum eclamptic seizures generally occur within the first 48 hours and usually within the first 24 hours after delivery, magnesium sulfate prophylaxis is continued for at least 24 hours. Close monitoring of fluid balance is continued. While on magnesium sulfate, the patient's blood pressure and urine output is monitored closely. Lung and deep tendon reflexes evaluation for evidence of pulmonary edema or magnesium sulfate toxicity are recommended.
2. Hypertension >150 mm Hg systolic or 100 mg Hg diastolic on at least two occasions 4 to 6 hours apart needs to be treated in the postpartum period with initiation of oral antihypertensive therapy. Some patients, although sufficiently stable for discharge, may require antihypertensive medications for up to 8 weeks after delivery. A short course of furosemide may decrease need for postnatal antihypertensive therapy.
3. Typically, blood pressures tend to decrease within the first 48 hours after delivery and increase 3 to 6 days later. It is recommended to monitor patients' blood pressures closely for 72 hours after delivery and then again at 7 to 10 days after delivery, either through in-person evaluation or home monitoring. If the patient develops symptoms of preeclampsia in the interim, he or she should be assessed in the office or hospital sooner.
4. Although nonsteroidal anti-inflammatory drugs (NSAIDs) can theoretically increase blood pressure and increase sodium retention, these agents are preferred over opioid analgesics for postpartum pain control. Recent studies have not shown differences in severity or duration of hypertension in postpartum patients managed with NSAIDs.

VIII. MANAGEMENT OF ECLAMPSIA

A. Approximately half of **eclamptic seizures** occur before delivery (majority of which occur in the third trimester), 20% occur during delivery, and another 30% occur in the postpartum period, the majority in the first 48 hours after delivery. Although there is no clear constellation of symptoms that will accurately predict which patients will have an eclamptic seizure, headache is a frequently reported heralding symptom (~80% of eclampsia cases), but most preeclamptic women with headaches do not develop seizures. Eclampsia can occur without hypertension or proteinuria prior to the first seizure episode (~20%).

B. Complications are higher in women who develop antepartum preeclampsia. This complications include death, intracerebral hemorrhage, aspiration pneumonia, DIC, pulmonary edema, renal failure, and HELLP syndrome.

C. **Basic principles of maternal resuscitation** should be followed in the initial management of an eclamptic seizure with the goals of preventing maternal injury, maintaining oxygenation, and minimizing aspiration. Airway protection, oxygen supplementation, left lateral displacement to prevent uterine compression of vena cava and reduces aspiration risk, IV access, and blood pressure control. Most eclamptic seizures are self-limited. Delivery should only occur AFTER maternal stabilization.

D. Magnesium sulfate should be initiated for **prevention of recurrent seizures**. Ten percent of women with eclamptic seizures will have a recurrent seizure after initiation of magnesium sulfate.

E. A **transient fetal bradycardia** or fetal heart rate deceleration is usually seen during the seizure followed by a **transient fetal tachycardia** with loss of variability. Ideally, the fetus should be resuscitated *in utero*. Fetal heart pattern generally improves after maternal resuscitation. If bradycardia or decelerations persist, placental abruption should be suspected.

F. Eclampsia is an indication for delivery but not necessarily an indication for cesarean delivery. No intervention should be initiated until maternal stability is ensured and the seizure is over. Mode of delivery should be determined based on gestational age, cervical exam, and maternal stability.

G. A neurologic exam should be performed once the patient recovers from the seizure. If the seizure is atypical (in clinical presentation or timing in relation to delivery—after 48 to 72 hours postpartum) or any neurologic deficit persists, **brain imaging** is indicated.

H. If a patient has recurrent seizures while on magnesium sulfate, a reloading dose of 2 to 4 g of magnesium sulfate can be given one or two times. If seizures persist after two additional boluses of magnesium sulfate, consideration should be given to adding IV lorazepam. Patients who have recurrent seizures despite treatment may warrant neurology consultation and evaluation of alternative diagnoses.

I. Eclampsia is often associated with posterior reversible encephalopathy syndrome (**PRES**) or reversible cerebral vasoconstriction syndrome (**RCVS**). Headaches, visual changes confusion, or focal neurologic deficits may occur. Antihypertensive and antiepileptic medication may be needed, and neurology follow-up is recommended.

IX. POSTPARTUM PREECLAMPSIA

A. Preeclampsia may present for the first time after delivery or may persist or worsen in those already diagnosed with a hypertensive disorder of pregnancy. All women should be discharged home with **education** about signs and symptoms of preeclampsia.

B. The early postpartum period is the **highest risk for stroke** and maternal mortality.

C. Women who present with **new-onset hypertension** and symptoms such as severe headache in the postpartum period should receive **magnesium sulfate**.

X. RECURRENCE RISK. Patients who have a history of preeclampsia are at increased risk for hypertensive disease in a subsequent pregnancy. Recurrence risk depends on severity and gestational age at onset of first episode. Recurrence risk is as high as 40% in women with preeclampsia before 32 weeks of gestation, as opposed to 10% or less in women with preeclampsia near term.

Eclampsia is also associated with 2% risk of recurrence. Racial differences exist, with Black women having higher recurrence rates. The recurrence rate for HELLP syndrome is approximately 5%. Low-dose aspirin can reduce risk of recurrent preeclampsia.

XI. LONG-TERM CARDIOVASCULAR RISK. Up to 20% of women with hypertensive disorders of pregnancy will develop chronic hypertension. Risk factors include obesity, severe disease, and need for blood pressure medications after delivery. Hypertensive disorders of pregnancy, regardless of type and even without known risk factors, are associated with increased risk of cardiovascular disease (heart failure and coronary heart disease), stroke, and cardiovascular mortality later in life. There is also increased risk of diabetes. In addition, women with recurrent preeclampsia, women with early-onset preeclampsia, and multiparas with a diagnosis of preeclampsia (even if not recurrent) may be at an even higher risk than those with just gestational hypertension. The mechanism by which preeclampsia leads to future cardiovascular disease is not clear, although many risk factors for preeclampsia and cardiovascular disease overlap. There is some suggestion that breastfeeding may decrease some of the cardiovascular risk. Given this high risk of future morbidity, the ACOG Task Force on Hypertension in Pregnancy recommends that women with a history of preeclampsia delivered prior to 37 weeks or who have had recurrent preeclampsia be screened annually for blood pressure, lipids, fasting blood glucose, and BMI.

XII. PROPOSED TREATMENTS

A. There are no tests that are reliable in predicting the onset or severity of preeclampsia.

B. Several analytic assays based on angiogenic factor biomarkers, such as soluble fms-like tyrosine kinase (sFLT-1), placental growth factor (PIGF), and soluble endoglin, and uterine artery Doppler studies have been evaluated as tools to predict early-onset preeclampsia. Screening tests, both alone or in combination with each other, have low positive predictive value in low risk women.

C. There is insufficient evidence to show effectiveness in nutritional interventions such as vitamins C and E, fish oil, garlic, vitamin D, folic acid, or calcium supplementation or sodium restriction in reducing risk of preeclampsia.

D. There is ongoing investigation as to whether the use of metformin, sildenafil, or statins may be effective at preventing preeclampsia. The agents should only be used as part of clinical trials.

XIII. IMPLICATIONS FOR THE NEWBORN

A. Infants born to mothers with preeclampsia with severe features or superimposed preeclampsia may show evidence of IUGR and are frequently delivered prematurely. They may tolerate labor poorly and therefore require resuscitation.

B. Medications used antepartum or intrapartum may affect the fetus.

1. **Short-term sequelae of hypermagnesemia**, such as hypotonia and respiratory depression, are sometimes seen. Long-term maternal administration of magnesium sulfate has rarely been associated with neonatal parathyroid abnormalities or other abnormalities of calcium homeostasis.
2. **Antihypertensive medications**, including calcium channel blockers, may have fetal effects, including hypotension in the infant. Commonly used medications such as labetalol, nifedipine, hydralazine, and magnesium sulfate generally are not contraindications to breastfeeding. Enalapril can be safely used in breastfeeding mothers as well.
3. **Low-dose aspirin therapy** does not appear to increase the incidence of intracranial hemorrhage, asymptomatic bruising, bleeding from circumcision sites, or persistent pulmonary hypertension.
4. Approximately one-third of infants born to mothers with early-onset preeclampsia with severe features have **decreased platelet counts at birth**, but the counts generally increase rapidly to normal levels. Approximately 40% to 50% of newborns have neutropenia that generally resolves before 3 days of age. These infants may be at increased risk for neonatal infection.

Suggested Readings

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4 Resuscitation in the Delivery Room

Elizabeth E. Foglia

KEY POINTS

- Anticipation and preparation are key to successful delivery room resuscitation.
- The primary goal during resuscitation after birth is to support ventilation.
- Providers should focus on thermal control and ensure the infant's temperature remains normal during transition.

I. GENERAL PRINCIPLES

A. Overview. A person skilled in basic neonatal resuscitation, whose primary responsibility is the newly born baby, should be present at every birth, and a provider capable of performing a complete resuscitation must be immediately available. Delivery of high-risk infants should be ideally attended by personnel who possess the skills required to perform a complete resuscitation.

The highest standard of care for delivery room resuscitation requires the following: (i) knowledge of perinatal physiology and principles of resuscitation; (ii) mastery of technical skills required; and (iii) clear coordination, communication, and teamwork among providers. The Newborn Resuscitation Program (NRP) of the American Academy of Pediatrics/American Heart Association provides an educational curriculum to ensure all caregivers have a consistent approach to resuscitation and team-based training. NRP provides an approach to resuscitation that is successful in a very high percentage of cases and aids clinicians to rapidly identify those unusual cases in which specialized interventions may be required. This chapter reviews basic principles of transitional physiology and neonatal resuscitation. Specific treatment recommendations for neonatal resuscitation are updated on an ongoing basis as new evidence emerges.

B. Perinatal physiology. Before birth, the fetal lungs are fluid filled, gas exchange occurs in the placenta, and fetal circulation is intact. Immediately after birth, the newborn must transition to pulmonary gas exchange and progress from fetal to postnatal circulation. Lung aeration from breathing is the key trigger for this process: The lungs expand, fetal lung fluid is cleared, effective air exchange is established, and the right-to-left circulatory shunts terminate. The critical period for these physiologic changes is during the first several breaths, which result in lung expansion and elevation of the

partial pressure of oxygen (PO_2) in both the alveoli and the arterial circulation. Elevation of the PO_2 from the fetal level of approximately 25 mm Hg to values of 50 to 70 mm Hg is associated with (i) decrease in pulmonary vascular resistance, (ii) decrease in right-to-left shunting through the ductus arteriosus, (iii) increase in venous return to the left atrium, (iv) rise in left atrial pressure, and (v) cessation of right-to-left shunt through the foramen ovale. The end result is conversion from fetal to transitional to neonatal circulatory pattern. Adequate systemic arterial oxygenation results from perfusion of well-expanded, well-ventilated lungs and adequate circulation.

Most newborns begin breathing at birth and successfully transition to the extrauterine environment without intervention. Conditions at delivery may compromise the newborn's ability to successfully make this transition. Premature infants or newborns with congenital anomalies may not be able to breathe independently or effectively. These patients require support targeted to their specific physiologic or anatomic challenges. Infants who experience compromise prior to or during delivery are depressed at birth. Human fetuses initially respond to hypoxia by becoming apneic. Even a relatively brief period of oxygen deprivation may result in **primary apnea**. Rapid recovery from this state is generally accomplished with appropriate stimulation and oxygen exposure. However, sustained hypoxia will induce **secondary apnea**. This state may occur remote from birth or in the peripartum period. Infants born during this period require resuscitation with assisted ventilation and oxygen (see section III.F).

C. Goals of resuscitation

1. **Minimizing immediate heat loss** by drying and providing warmth, thereby decreasing oxygen consumption by the neonate
2. **Supporting neonatal transition** by deferring umbilical cord clamping at least 30 to 60 seconds after birth, stimulating spontaneous breathing, and providing continuous positive airway pressure (CPAP) for spontaneously breathing infants who demonstrate signs of respiratory distress
3. **Establishing lung expansion and effective ventilation** using positive pressure ventilation (PPV) for infants who do not breathe spontaneously or effectively
4. **Increasing arterial PO_2** by providing adequate alveolar ventilation. The **routine** use of added oxygen is not warranted, but this therapy may be necessary in some situations.
5. **Supporting adequate cardiac output** as needed

II. PREPARATION

A. Anticipation and knowledge sharing. Anticipation is key to ensuring that adequate preparations have been made for a neonate likely to require resuscitation at birth. As many as 10% of neonates require some assistance at birth, whereas <1% require extensive resuscitative measures. Although known identifiable risk factors increase the probability a newborn will receive resuscitation, some infants without any known risk factors

unexpectedly require resuscitation. Therefore, at every birth, there should be at least one provider whose sole responsibility is the newborn baby and who is capable of initiating resuscitation and performing PPV.

B. Risk factors for resuscitation. Ideally, the obstetrical team should notify the pediatric team well in advance of delivery. The pediatric caregivers may then review the history and events leading to the high-risk delivery and prepare for the specific problems that are anticipated. If time permits, the problems should be discussed with the parent(s). The following antepartum and intrapartum events warrant the presence of at least two providers at delivery:

1. Prematurity (<37 weeks), postmaturity (>41 weeks), anticipated low birth weight (<2.0 kg) or high birth weight (>4.5 kg)
2. Major congenital anomalies diagnosed prenatally
3. Oligohydramnios or polyhydramnios
4. Fetal anemia
5. Hydrops fetalis
6. Multiple gestation
7. Maternal hypertension, preeclampsia, or eclampsia
8. Emergency cesarean section
9. Category II or III fetal tracing
10. Meconium-stained amniotic fluid
11. History of an acute perinatal event (e.g., placental abruption, cord prolapse, or intrapartum bleeding)
12. Breech presentation
13. Assisted delivery (vacuum or forceps) or shoulder dystocia
14. Maternal medication therapy (general anesthesia magnesium therapy, maternal opioid administration within 4 hours of delivery)

C. Necessary equipment. Each delivery room should be equipped with equipment and supplies to perform a complete resuscitation.

1. **Thermoregulation equipment.** Radiant warmer, warm towels or blankets, and hat. For a very low birth weight (VLBW) infant, additional warming techniques should be available, which might include prewarming the delivery room to 26°C, plastic wrap for covering the baby, or the use of an exothermic mattress. When used in combination, care should be taken to avoid hyperthermia.
2. **A blended oxygen source (adjustable between 21% and 100%)** with adjustable flowmeter and adequate length of tubing. A humidifier and heater may be desirable.
3. **Respiratory device capable of delivering PPV and 100% oxygen.** T-piece resuscitator, flow-inflating bag with adjustable pop-off valve, or self-inflating bag with reservoir. Bags should be appropriately sized for neonates (generally about 750 mL).
4. **Face mask(s)** of appropriate size for the anticipated infant
5. **Laryngeal mask**
6. **Suction supplies.** Bulb syringe, suction catheter (10 or 12 French), and suction source (portable or wall suction)

Table 4.1. Neonatal Intubation Supplies

Patient Weight	Endotracheal Tube Size (Internal Diameter)	Laryngoscope Blade
<1 kg	2.5 mm	00 or 0 blade
1–2 kg	3 mm	0 blade
>2 kg	3.5 mm	0 or 1 blade

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7. **Stethoscope** with infant- or premature-sized head
8. **Intubation supplies** (Table 4.1)
   - **a.** Laryngoscope with no. 0 and no. 1 blades. For extremely low birth weight infants, a no. 00 blade may be preferred.
   - **b.** Endotracheal tubes (2.5-, 3.0-, and 3.5-mm internal diameters)
   - **c.** Stylet
   - **d.** Tape or tube-securing device and scissors
9. **Equipped emergency box or cart**
   - **a.** Drugs, including epinephrine (1:10,000), and sodium chloride (NaCl) 0.9% (normal saline)
   - **b.** Umbilical catheterization tray with 3.5 and 5 French catheters
   - **c.** Syringes (1.0, 3.0, 5.0, 10.0, and 20.0 mL), needles (18 to 25G), T connectors, and stopcocks
10. **Monitoring equipment**
    - **a.** Pulse oximeter and sensors
    - **b.** Cardiac monitor and appropriately sized leads
    - **c.** End-tidal carbon dioxide (CO_2) monitor/indicator to confirm endotracheal (ET) tube position after intubation
11. **Transport incubator** with battery-operated heat source and portable-blended oxygen supply, if the delivery room is not close to the nursery

D. Equipment preparation. Prior to delivery, the resuscitation providers should prepare the equipment.

1. Ensure that the radiant warmer is on and that warm blankets are available.
2. Connect a properly sized facemask to the respiratory device.
   - **a.** Turn on the gas source and adjust the flow to 10 L/minute.
   - **b.** Set the oxygen blender to the appropriate starting concentration of oxygen. Based on the available evidence, current recommendations are to use **21% oxygen as the initial concentration for term babies** and **21% to 30% oxygen** for premature babies <35 weeks' gestation.
   - **c.** Adjust the respiratory device to provide PPV with an initial peak inspiratory pressure (PIP) of 20 cm H_2O and positive end-expiratory pressure (PEEP) of 5 cm H_2O.

3. Connect the suction catheter to the wall suction and set suction to 80 to 100 mm Hg.
4. Prepare intubation equipment:
   a. Make sure the laryngoscope light is functional and has an appropriate blade for the newborn's anticipated weight.
   b. Set out an appropriate ET tube for the expected birth weight (see Table 4.1). An intubation stylet may be used if the tip is kept at least 0.5 cm from the distal end of the ET tube.
5. If the clinical situation suggests that extensive resuscitation may be needed, the following actions may be required:
   a. Set up an umbilical catheterization tray for venous catheterization.
   b. Draw up 1:10,000 epinephrine and isotonic saline for catheter flush solution and volume replacement.
   c. Check that other potentially necessary drugs are present and ready for administration.
6. Consider any other positioning devices or supplies needed for newborns with congenital anomalies.
7. In the case of multiple gestations, prepare a fully equipped resuscitation station for each newborn.

E. Universal precautions. Exposure to blood or other body fluids is inevitable in the delivery room. Universal precautions must be practiced by wearing caps, goggles or glasses, gloves, and impervious gowns until the cord is cut and the newborn is dried and wrapped.

III. DURING DELIVERY.

Immediately prior to delivery, the resuscitation team should communicate with the obstetrical team to determine the gestational age, the color of the amniotic fluid, whether any additional risk factors are present, and the anticipated plan for umbilical cord management (based on known maternal and fetal conditions).

A. Immediately following delivery, begin a process of evaluation, decision, and action (resuscitation). The NRP recommends that at the time of birth, the baby should be assessed by posing three basic questions: (i) Is it a term gestation? (ii) Does the baby have good muscle tone? (iii) Is the baby crying or breathing? If the answer to any of these questions is "no," then the initial steps of resuscitation should commence. In the newly born infant, essentially all resuscitation problems within the initial postnatal period occur as a result of inadequate respiratory effort or some obstruction to the airway. Therefore, the initial focus must be on ensuring an adequate airway and adequate breathing.

B. Timing of cord clamping. For the majority of infants, no additional steps are needed beyond drying and provision of warmth and initial stimulation. If the infant is breathing spontaneously at birth, the cord should not be clamped and divided until at least 30 to 60 seconds have passed. For newborns who require the initial steps of resuscitation (drying, stimulation), these can occur prior to umbilical cord clamping.

For those infants who require resuscitation beyond the initial steps because of inadequate or absent respiratory effort, the cord should be clamped and divided shortly after birth. Ongoing studies continue to evaluate the

Table 4.2. Target Preductal Oxygen Saturation (SpO_2) during the First 10 Minutes after Birth

1 minute	60%–65%
2 minutes	65%–70%
3 minutes	70%–75%
4 minutes	75%–80%
5 minutes	80%–85%
10 minutes	85%–95%

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feasibility and effectiveness of providing resuscitation with the umbilical circulation still intact.

C. Evaluate for need and response to resuscitation. Assess whether the infant is **breathing spontaneously**, whether the **heart rate is >100 bpm**, and whether the oxygen saturation level is appropriate (Table 4.2). If any of these three characteristics is abnormal, take immediate steps to correct the deficiency and reevaluate every 15 to 30 seconds until all characteristics are present and stable. In this way, adequate support will be given while overly vigorous interventions are avoided when newborns are making adequate progress on their own. Some interventions are required in specific circumstances.

D. Initial steps of resuscitation. If the newborn has poor respiratory effort or muscle tone, the initial steps of resuscitation should be performed.

1. Ensure adequate thermoregulation:
   a. For late preterm and term infants, dry the infant completely and discard the wet linens, including those on which the infant is lying. Drying should be thorough but gentle; avoid vigorous rubbing or attempts to clean all blood or vernix from the baby. Ensure that the infant remains warm.
   b. Preterm infants require extra warming techniques such as wrapping the body and extremities in a plastic wrap or bag, applying a hat, and/or using of an exothermic mattress.
2. Place the infant with head in midline position, with slight neck extension.
3. Suction the mouth, oropharynx, and nares thoroughly with a suction bulb if there is obvious obstruction or the baby requires PPV. Deep pharyngeal stimulation with a suction catheter may cause arrhythmias that are probably of vagal origin and should be avoided.
4. If the infant is apneic (**primary apnea**), provide tactile stimulation, including vigorous flicking of the soles of the feet or rubbing the back. More vigorous or other techniques of stimulation have no therapeutic value and are potentially harmful. If breathing does not respond to tactile stimulation within 30 seconds, the baby should be considered

to be in **secondary apnea**, and respiratory support should be initiated. It is better to overdiagnose secondary apnea in this situation than to continue attempts at stimulation that are not successful.

E. Supplemental oxygen and/or CPAP are indicated for hypoxemia or labored breathing. In the normal fetal environment, oxygen saturation levels are well below those necessary during extrauterine life. These levels do not completely rise to the normal postnatal range for about 10 minutes after birth, and oxygen saturation levels of 70% to 80% are normal for several minutes. During this time, the baby may appear cyanotic, although clinical assessment of cyanosis has been shown to be an unreliable indicator of actual oxyhemoglobin saturation. However, either insufficient or excessive oxygenation can be harmful to the newborn.

If the newborn is breathing spontaneously with a heart rate >100 bpm but appears cyanotic or has labored breathing, a pulse oximeter should be placed on right upper extremity (usually the hand) as soon as possible after birth. If the measured levels are below the recommended range for minute after birth (see Table 4.2), supplemental oxygen should be administered. Blow-by oxygen can be delivered by holding an oxygen source near the newborn's mouth (but not occluding the mouth). Oxygen sources include oxygen tubing, the facemask from a T-piece device or flow-inflating bag, or the oxygen reservoir (tail) of a self-inflating bag. An initial concentration of 30% fraction of inspired oxygen (FiO_2) is appropriate.

CPAP may be indicated for spontaneously breathing infants with sustained labored respirations, such as grunting, and/or hypoxemia. An initial CPAP of 5 cm H_2O is appropriate. Subsequently, supplemental oxygen and CPAP should be titrated to maintain oxygen saturation levels within the reference range based on minute after birth. CPAPs should be increased cautiously to avoid the risk of pneumothorax.

F. PPV should be performed if the **infant is apneic or has a heart rate of <100 bpm despite tactile stimulation**, as this represents **secondary apnea**. When starting this intervention, call for assistance if your team is not already present.

1. The facemask should be used in conjunction with the respiratory device. The mask should cover the chin and nose but leave eyes uncovered.
2. After positioning the newborn's head in the midline with slight extension, the initial inflations should be delivered at a peak pressure that is adequate to produce appropriate chest rise. An initial peak pressure of 20 cm H_2O is appropriate. A rate of 40 to 60 breaths per minute should be used, and the infant should be reassessed in 15 to 30 seconds.
3. Troubleshooting PPV. The single best indicator of effective ventilation is a rising heart rate. If the heart rate remains <100 bpm, providers should troubleshoot PPV performance to address common impediments. Following each adjustment, providers should continue to assess for chest rise and rising heart rate.

   a. Mask and repositioning. Ensure there is no leak around the facemask and reposition the infant to ensure there is no airway obstruction. The infant should be in a "sniffing position," with slight extension of the neck.

   b. Suction and open mouth. Suction the mouth and nares and ensure the mouth is open. This is best achieved by first opening the mouth,

placing the bottom of the facemask over the chin and then gently rolling the mask over the bridge of the nose.

c. Increase pressure. If the heart rate remains <100 bpm despite these steps, there may be inadequate pressure to aerate the lungs. Peak pressures of 30 to 40 cm H_2O may be needed in the term infant to aerate the lungs. Once chest rise is achieved and the heart rate begins to rise, inspiratory pressures for subsequent inflations should be adjusted to ensure that there is adequate but not excessive chest rise. Especially in premature infants, every effort should be made to use the minimal pressures necessary for chest rise and restoration of heart rate.

d. Alternative airway (see section III.G)

4. Duration of PPV. PPV should be continued until respirations are spontaneous, and the heart rate is >100 bpm. If the heart rate is >100 bpm and rising and the infant appears to be breathing spontaneously, PPV can be gradually discontinued, without close ongoing clinical assessment of respiratory effort, heart rate, and oxygen saturation.

G. Alternative airways should be used if PPV via facemask remains ineffective, after troubleshooting common impediments.

1. **Laryngeal masks** are easy to insert and are effective for ventilating newborns >2,000 g. They should be considered when facemask PPV is not effective and intubation is unsuccessful or not possible. Laryngeal masks should be prepared especially in cases when an airway or facial anomaly is anticipated that may interfere with facemask PPV.

2. **Intubation** is recommended when bag-and-mask ventilation is ineffective, when chest compressions are administered, or when the infant requires transportation for more than a short distance after stabilization. Even in these situations, effective ventilation with a bag and mask may be done for long periods, and it is preferred over repeated unsuccessful attempts at intubation or attempts by unsupervised personnel unfamiliar with the procedure. If only inexperienced personnel are available, a laryngeal mask should be considered if an alternate airway is required. Intubation should be accomplished rapidly by a skilled person. If inadequate ventilation was the sole cause of the bradycardia, successful intubation will result in an increase in heart rate to >100 bpm and a rapid improvement in oxygen saturation. Detection of expiratory CO_2 by a colorimetric detector is an effective means of confirming appropriate tube positioning, especially in the smallest infants.

   The key to successful intubation is to correctly position the infant and laryngoscope and to know the anatomic landmarks. If the baby's chin, sternum, and umbilicus are aligned in a single plane and if, after insertion into the infant's mouth, the laryngoscope handle and blade are aligned in that plane and lifted vertically at approximately a 60-degree angle to the baby's chest, only one of four anatomic landmarks will be visible to the intubator: From cephalad to caudad, these include the posterior tongue, the vallecula and epiglottis, the larynx (trachea and vocal cords), or the esophagus. The successful intubator will view the laryngoscope tip and a landmark and should then know whether the landmark being observed is cephalad or caudad to the larynx. The intubator can

adjust the position of the blade by several millimeters and locate the vocal cords. The ET tube can then be inserted under direct visualization (see Chapter 69).

H. Circulation. If the heart rate remains <60 bpm after intubation and 30 seconds of ventilation with 100% oxygen, **cardiac compressions** should be instituted. The best technique is to encircle the chest with both hands, placing the thumbs together over the lower third of the sternum, with the fingers wrapped around and supporting the back. If the infant is intubated, this can be done effectively while standing at the head of the bed next to the person performing ventilation and encircling the chest with the thumbs pointing toward the infant's feet. This approach ensures that other caregivers can access the infant for assessment and/or placement of an umbilical catheter. Alternatively, one can stand at the side of the infant and encircle the chest with both hands, a configuration that is "upside down" from the first method. In either method, compress the sternum about one-third the diameter of the chest at a rate of 90 times per minute in a ratio of three compressions for each inflation. PPV through the ET tube should be continued at a rate of 30 breaths per minute, coordinated after every third compression.

Periodically (60 seconds), briefly suspend compressions to assess heart rate. Avoid frequent or prolonged interruptions of compressions, as these will compromise maintenance of systemic and coronary perfusion. If the heart rate is >60 bpm, chest compressions should be discontinued and ventilation continued until respiration is spontaneous. If the heart rate is <60 bpm, coordinated cardiac compressions and ventilation should be continued.

Infants requiring ventilatory and circulatory support are markedly depressed and require immediate, vigorous resuscitation. This will require at least three trained people working together.

I. Medications and volume expansion

1. **Epinephrine.** If the heart rate remains <60 bpm despite adequate ventilation with 100% oxygen and chest compressions, **epinephrine** is indicated. For rapid calculations, use 1, 2, or 3 kg as the estimate of birth weight. Epinephrine is a powerful adrenergic agonist and works in both adults and neonates by inducing an intense vasoconstriction and improved coronary (and cerebral) artery perfusion. The recommended dose is extrapolated from the apparently efficacious dose in adults and is based on both measured responses and empiric experience. The intravenous (IV) dose of 0.2 mL/kg (0.02 mg/kg) of a 1:10,000 epinephrine solution should ideally be given through the umbilical venous catheter and flushed into the central circulation. This dose may be repeated every 3 to 5 minutes if necessary.
2. **Volume expansion.** If ventilation and oxygenation have been established but blood pressure is still low or the peripheral perfusion is poor, volume expansion may be indicated. In most instances, the use of 10 mL/kg of normal saline is effective, but in specific cases, the use of emergency whole blood may be a better choice. Additional indications for volume expansion include evidence of acute bleeding or poor response to resuscitative efforts. Volume expansion should be carried out cautiously in newborns in whom hypotension may be caused by asphyxial

myocardial damage rather than hypovolemia. It is important to use the appropriate gestational age– and birth weight–related blood pressure norms to determine volume status (see Chapter 40).

3. In most situations, there is no value to the administration of bicarbonate or other buffers during immediate resuscitation. Because there are potential risks as well as benefits for all medications, drug administration through the umbilical vein should be reserved for those newborns in whom bradycardia persists despite adequate oxygen delivery and ventilation, only after establishment of an adequate airway.
4. **Route of administration.** The most accessible IV route for neonatal administration of medications is catheterization of the umbilical vein (see Chapter 69), which can be done rapidly and aseptically. Although the saline-filled catheter can be advanced into the inferior vena cava (i.e., 8 to 10 cm), in 60% to 70% of neonates, the catheter may become wedged in an undesirable or dangerous location (e.g., hepatic, portal, or pulmonary vein). Therefore, the catheter should only be advanced approximately 2 to 3 cm past the abdominal wall (4 to 5 cm total in a term neonate), just to the point of easy blood return, to a position that is safest for injection of drugs. In this position, the catheter tip will be in or just below the ductus venosus. It is important to flush all medications through the catheter because there is no flow through the vessel after cord separation.

IV. SPECIAL SITUATIONS

A. Meconium aspiration

1. The newborn should immediately be assessed to determine whether it is vigorous, as defined by strong respiratory effort, good muscle tone, and a heart rate >100 bpm. Infants who are vigorous should be treated as normal, despite the presence of meconium-stained fluid. If both the obstetric provider and the pediatric team in attendance agree that the infant is vigorous, it is not necessary to take the infant from his or her mother after birth.

   If the infant is not vigorous, appropriate resuscitative measures should be given, starting with initial steps and proceeding to PPV for ongoing apnea. **Routine tracheal suctioning is not recommended**, but it is important to maintain vigilance for possible airway obstruction by thick secretions and to suction as necessary.
2. For infants at risk for meconium aspiration syndrome who show initial respiratory distress, oxygen saturation levels should be monitored and kept in the normal range by administering adequate respiratory support (supplemental oxygen and/or CPAP).

B. Shock. Some newborns present with pallor and shock in the delivery room (see Chapter 40). Shock may result from significant intrapartum blood loss because of placental separation, fetal–maternal hemorrhage, avulsion of the umbilical cord from the placenta, vasa or placenta previa, incision through an anterior placenta at cesarean section, twin–twin transfusion, or rupture of an abdominal viscus (liver or spleen) during a difficult delivery. It may also result from vasodilation or loss of vascular tone because of septicemia or hypoxemia

and acidosis. These newborns will be pale, tachycardic (>180 bpm), tachypneic, and hypotensive with poor capillary filling and weak pulses.

After starting respiratory support, immediate transfusion with O-negative packed red blood cells and administration of normal saline boluses may be necessary if acute blood loss is the underlying cause. If clinical improvement is not seen, causes of further blood loss should be sought, and more vigorous blood and possible colloid replacement should be continued. It is important to remember that the hematocrit may be normal immediately after delivery if the blood loss occurred acutely during the intrapartum period. Except in cases of massive acute blood loss, the emergent use of blood replacement is not necessary, and acute stabilization can be achieved with crystalloid solutions. Normal saline is the primary choice of replacement fluid. This allows time to obtain proper products from the blood bank, if blood replacement is subsequently needed.

C. Air leak. If an infant fails to respond to resuscitation despite apparently effective ventilation, chest compressions, and medications, consider the possibility of air leak syndromes. Pneumothoraces (unilateral or bilateral) and pneumopericardium should be ruled out by transillumination, chest radiograph, or diagnostic thoracentesis (see Chapter 69) and treated if present.

D. Prematurity. Premature infants require additional special care in the delivery room, including thermoregulatory support with plastic wraps or bags, and/or the use of exothermic mattresses to prevent heat loss because of thinner skin and an increased surface-area-to-body-weight ratio. Apnea is more likely at lower gestational ages, and PPV should be anticipated. Surfactant-deficient lungs are poorly compliant, and higher ventilatory pressures may be needed for the first and subsequent breaths. The early initiation of CPAP to a preterm infant who is spontaneously breathing but exhibiting respiratory distress in the delivery room is strongly advocated. In pooled analysis of trials enrolling extremely preterm infants, prioritizing noninvasive support with CPAP immediately after birth (compared with empiric intubation and mechanical ventilation) was more effective at preventing death or bronchopulmonary dysplasia.

E. Congenital anomalies. Anomalies may significantly alter the newborn's physiologic transition after birth. Ideal delivery preparation includes identifying any specialists whose presence is required immediately after birth, such as an otolaryngologist for newborns with critical airway anomalies. Resuscitation teams should tailor their approach to the anticipated physiology associated with the specific anomaly. For example, newborns with pulmonary hypoplasia are likely to need increased respiratory support to establish lung aeration and effective ventilation, and newborns with congenital diaphragmatic hernia should be intubated immediately after birth. Newborns with cyanotic congenital heart disease will experience trends in oxygen saturation after birth that are distinct from newborns without cardiac disease. Finally, teams should be prepared for special handling and positioning of any external anomalies (such as myelomeningocele or omphalocele) to avoid trauma or infection.

F. Maternal opiate exposure. Reversal of narcotic depression is rarely necessary during the primary steps of resuscitation and is not recommended. If the mother has received narcotic analgesia within a few hours of delivery, the newborn may manifest respiratory depression and require ongoing respiratory support until the drug effect abates.

V. MONITORING RESUSCITATION.

Evaluation and decisions regarding resuscitation measures should be guided by assessment of respiration, heart rate, and oxygen saturation. Physiologic monitors are recommended to provide accurate and reliable measures of heart rate and oxygen saturation.

A. Pulse oximetry is recommended when supplemental oxygen, CPAP, or PPV are provided. Several studies have examined the change in oxygen saturation levels in the minutes following birth and have defined percentile ranges for uncompromised babies born at full term. The best defined data have been obtained using readings made at a "preductal" site (i.e., the right upper extremity) in order to avoid the potentially confounding effect of shunting during the transition to postnatal circulation. Once assisted ventilation or supplemental oxygen is provided, the oxygen concentration should be adjusted so that the measured preductal oxygen saturation value lies within a specified minute-specific reference range (see Table 4.2) as advocated by the NRP. The best available reference is the interquartile range of saturations measured in healthy term babies following vaginal birth at sea level.

Pulse oximetry sensors can be applied immediately after birth and successfully used to provide information on oxygen saturation. It may take around 60 to 90 seconds to obtain an accurate reading; pulse oximetry may fail if cardiac output is low or perfusion is poor.

B. Cardiac monitor (electrocardiogram) is recommended to provide a more accurate measurement of heart rate during extensive resuscitation. Clinical assessments of heart rate from palpation and auscultation are not accurate during delivery room resuscitation. The pulse rate from pulse oximeters tends to underestimate the heart rate compared with electrocardiograms in the initial minutes after birth, likely due to poor perfusion. Therefore, if the resuscitation is progressing toward intubation, a cardiac monitor should be used to provide a rapid and accurate method of assessing heart rate, which is the primary parameter used to assess the effectiveness of resuscitative interventions. Leads can be quickly applied and the heart rate determined within 30 seconds. Caregivers must be aware of the possibility that pulseless electrical activity may occur in the depressed newborn.

C. End-tidal or expiratory CO_2 detectors are recommended to confirm appropriate ET tube placement in the trachea after intubation.

D. Apgar scores are conventionally assigned after birth and recorded in the newborn's chart. The Apgar score consists of the total points assigned to five objective signs in the newborn. Each sign is evaluated and given a score of 0, 1, or 2. Total scores at 1 and 5 minutes after birth are usually noted. If the 5-minute score is 6 or less, the score is then noted at successive 5-minute intervals until it is >6 (Table 4.3). A score of 10 indicates an infant in perfect condition; this is quite unusual because most babies have some degree of acrocyanosis.

VI. POSTRESUSCITATIVE CARE

A. General principles. Newborns who receive delivery room resuscitation may experience physiologic deterioration even after vital signs and physical exam normalize. Ongoing monitoring of temperature, respiratory status,

Table 4.3. Apgar Scoring System

	Score		
Sign	**0**	**1**	**2**
Heart rate	Absent	<100 bpm	>100 bpm
Respiratory effort	Absent	Slow (irregular)	Good crying
Muscle tone	Limp	Some flexion of extremities	Active motion
Reflex irritability	No response	Grimace	Cough or sneeze
Color	Blue, pale	Pink body, blue extremities	All pink

Source: Adapted with permission from Apgar V. A proposal for a new method of evaluation of the newborn infant. *Curr Res Anesth Analg* 1953;32(4):260–267.

blood pressure, glucose and electrolytes, and neurologic status may be indicated. The ideal location for the newborn after delivery (nursery vs. neonatal intensive care unit) depends on the intensity of resuscitation and clinical status of the newborn after resuscitation.

B. Postresuscitative care after extensive resuscitation (intubation or cardiac compressions). Once an adequate airway has been established, adequate ventilation achieved, and the heart rate exceeds 100 bpm, the infant should be moved to the neonatal intensive care unit. Physical examination, vital sign assessment, and test results including a chest radiograph will help to more clearly identify needs for specific interventions.

C. Induced therapeutic hypothermia initiated within 6 hours of birth is the standard therapy for infants born at ≥36 weeks' gestation who manifest moderate to severe hypoxic-ischemic encephalopathy (HIE) to improve neurodevelopmental outcomes. The role for passive cooling similarly requires more complete evaluation, but it does make sense to avoid active warming of an infant for whom this therapy is being considered while taking care to ensure that the infant's temperature does not drop below about 33.5°C. Avoidance of maternal or neonatal **hyperthermia** is warranted and may prevent subtle neurologic injury (see Chapter 55). The efficacy of therapeutic hypothermia to improve neurologic outcomes for other populations is an ongoing topic of research. These include infants with mild HIE and preterm infants with moderate to severe HIE. At present, therapeutic hypothermia is not recommended for these populations.

VII. WITHHOLDING OR DISCONTINUING RESUSCITATION

A. Withholding resuscitation. Decisions to not initiate or to limit the intensity or duration of resuscitation may be appropriate when survival is unlikely or associated morbidity is very high. This may be considered at the

lower limits of viability or in the setting of major congenital anomalies. In these cases, parents should be considered as the best spokespeople for the newborn.

B. Discontinuing resuscitation. If the newborn has no or limited response to a complete extensive resuscitation and reversible causes have been excluded, it may be appropriate to discontinue resuscitative efforts. Historically, this decision was considered after 10 minutes of resuscitation without response. However, emerging data suggest that survival without significant neurodevelopmental impairment is possible even for some infants with ongoing cardiopulmonary resuscitation beyond 10 minutes after birth.

Ultimately, no uniform duration of resuscitation exists that will optimize survival or neurodevelopmental outcomes after prolonged delivery room resuscitation. Therefore, the decision to stop resuscitation should be individualized, with consideration of whether the resuscitation interventions have been optimized, the availability of advanced intensive care (including therapeutic hypothermia), the baby's gestational age, and any specific circumstances prior to birth related to the presumed etiology and timing of the perinatal events. A reasonable timeframe to discuss discontinuing resuscitation with the family and resuscitation team is around 20 minutes after birth.

VIII. TEAMWORK DURING NEONATAL RESUSCITATION.

Most neonatal resuscitations are performed by two or more providers, and each provider brings specific knowledge and skills to the resuscitation. One unique aspect of health care teams is that they are not static. Therefore, team members attending a delivery may not have previously worked together. Teamwork is therefore essential to optimize team performance during delivery room resuscitation. Briefing and debriefing are recommended practices to facilitate teamwork and identify opportunities for teams to improve their performance.

A. Team briefing. A structured team briefing is an important aspect of predelivery planning and preparation. A standardized script or checklist is a useful cognitive aid to ensure the team briefing addresses the following key elements:

1. Define the situation and ensure essential information is shared among the team.
2. Assign roles and outline clear expectations for each provider's role.
3. Position team members appropriately within the environment.

B. Team debriefing. A team debriefing following the resuscitation provides the opportunity to review the decisions and actions taken during resuscitation and to identify both successful behaviors and opportunities for improvement. Debriefings can either occur immediately after resuscitation (hot debrief) or can be a more structured debriefing or resuscitation review scheduled at a later time (cold debrief). In settings where video recording is available, videos support team debriefings by providing a reliable record of the resuscitation.

Suggested Readings

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5 Nonimmune Hydrops Fetalis

Kevin Dysart and Julie Moldenhauer

KEY POINTS

- Hydrops fetalis has classically been defined as the presence of extracellular fluid in at least two fetal body compartments.
- With routine use of Rhesus (Rh) immune globulin for the prevention of Rh alloimmunization, 85% to 90% of hydrops cases are classified as nonimmune.
- Treatment focuses on the etiology of hydrops, although many cases remain idiopathic.
- Plans for neonatal resuscitation should account for the location and severity of extravascular fluid collections and assess the need for immediate drainage as part of the initial resuscitation.

I. DEFINITION. Hydrops fetalis has classically been defined as the presence of extracellular fluid in at least two fetal body compartments. These fluid collections include skin edema (>5-mm thickness), pericardial effusion, pleural effusions, and ascites; all are easily recognized on prenatal ultrasound (Figs. 5.1–5.4). Frequent additional findings included polyhydramnios (deepest vertical pocket of amniotic fluid of >8 cm or amniotic fluid index >24 cm) and placentomegaly (>4-cm thickness in the second trimester or >6-cm thickness in the third trimester).

II. INCIDENCE. The reported incidence of nonimmune hydrops fetalis (NIHF) varies between 1 in 1,700 and 1 in 3,700 pregnancies.

III. ETIOLOGY (Table 5.1). The advent of the widespread use of Rh immune globulin for the prevention of RhD alloimmunization has resulted in a shift to nonimmune etiologies of fetal hydrops. In 1970, McAfee et al. reported that 82% of cases of fetal hydrops were related to red cell alloimmunization, whereas in one more recent series, 95% of cases of hydrops were classified as nonimmune. The etiology of NIHF is diverse. A systematic literature review of reports involving >10 cases was undertaken by Bellini et al. between 1979 and 2007. Fifty-one papers met the criteria of the authors and involved 5,437 patients. They found that cardiovascular malformations represented the most common etiology followed by idiopathic causes, chromosomal abnormalities, and hematologic etiologies.

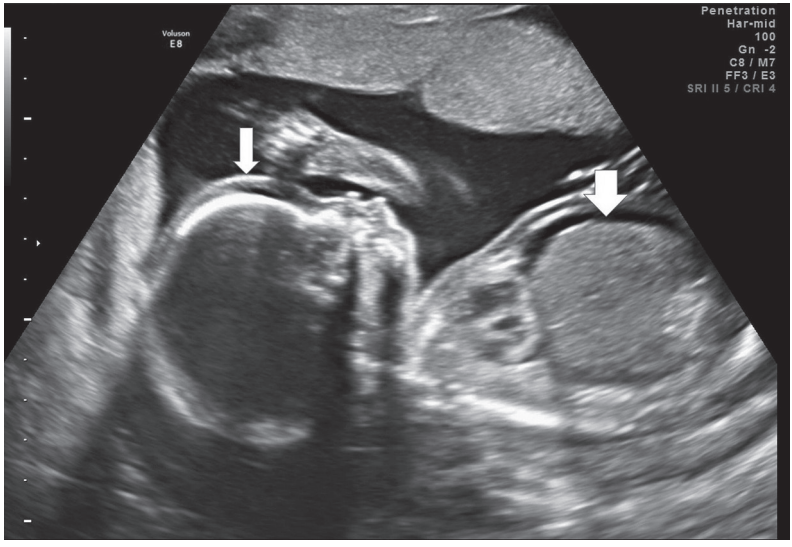

Figure 5.1. Scalp edema (*small arrow*) and ascites (*larger arrow*) in a case of nonimmune hydrops fetalis secondary to parvovirus at 22 weeks' gestation.

A subsequent review by the same authors using strict selection criteria of publications between 2007 and 2013 included 24 papers involving 1,338 patients. A decreased trend in chromosomal abnormalities, thoracic problems, urinary tract malformations, and twin–twin transfusion was noted between the two consecutive time periods, whereas etiologies of lymphatic dysplasia and gastrointestinal

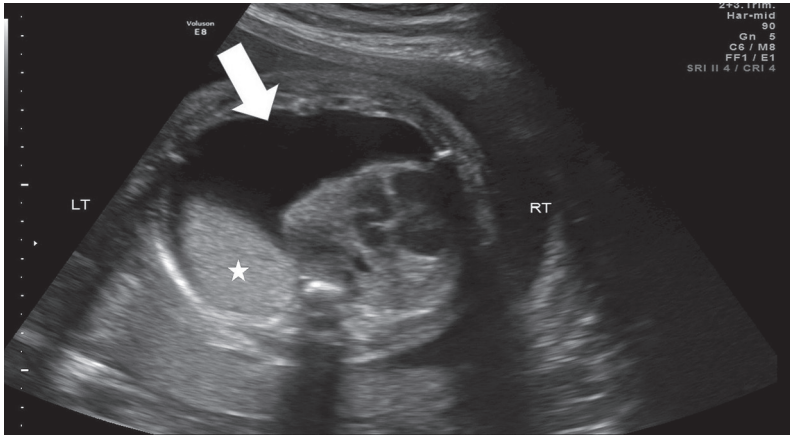

Figure 5.2. Large left-sided pleural effusion (*arrow*) in a fetus at 28 weeks' gestation with bronchopulmonary sequestration (lesion indicated by *star*).

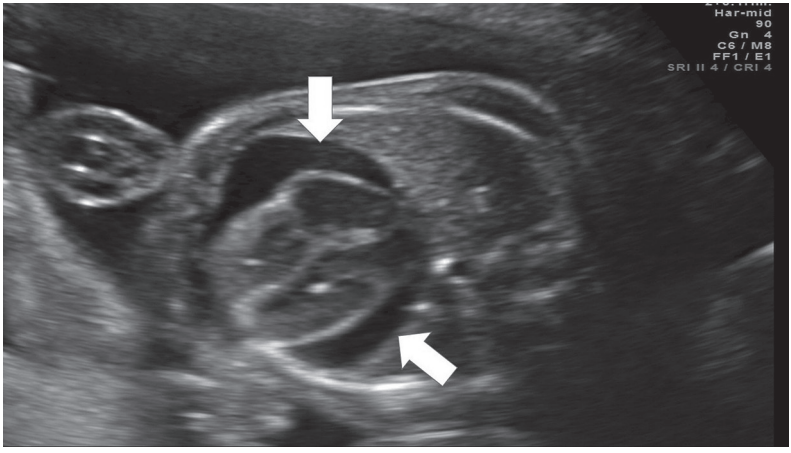

Figure 5.3. Pericardial effusion (between the *arrows*) in a recipient twin with severe twin–twin transfusion at 24 weeks' gestation.

causes increased. The overall contributions of the various etiologies from the two series are noted in Table 5.1.

Lysosomal storage disease should also be considered as an etiology in cases of NIHF. The incidence is estimated to be approximately 5% of all cases tested and between 15% and 29% of "idiopathic" cases of NIHF. The most common diagnoses include galactosialidosis, sialic acid storage disease, mucopolysaccharidosis type VII, Gaucher disease, and GM1 gangliosidosis.

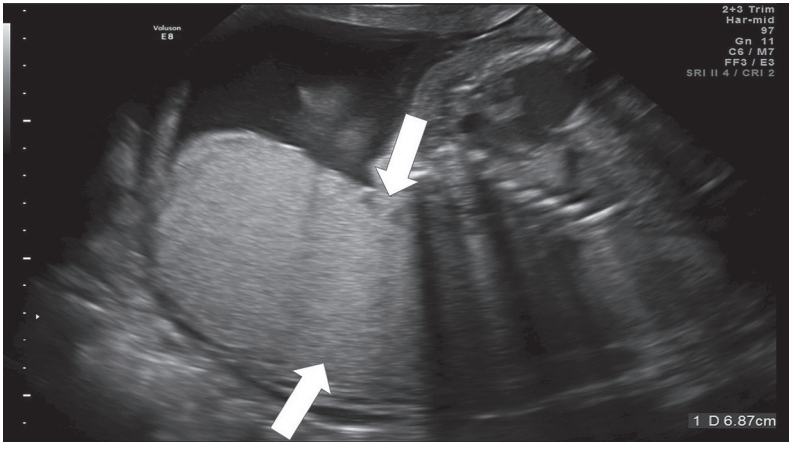

Figure 5.4. Placentomegaly (between the *arrows*) at 25 4/7 weeks' gestation associated with nonimmune hydrops fetalis in a fetus with an unbalanced atrioventricular canal defect and heterotaxy syndrome.

Table 5.1. Etiologies of Nonimmune Hydrops

Category	%	Typical Causes
Cardiovascular	20.1	Hypoplastic left heart, Ebstein anomaly, endocardial cushion defect, bradyarrhythmias/tachyarrhythmias
Idiopathic	19.8	—
Chromosomal	9.0	45 XO, trisomy 21, trisomy 18
Hematologic	9.3	α-Thalassemia, fetomaternal hemorrhage
Lymphatic dysplasia	15.0	Congenital lymphatic dysplasia
Infections	7.0	Parvovirus, CMV, adenovirus, enterovirus
Thoracic	2.3	CCAM, diaphragmatic hernia, extrapulmonary sequestration, hydrothorax, chylothorax
Twin–twin transfusion	4.1	Donor/recipient fetus (more common)
Syndromic	5.5	Noonan syndrome
Miscellaneous	3.6	—
Urinary tract malformations	0.9	Urethral obstruction, prune belly syndrome
Inborn errors of metabolism	1.3	Lysosomal storage diseases
Extrathoracic tumors	0.7	Vascular tumors, teratomas, leukemia, hepatic tumors, neuroblastoma
Gastrointestinal	1.3	Meconium peritonitis, GI obstruction

CMV, cytomegalovirus; CCAM, congenital cystic adenomatoid malformation; GI, gastrointestinal.

Source: From Bellini C, Donarini G, Paladini D, et al. Etiology of non-immune hydrops fetalis: an update. *Am J Med Genet A* 2015;167A(5):1082–1088. Copyright © 2015 Wiley Periodicals, Inc. Modified by permission of John Wiley & Sons, Inc.

IV. PATHOPHYSIOLOGY. Because the etiology of NIHF is so diverse, few studies have addressed the pathophysiology of this condition. In many cases, lymphatic return of interstitial fluid to the vascular space is either inadequate or compromised. However, the etiology of this imbalance depends on the specific diagnosis. Anatomical obstruction is present in cases of Turner syndrome associated with cystic hygroma or lymphatic dysplasia as well as in cases of intrathoracic tumors (congenital pulmonary airway malformation) that can cause

obstruction of venous or arterial blood flow due to mediastinal shift. Structural cardiac disease can result in increased right heart pressure leading to an increase in central venous pressure. Severe fetal anemia can lead to high-output cardiac failure (e.g., in fetal parvovirus infection or hemoglobinopathies). Alternatively, vasculitis from fetal infection (e.g., cytomegalovirus) can result in intravascular protein loss and enhanced interstitial fluid production. Congenital nephrosis leads to profound hypoproteinemia resulting in NIHF. Complications unique to monochorionic twins can be associated with NIHF such as twin–twin transfusion syndrome (most commonly seen in the recipient twin) or twin reversed arterial perfusion (TRAP) sequence in which the structurally normal pump twin develops hydrops due to the demands of a large parabiotic co-twin.

In a series of 20 fetuses with NIHF, umbilical venous pressure was elevated at the time of cordocentesis in 65% of the cases. Correction of some of the lesions resulted in normalization of the venous pressure on subsequent measurement, which was accompanied by resolution of the hydrops. The author concluded that an elevated umbilical venous pressure signaled inadequate cardiac output as the cause of the NIHF. Normalization of the venous pressure after correction of the fetal condition invariably resulted in perinatal survival.

V. EVALUATION (Table 5.2). The initial diagnosis of NIHF is often made at the time of a routine ultrasound examination (Fig. 5.5). At other times, the patient complains of a decrease in fetal movement or a rapid increase in weight gain or abdominal girth—signs of significant polyhydramnios.

A comprehensive ultrasound examination including thorough anatomical evaluation of the fetus, as well as umbilical cord and placenta, should be undertaken. Amniotic fluid volume should be assessed. A fetal echocardiogram should be performed with special emphasis on cardiac structure and rhythm. The peak systolic velocity of the middle cerebral artery (MCA) should also be measured as an elevated value of >1.5 multiples of the median corrected for gestational age has been associated with fetal anemia in cases of NIHF.

Obtaining a thorough maternal history including reproductive history, medical history, exposures to medications and illness during the pregnancy, and a detailed family history should then be undertaken. This should include queries regarding exposure to children with fifth disease ("slapped cheek" disease caused by parvovirus B19). Maternal symptoms that would indicate subsequent infection would include fever, arthralgia, and an exanthema on the upper body; however, as many as one-third of maternal infections are not accompanied by symptoms. A previous obstetrical history of stillbirth or a hydropic fetus should lead the investigator to consider lysosomal storage diseases or other genetic syndromes as part of the differential diagnosis. Similarly, a consanguineous relationship would also lead one to consider autosomal recessive diseases as the etiology. If the couple is of Southeast Asian descent, review of the maternal red cell mean corpuscular volume (MCV) (<80 = abnormal) should lead to an evaluation for α-thalassemia and the possibility of hemoglobin Bart in the fetus.

The next step in the diagnostic evaluation usually entails maternal blood work. Tests should include an antibody screen for anti–red cell antibodies, rapid test for syphilis, and a Kleihauer-Betke test or fetal cell stain by flow cytometry to

Table 5.2. Evaluation of Hydrops Fetalis

Prenatal Evaluation (Alive Fetus)	Prenatal Evaluation (Intrauterine Demise)
■ Maternal history* ■ Maternal blood type and screen* ■ Fetal echocardiogram ■ Comprehensive obstetrical ultrasound ■ MCA Doppler* ■ Amniotic fluid analysis (viral PCR, karyotype, FISH, CMA) ■ MRI	■ Autopsy (+ placenta) ■ Fetal DNA ■ Fibroblast culture ■ Skeletal survey ■ Immunohistochemical studies ■ Photographs ■ Frozen tissues
Postnatal Evaluation (Alive Newborn)	**Postnatal Evaluation (Neonatal Demise)**
■ Physical exam ■ Echocardiogram* ■ Ultrasound: head and abdomen ■ Chromosomes (karyotype and/or microarray) ■ Viral cultures ■ Blood gas* ■ Blood count* ■ Blood type + Coombs test* ■ Electrolytes ■ Urinalysis ■ Analysis of fluid (ascites, pleural effusion) ■ Liver functions ■ Radiographs	■ Autopsy (+ placenta) ■ Fetal DNA ■ Fibroblast culture ■ Skeletal survey ■ Immunohistochemical studies ■ Photographs ■ Frozen tissues

*Evaluations performed in immune hydrops fetalis. In all cases, DNA should be reserved for additional genetic studies.

MCA, middle cerebral artery; PCR, polymerase chain reaction; FISH, fluorescent *in situ* hybridization; CMA, chromosome microarray; MRI, magnetic resonance imaging.

Source: From Bellini C, Donarini G, Paladini D, et al. Etiology of non-immune hydrops fetalis: an update. *Am J Med Genet A* 2015;167A(5):1082–1088. Copyright © 2015 Wiley Periodicals, Inc. Modified by permission of John Wiley & Sons, Inc.

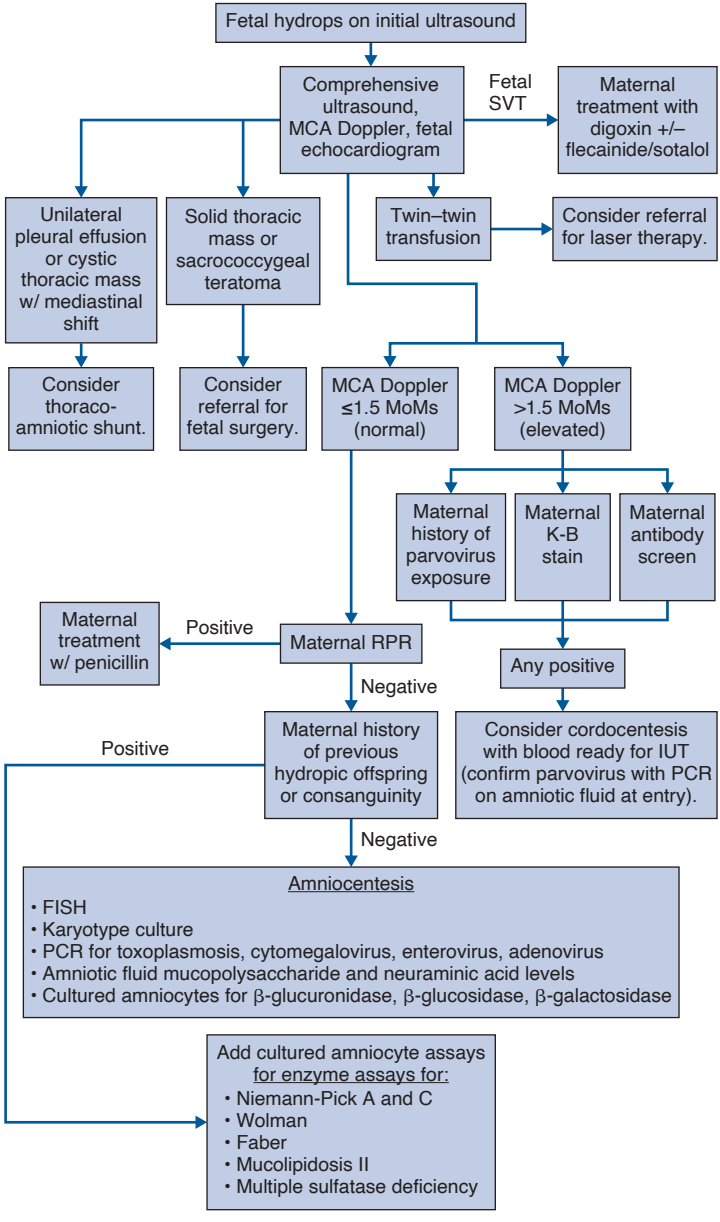

Figure 5.5. Algorithm for the management and treatment of nonimmune hydrops fetalis. MCA, middle cerebral artery; SVT, supraventricular tachycardia; MoM, multiples of median; K-B, Kleihauer-Betke; RPR, rapid plasma reagin; IUT, intrauterine transfusion; PCR, polymerase chain reaction; FISH, fluorescent *in situ* hybridization.

evaluate for fetomaternal hemorrhage. Maternal serologies (immunoglobulin G [IgG] and immunoglobulin M [IgM]) for toxoplasmosis, cytomegalovirus, and parvovirus are often ordered (toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus [TORCH] panel). Unfortunately, these tests can be nonspecifically elevated, and awaiting their result can lead to a significant delay in treatment.

Amniocentesis is warranted to complete the acute investigation. Samples should be sent for fluorescent *in situ* hybridization (FISH), karyotype and/or chromosomal microarray, and polymerase chain reaction (PCR) testing for toxoplasmosis, cytomegalovirus, parvovirus, adenovirus, and enterovirus. Cultured amniocytes can be held in reserve and later sent to specific laboratories for further investigation for additional etiologies such as lysosomal storage disease panels, hemoglobinopathy testing, or whole exome sequencing. If the family history is consistent with a previously affected fetus/neonate, including reserved DNA from the prior affected in the familial assessment can often be helpful in determining the etiology.

VI. PRENATAL TREATMENT.

A limited number of cases of NIHF can be treated *in utero*; however, these cases are based on an accurate determination of the specific etiology (see Table 5.1).

A. Parvovirus infection. Parvovirus has been associated with profound fetal anemia and hydrops fetalis when maternal infection occurs prior to 20 weeks' gestation with a peak incidence between 21 and 24 weeks (see Chapter 48). The presence of hydrops in association with parvovirus infection results in fetal loss of 24% compared to 3.4% when hydrops is not present. Additionally, in cases of parvovirus with hydrops, spontaneous resolution occurs in 5.2% of cases compared to 49.6% of cases without hydrops. In a recent systematic review, the risk of fetal loss and fetal hydrops in parvovirus-infected women was 7.6% and 9.3%, respectively. Although maternal serology (positive IgM or new presence of an IgG antibody in a patient that was previously seronegative) can be used to confirm cases, amniocentesis for PCR determination of parvovirus can usually be diagnostic in 24 to 48 hours. The MCA Doppler can be used to confirm the presence of fetal anemia when there is an elevated peak systolic velocity of >1.5 multiples of the median. In one review, intrauterine transfusion (IUT) of packed red cells was associated with survival in 82% of cases compared to 55% of nontransfused fetuses. However, the fetal loss rate has been reported as much higher in those fetuses with hydrops (28.9%) compared to those without (5.5%).

B. Other causes of fetal anemia. IUTs have also proven successful in cases of fetal hydrops secondary to fetomaternal hemorrhage. If a recurrent decline in fetal hematocrit is detected due to a persistent fetomaternal bleed, abandonment of additional transfusions may be warranted. Fetal α-thalassemia with hemoglobin Bart and NIHF has been treated with serial IUTs. Continued transfusion therapy, chelation, and eventual bone marrow transplant are required after birth due to abnormal hemoglobin production in these cases. Gestational age must also be taken into consideration when approaching fetal therapy as delivery with neonatal treatment may be the more optimal clinical plan.

C. Other infections. Other treatable bacterial, parasitic, and viral infections associated with NIHF include syphilis, toxoplasmosis, and adenovirus. Fetal infection with syphilis that results in NIHF can reverse with maternal treatment with penicillin; however, the overall prognosis due to cerebral complications remains high. NIHF related to fetal toxoplasmosis has resolved after maternal administration of pyrimethamine, sulfadiazine, and folinic acid with good short-term neurologic outcome. Adenovirus can cause fetal myocarditis with resulting hydrops. Maternal administration of digoxin has been successful in increasing fetal myocardial function resulting in resolution of the hydrops.

D. Cardiac arrhythmias. Both fetal bradyarrhythmias and tachyarrhythmias have been associated with fetal hydrops. Ventricular rates of <50 bpm due to structural cardiac lesions or inflammation secondary to maternal anti-Ro antibodies are not amenable to therapy. The administration of maternal beta-mimetics has not been successful at increasing the fetal heart rate. Attempts at direct fetal pacing have also failed. Both fetal atrial flutter and supraventricular tachycardia are associated with NIHF. Maternal administration of digoxin followed by the addition of flecainide or sotalol is often successful in converting these to a sinus rhythm with subsequent resolution of NIHF.

E. Fetal lung lesions. Unilateral pleural effusions (typically a chylothorax) or large, predominantly congenital cystic adenomatoid malformations (CCAMs) or congenital pulmonary airway malformations (CPAMs) of the fetal lung represent space-occupying lesions that can shift the mediastinum to the opposite side of the fetal chest. These lesions can therefore cause an obstruction to venous return as well as decreased cardiac output and subsequent development of NIHF. In both lesions, thoracoamniotic shunt placement under ultrasound guidance has been successful in decreasing the size of the lesion resulting in a return of the mediastinum to its midline position. Hydrops will usually resolve within several weeks. In solid CCAMs with mediastinal shift and NIHF, maternal steroid administration has resulted in resolution of the hydrops. In cases of bronchopulmonary sequestration with NIHF, needle-guided laser therapy to coagulate the arterial feeder vessel has resulted in resolution of the hydrops.

F. Twin–twin transfusion. The recipient twin in twin–twin transfusion syndrome can exhibit NIHF in up to 7% of cases. Laser photocoagulation of the putative placental anastomoses can result in complete resolution of the NIHF with a 70% to 80% perinatal survival. Most cases of donor twin NIHF occur after successful laser therapy. These cases are thought to the result of the acute anemia that can occur during the laser procedure; it is typically transient and usually resolves spontaneously.

VII. MATERNAL COMPLICATIONS OF FETAL HYDROPS

(Table 5.3). Fetal hydrops is often associated with polyhydramnios leading to such maternal complications as supine hypotension syndrome, preterm labor, and preterm premature rupture of the membranes. If placental hydrops is significant, an additional life-threatening complication has been described—Ballantyne syndrome (also known as mirror syndrome, triple edema, and pseudotoxemia). First described in association with hydrops secondary to maternal Rh

Table 5.3. Maternal Symptoms with Mirror Syndrome

Symptom	Frequency (%)
Edema/weight gain	84
Hypertension	60.1
Anemia	51.3
Dyspnea or pulmonary edema	30
Elevated uric acid/creatinine	20.3
Elevated hepatic enzymes	19.4
Oliguria	15
Headache	12.3

Source: Modified from Allarakia S, Khayat HA, Karami MM, et al. Characteristics and management of mirror syndrome: a systematic review (1956-2016). *J Perinat Med* 2017;45(9):1013–1021. Copyright © 2017 Walter de Gruyter GmbH, Berlin/Boston.

alloimmunization in 1892, many subsequent case descriptions have appeared in the literature secondary to NIHF due to a variety of etiologies. A recent review of 113 cases published between 1956 and 2016 noted clinical and laboratory findings similar to preeclampsia (see Table 5.3). However, unlike preeclampsia where hemoconcentration secondary to a reduced intravascular volume is the rule, mirror syndrome appears to be routinely associated with an expanded intravascular volume. Maternal hematocrit and albumin are low with minimal or no loss of urinary protein. Although the pathophysiology is largely unknown, hyperplacentosis is thought to be central to the cause. Reversal of maternal symptoms has been reported with the resolution of fetal hydrops after *in utero* treatment. Severe maternal complications have been reported with pulmonary edema in 25% of cases; progression to eclampsia has also been reported. In these situations, delivery is indicated.

VIII. DELIVERY CONSIDERATIONS. All efforts should be undertaken to determine the etiology of NIHF because, in many instances, this will determine the chance for perinatal survival. The maternal condition should also be taken into account because early signs of mirror syndrome warrant consideration for delivery unless an etiology for the NIHF can be identified and treated with *in utero* therapy provided the maternal status remains stable. Findings of trisomy 18 or severe Ebstein anomaly warrant consultation with the palliative care team because prolonged survival after birth is unlikely. In cases of idiopathic NIHF, perinatal mortality rates approach 50%. Collaborative consultation between maternal–fetal medicine (MFM) and neonatology is paramount. In fetal or perinatal deaths, autopsy should be offered to assist in determination of a diagnosis and optimal counseling regarding risk for recurrence.

IX. NEONATAL MANAGEMENT OF FETAL HYDROPS

A. Predelivery consultation. Outpatient prenatal consultation with neonatology, pediatric subspecialty services, and perinatal palliative care team should be considered at tertiary care centers with an MFM delivery service. Prenatal consultations include discussion of postdelivery care of the fetal condition with and without premature delivery, tour of neonatal intensive care unit, and opportunity to address specific neonatal questions (resuscitation, hospitalization course, outcomes, and possible birth plan). Consultation discussions should be added to maternal records for communication between services and in the event of an emergent delivery at a later date. Institutions unable to provide the needed level of maternal or neonatal care should consider a predelivery maternal transfer to a tertiary care center if possible.

B. Delivery room management. Resuscitation team preparation should occur well before delivery when possible. Plans for resuscitation should account for the location and severity of extravascular fluid collections and assess the need for immediate drainage as part of the initial resuscitation. Large pleural fluid collections or ascites may severely restrict ventilation of the lungs until adequately drained. Needle drainage under ultrasound guidance of large fluid-filled chest lesions (CPAM) or pleural effusions just prior to delivery by MFM can greatly assist in the neonatal resuscitative effort. Appropriate equipment and health care personnel with skills in ventilation and emergency procedures (endotracheal intubation, thoracentesis, paracentesis, thoracotomy tube placement, umbilical line placement) should be immediately available in the delivery room (Table 5.4). Associated fetal health issues may warrant other subspecialty presence (i.e., pediatric cardiology, pediatric anesthesia) for management (cardiac arrhythmia, pericardial effusion, abnormal airway) during resuscitation.

C. Postdelivery management. Management after delivery is focused on treating the hydrops etiology (if known) and measures to correct abnormalities associated with hydrops. Patients with heart failure frequently will suffer from respiratory failure, anemia, hypoproteinemia, metabolic acidosis, hypotension, oliguria, and pulmonary hypertension. Hemodynamic instability is common secondary to rapid fluid shifts secondary to extravascular fluid drainage and the presence of hypoalbuminemia and hypoproteinemia.

D. Ventilatory management can be complicated by pulmonary hypoplasia, reaccumulation of pleural fluid and/or ascites, and persistent pulmonary hypertension. Chest or peritoneal tube placement may be needed to evacuate reaccumulating fluid in the pleural and peritoneal space. Exogenous surfactant administration should be considered if the infant is premature or there is evidence of surfactant deficiency disease.

E. Fluid management should be based on a calculated "dry weight" of the patient (usually the 50th percentile for gestational age). Maintenance intravenous fluids should start at 40 to 60 mL/kg/day of 10% dextrose solution and adjusted for serum glucose levels. Frequent evaluation of serum electrolytes, urine, and fluid drainage composition along with total fluid intake and output are necessary for fluid management. Free water and salt intake

Table 5.4. Suggested Hydrops Fetalis Resuscitation Equipment and Personnel

Equipment	Personnel
Three thoracentesis/paracentesis kits (one for each side of the chest and one for the abdomen)	Team leader (neonatologist)
One pericardiocentesis kit (prepare if known pericardial effusion)	A resuscitation team member for each anticipated procedure (minimum of four)
Two thoracotomy kits (available in the event of pneumothorax during resuscitation)	Nursing personnel for code drugs and recording (preferably two)
Umbilical catheter setup (one for emergent umbilical venous catheter)	Respiratory therapist
Normal saline for infusion (avoid 5% albumin)	Consider pediatric subspecialist for anticipated airway or medical stabilization.
Resuscitation medications: epinephrine (Use dry weight at 50th percentile for gestational age.)	
Type O, RhD-negative blood cross-matched with mother if severe anemia is suspected	
Blood gas syringes	
Code medications and code sheet	

should be restricted in the first few days because these patients have high extravascular salt and water content. Use of diuretics should be cautious and include frequent electrolyte monitoring.

F. Hemodynamic management may require the use of inotropes to improve cardiac output. In addition to placement of central venous and arterial lines for monitoring and management, an echocardiogram should be obtained to evaluate ventricular function, cardiac filling, and pulmonary pressures. Most hydropic infants are normovolemic, so care should be taken to not volume overload if there is evidence of cardiac failure.

G. Hematology management includes evaluation of hematocrit and clotting factors. Euvolemic partial exchange transfusion should be considered in the anemic heart failure patient (hematocrit <30%) to improve oxygen-carrying capacity and increase hematocrit.

Suggested Readings

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6 Birth Trauma

Elisa Abdulhayoglu

KEY POINTS

- Birth injury is defined by the National Vital Statistics Report as "an impairment of the infant's body function or structure due to adverse influences that occurred at birth."
- When fetal size, immaturity, or malpresentation complicate delivery, the normal intrapartum compressions forces can lead to injury in the newborn.
- A newborn at risk for birth injury should have a thorough examination, including a detailed neurologic evaluation.
- The birth injury rate has been decreasing steadily in the past decade.
- Injury may occur antenatally, intrapartum, or during resuscitative efforts.
- Not all birth injury is avoidable.
- Long-term prognosis for most birth injuries is resolution without permanent injury.

I. BACKGROUND. Birth injury is defined by the National Vital Statistics Report as "an impairment of the infant's body function or structure due to adverse influences that occurred at birth." Injury may occur antenatally, intrapartum, or during resuscitation and may be avoidable or unavoidable.

A. Incidence. The birth injury rate in 2017 as reported by Agency for Healthcare Research and Quality in July 2020 was 4.77 per 1,000.

B. Risk factors. When fetal size, immaturity, or malpresentation complicates delivery, the normal intrapartum compressions, contortions, and forces can lead to injury in the newborn. Obstetrical instrumentation may increase the mechanical forces, amplifying or inducing a birth injury. Per the National Vital Statistics Report, in 2018, forceps-assisted deliveries were 0.5% of all births, whereas vacuum-assisted ones made up 2.5%. Breech presentation carries the greatest risk of injury; however, cesarean delivery without labor does not prevent all birth injuries. The following factors may contribute to an increased risk of birth injury:

1. Primiparity
2. Small maternal stature
3. Maternal pelvic anomalies
4. Prolonged or unusually rapid labor

5. Oligohydramnios
6. Malpresentation of the fetus
7. Use of vacuum extraction
8. Versions and extraction
9. Very low birth weight or extreme prematurity
10. Fetal macrosomia or large fetal head
11. Fetal anomalies
12. Maternal obesity—body mass index >40 kg/m^2

C. Evaluation. A newborn at risk for birth injury should have a thorough examination, including a detailed neurologic evaluation. Newborns who require resuscitation after birth should be evaluated because occult injury may be present. Particular attention should be paid to symmetry of structure and function, cranial nerves, range of motion of individual joints, and integrity of the scalp and skin.

II. TYPES OF BIRTH TRAUMA

A. Head and neck injuries

1. Injuries associated with intrapartum fetal monitoring. Placement of an electrode on the fetal scalp or presenting part for fetal heart monitoring occasionally causes superficial abrasions or lacerations. These injuries require minimal local treatment, if any. Facial or ocular trauma may result from a malpositioned electrode. Abscesses rarely form at the electrode site.

2. Extracranial hemorrhage

a. Caput succedaneum

i. **Caput succedaneum** is a commonly occurring subcutaneous, extraperiosteal fluid collection that is occasionally hemorrhagic. It has poorly defined margins and can extend over the midline and across suture lines. It typically extends over the presenting portion of the scalp and is usually associated with molding.

ii. The lesion usually resolves spontaneously without sequelae over the first several days after birth. It rarely causes significant blood loss or jaundice. There are rare reports of scalp necrosis with scarring.

iii. **Vacuum caput** is a caput succedaneum with margins well demarcated by the vacuum cup.

b. Cephalohematoma

i. A **cephalohematoma** is a subperiosteal collection of blood resulting from rupture of the superficial veins between the skull and periosteum. The lesion is always confined by suture lines. It may occur in as many as 2.5% of all live births. It is more commonly seen in instrumented deliveries.

ii. An extensive cephalohematoma can result in significant hyperbilirubinemia due to red cell breakdown. Hemorrhage is rarely serious enough to necessitate blood transfusion. Infection is also

a rare complication and usually occurs in association with septicemia and meningitis. Skull fractures have been associated in up to 10% of cephalohematomas. Head magnetic resonance imaging (MRI) should be obtained if neurologic symptoms are present. Most cephalohematomas resolve within 8 weeks. Occasionally, they calcify and persist for several months or years.

iii. Management is limited to observation in most cases. Incision and aspiration of a cephalohematoma may introduce infection and is contraindicated in the majority of cases. Anemia or hyperbilirubinemia should be treated as needed.

c. Subgaleal hematoma

i. Subgaleal hematoma is hemorrhage under the aponeurosis of the scalp. It is more often seen after vacuum- or forceps-assisted deliveries.

ii. Because the subgaleal or subaponeurotic space extends from the orbital ridges to the nape of the neck and laterally to the ears, the hemorrhage can spread across the entire calvarium.

iii. The initial presentation typically includes pallor, poor tone, and a fluctuant swelling on the scalp. The hematoma may grow slowly or increase rapidly and result in shock. With progressive spread, the ears may be displaced anteriorly and periorbital swelling can occur. Ecchymosis of the scalp may develop. The blood is resorbed slowly, and swelling gradually resolves. The morbidity may be significant in infants with severe hemorrhage who require intensive care for this lesion. The mortality rate can be up to 14%. Death is attributed to significant volume loss, resulting in hypovolemic shock and coagulopathy.

iv. There is no specific therapy. The infant must be observed closely for signs of hypovolemia, and blood volume should be maintained as needed with transfusions. Phototherapy should be provided for hyperbilirubinemia. An investigation for a bleeding disorder should be considered. Surgical drainage should be considered only for unremitting clinical deterioration. A subgaleal hematoma associated with skin abrasions may become infected; it should be treated with antibiotics and may need drainage.

3. Intracranial hemorrhage (see Chapter 54)

4. Skull fracture

a. Skull fractures may be either linear, usually involving the parietal bone, or depressed, involving the parietal or frontal bones. The latter are often associated with forceps use. Occipital bone fractures are most often associated with breech deliveries.

b. Most infants with linear or depressed skull fractures are asymptomatic unless there is an associated intracranial hemorrhage (e.g., subdural or subarachnoid hemorrhage). Occipital osteodiastasis is a separation of the basal and squamous portions of the occipital bone that often results in cerebellar contusion and significant hemorrhage. It may be a lethal complication in breech deliveries. A linear fracture that is associated with a dural tear may lead to herniation of the meninges and brain, with development of a leptomeningeal cyst.

c. Uncomplicated linear fractures usually require no therapy. The diagnosis is made by a radiograph of the skull. Head MRI should be obtained if intracranial injury is suspected or if neurologic symptoms develop. Depressed skull fractures require neurosurgical evaluation. Some may be elevated using closed techniques. Comminuted or large skull fractures associated with neurologic findings need immediate neurosurgical evaluation. If leakage of cerebrospinal fluid from the nares or ears is noted, antibiotic therapy should be started and neurosurgical consultation obtained. Follow-up imaging should be performed at 8 to 12 weeks to evaluate possible leptomeningeal cyst formation.

5. Facial or mandibular fractures.

a. Facial fractures can be caused by numerous forces including natural passage through the birth canal, forceps use, or delivery of the head in breech presentation.

b. Fractures of the mandible, maxilla, and lacrimal bones warrant immediate attention. They may present as facial asymmetry with ecchymoses, edema, and crepitance or respiratory distress with poor feeding. Untreated fractures can lead to facial deformities with subsequent malocclusion and mastication difficulties. Treatment should begin promptly because maxillar and lacrimal fractures begin to heal within 7 to 10 days, and mandibular fractures start to repair at 10 to 14 days. Treated fractures usually heal without complication.

c. Airway patency should be closely monitored. A plastic surgeon or otorhinolaryngologist should be consulted and appropriate radiographic studies obtained. Head computed tomography (CT) scan or MRI may be necessary to evaluate for retro-orbital or cribriform plate disruption. Antibiotics should be administered for fractures involving the sinuses or middle ear.

6. Nasal injuries

a. Nasal fracture and dislocation may occur during the birth process. The most frequent nasal injury is dislocation of the nasal cartilage, which may result from pressure applied by the maternal symphysis pubis or sacral promontory. The reported prevalence of dislocation is $<1\%$.

b. Infants with significant nasal trauma may develop respiratory distress. Similar to facial fractures, nasal fractures begin to heal in 7 to 10 days and must be treated promptly. Rapid healing usually occurs once treatment is initiated. If treatment is delayed, deformities are common.

c. A misshapen nose may appear dislocated. To differentiate dislocation from a temporary deformation, compress the tip of the nose. With septal dislocation, the nares collapse and the deviated septum is more apparent. With a misshapen nose, no nasal deviation occurs. Nasal edema from repeated suctioning may mimic partial obstruction. Patency can be assessed with a cotton wisp under the nares. Management involves protection of the airway and otorhinolaryngology consultation.

d. If nasal dislocations are left untreated, there is an increased risk of long-term septal deformity.

7. Ocular injuries

a. Retinal and subconjunctival hemorrhages are commonly seen after vaginal delivery. They result from increased venous congestion and pressure during delivery. Malpositioned forceps can result in ocular and periorbital injury including hyphema, vitreous hemorrhage, lacerations, orbital fracture, lacrimal duct or gland injury, and disruption of Descemet membrane of the cornea (which can lead to astigmatism and amblyopia). Significant ocular trauma occurs in <0.5% of all deliveries.

b. Retinal hemorrhages usually resolve within 1 to 5 days. Subconjunctival hemorrhages resorb within 1 to 2 weeks. No long-term complications usually occur. For other ocular injuries, prompt diagnosis and treatment are necessary to ensure a good long-term outcome.

c. Management. Prompt ophthalmologic consultation should be obtained when there is clinical concern for significant ocular or periorbital injury.

8. Ear injuries

a. Ears are susceptible to injury, particularly with forceps application. More significant injuries occur with fetal malposition. Abrasions, hematomas, and lacerations may develop.

b. Abrasions generally heal well with local care. Hematomas of the pinna may lead to the development of a "cauliflower" ear. Lacerations may result in perichondritis. Temporal bone injury can lead to middle and inner ear complications, such as hemotympanum and ossicular disarticulation.

c. Hematomas of the pinna should be drained to prevent clot organization and development of cauliflower ear. If the cartilage and temporal bone are involved, an otolaryngologist should be consulted. Antibiotic therapy may be required.

9. Sternocleidomastoid (SCM) injury

a. SCM injury is also referred to as congenital or muscular torticollis. The etiology is uncertain. The most likely cause is a muscle compartment syndrome resulting from intrauterine positioning. Torticollis can also arise during delivery as the muscle is hyperextended and ruptured, with development of a hematoma and subsequent fibrosis and shortening. Congenital torticollis can be seen in up to 2% of the newborn population.

b. Torticollis may present at birth with a palpable 1- to 2-cm mass in the SCM region and head tilt to the side of the lesion. More often, it is noted at 1 to 4 weeks of age. Facial asymmetry may be present along with hemihypoplasia on the side of the lesion. Prompt treatment may lessen or correct the torticollis.

c. Other conditions may mimic congenital torticollis and should be ruled out. These include cervical vertebral anomalies, hemangioma, lymphangioma, and teratoma.

d. Treatment is initially conservative. Stretching of the involved muscle should begin promptly and be performed several times per day. The earlier the diagnosis and initiation of treatment, the greater the percentage of infants achieving full range of motion. Ninety-eight percent of newborns treated before 1 month of age will achieve normal range of motion within 1.5 months. A tubular orthosis for torticollis (TOT)

collar can be used in infants older than 4 months of age. Surgery is needed if torticollis persists after 6 months of physical therapy.

e. In up to 20% of patients with congenital torticollis, congenital hip dysplasia may be present. A careful hip examination is warranted with further evaluation as indicated.

f. Visual function should also be assessed, including alignment, red reflexes, and fixing/following of light. Weakness of oculomotor muscles can be present.

10. Pharyngeal injury

a. Minor submucosal pharyngeal injuries can occur with postpartum bulb suctioning. More serious injury, such as perforation into the mediastinal or pleural cavity, may result from nasogastric or endotracheal tube placement. Affected infants may have copious secretions and difficulty swallowing, and it may be difficult to advance a nasogastric tube.

b. Mild submucosal injuries typically heal without complication. More extensive trauma requires prompt diagnosis and treatment for complete resolution.

c. The diagnosis of a retropharyngeal tear is made radiographically using water-soluble contrast material. Infants are treated with broad-spectrum antibiotics, and oral feedings are usually withheld for 2 weeks. The contrast study may be repeated to confirm healing before feeding is restarted. Infants with pleural effusions may require chest tube placement. Surgical consultation should be obtained particularly if the leak persists or the perforation is large.

B. Cranial nerve, spinal cord, and peripheral nerve injuries

1. Cranial nerve injuries

a. Facial nerve injury (cranial nerve VII)

i. Injury to the facial nerve is the most common peripheral nerve injury in neonates, occurring in up to 1% of live births. The exact incidence is unknown, as many cases are subtle and resolve readily. The etiology includes compression of the facial nerve by forceps (particularly midforceps), pressure on the nerve secondary to the fetal face lying against the maternal sacral promontory, or, rarely, from pressure of a uterine mass (e.g., fibroid).

ii. Facial nerve injury results in asymmetric crying facies.

a) **Central facial nerve injury** occurs less frequently than peripheral nerve injury. Paralysis is limited to the lower half to two-thirds of the contralateral side, which is smooth with no nasolabial fold present. The corner of the mouth droops. Movement of the forehead and eyelid is unaffected.

b) **Peripheral injury** involves the entire side of face and is consistent with a lower motor neuron injury. The nasolabial fold is flattened, and the mouth droops on the affected side. The infant is unable to wrinkle the forehead and close the eye completely. The tongue is not involved.

c) **Peripheral nerve branch injury** results in paralysis that is limited to only one group of facial muscles: the forehead, eyelid, or mouth.

iii. Differential diagnosis includes Möbius syndrome (nuclear agenesis), intracranial hemorrhage, congenital hypoplasia of the depressor anguli oris muscle, and congenital absence of facial muscles or nerve branches.

iv. The prognosis of acquired facial nerve injury is excellent, with recovery usually complete by 3 weeks. Initial management is directed at prevention of corneal injuries by using artificial tears and protecting the open eye by patching. Electromyography may be helpful to predict recovery or potential residual effects. Full recovery is most likely.

b. Recurrent laryngeal nerve injury

i. Unilateral abductor paralysis may be caused by recurrent laryngeal injury secondary to excessive traction on the fetal head during breech delivery or lateral traction on the head with forceps. The left recurrent laryngeal nerve is involved more often because of its longer course. Bilateral recurrent laryngeal nerve injury can be caused by trauma but is usually due to hypoxia or brainstem hemorrhage.

ii. A neonate with unilateral abductor paralysis is often asymptomatic at rest but has hoarseness and inspiratory stridor with crying. Unilateral injury is occasionally associated with hypoglossal nerve injury and presents with difficulty with feedings and secretions. Bilateral paralysis usually results in stridor, severe respiratory distress, and cyanosis.

iii. Differential diagnosis of symptoms similar to unilateral injury includes congenital laryngeal malformations. Particularly with bilateral paralysis, intrinsic central nervous system (CNS) malformations must be ruled out, including Chiari malformation and hydrocephalus. If there is no history of birth trauma, cardiovascular anomalies and mediastinal masses should be considered.

iv. The diagnosis can be made using direct or flexible fiberoptic laryngoscopy. A modified barium swallow and speech pathology consultation may be helpful to optimize feeding. Unilateral injury usually resolves by 6 weeks of age without intervention and treatment. Bilateral paralysis has a variable prognosis; tracheostomy may be required.

2. Spinal cord injuries

a. Vaginal delivery of an infant with a hyperextended head or neck, breech delivery, and severe shoulder dystocia are risk factors for spinal cord injury. However, significant spinal cord injuries are rare with a prevalence rate of <0.2 per 10,000 live births. Injuries include spinal epidural hematomas, vertebral artery injuries, traumatic cervical hematomyelia, spinal artery occlusion, and transection of the cord.

b. Spinal cord injury presents in four ways:

i. Some infants with severe high cervical or brainstem injury present as stillborn or in poor condition at birth, with respiratory depression, shock, and hypothermia. Death generally occurs within hours of birth.

ii. Infants with an upper or midcervical injury present with central respiratory depression. They have lower extremity paralysis, absent deep tendon reflexes and sensation in the lower half of

the body, urinary retention, and constipation. Bilateral brachial plexus injury may be present.

iii. Injury at the seventh cervical vertebra or lower may be reversible. However, permanent neurologic complications may result, including muscle atrophy, contractures, bony deformities, and constant micturition.

iv. Partial spinal injury or spinal artery occlusions may result in subtle neurologic signs and spasticity.

c. Differential diagnosis includes amyotonia congenita, myelodysplasia associated with spina bifida occulta, spinal cord tumors, and cerebral hypotonia.

d. The prognosis depends on the severity and location of the injury. If a spinal injury is suspected at birth, efforts should focus on resuscitation and prevention of further damage. The head, neck, and spine should be immobilized. Neurology and neurosurgical consultations should be obtained. Careful and repeated examinations are necessary to help predict long-term outcome. Cervical spine radiographs, CT scan, and MRI may be helpful.

3. Cervical nerve root injuries

a. Phrenic nerve injury (C3, C4, or C5)

i. Phrenic nerve damage leading to paralysis of the ipsilateral diaphragm may result from a stretch injury due to lateral hyperextension of the neck at birth. Risk factors include breech and difficult forceps deliveries. Injury to the nerve is thought to occur where it crosses the brachial plexus. Therefore, approximately 75% of patients also have brachial plexus injury. Occasionally, chest tube insertion or surgery injures this nerve.

ii. Respiratory distress and cyanosis are often seen. Some infants present with persistent tachypnea and decreased breath sounds at the lung base. There may be decreased movement of the affected hemithorax. Chest radiographs may show elevation of the affected diaphragm, although this may not be apparent if the infant is on continuous positive airway pressure (CPAP) or mechanical ventilation. If the infant is breathing spontaneously and not on CPAP, increasing atelectasis may develop. The diagnosis is confirmed by ultrasonography or fluoroscopy that shows paradoxical (upward) movement of the diaphragm with inspiration.

iii. Differential diagnosis includes cardiac, pulmonary, and other neurologic causes of respiratory distress. These can usually be evaluated by a careful examination and appropriate imaging. Congenital absence of the nerve is rare.

iv. The initial treatment is supportive. CPAP or mechanical ventilation may be needed, with airway care to avoid atelectasis and pneumonia. Most infants recover in 1 to 2 months without permanent sequelae. Diaphragmatic plication is considered in refractory cases. Phrenic nerve pacing is possible for bilateral paralysis.

b. Brachial plexus injury

i. The incidence of brachial plexus injury is 0.9 per 1,000 live births. The cause is excessive traction on the head, neck, and arm

during birth. Risk factors include maternal diabetes, macrosomia, shoulder dystocia, malpresentation, and instrumented deliveries. Injury usually involves the nerve root, especially where the roots come together to form the nerve trunks of the plexus.

ii. Duchenne-Erb palsy involves the upper trunks (C5, C6, and occasionally C7) and is the most common type of brachial plexus injury, accounting for approximately 90% of cases. Total brachial plexus palsy occurs in some cases and involves all roots from C5 to T1. Klumpke palsy involves C7/C8–T1 and is the least common.

a) **Duchenne-Erb palsy.** The arm is typically adducted and internally rotated at the shoulder. There is extension and pronation at the elbow and flexion of the wrist and fingers in the characteristic "waiter's tip" posture. The deltoid, infraspinatus, biceps, supinator and brachioradialis muscles, and the extensors of the wrist and fingers may be weak or paralyzed. The Moro, biceps, and radial reflexes are absent on the affected side. The grasp reflex is intact. Sensation is variably affected. Diaphragm paralysis occurs in 5% of cases.

b) **Total brachial plexus injury.** Accounts for approximately 10% of all cases. The entire arm is flaccid. All reflexes, including grasp and sensation, are absent. If sympathetic fibers are injured at T1, Horner syndrome may be seen.

c) **Klumpke palsy.** The rarest of the palsies, accounting for <1% of brachial plexus injuries. The lower arm paralysis affects the intrinsic muscles of the hand and the long flexors of the wrist and fingers. The grasp reflex is absent. However, the biceps and radial reflexes are present. There is sensory impairment on the ulnar side of the forearm and hand. Because the first thoracic root is usually injured, its sympathetic fibers are damaged, leading to an ipsilateral Horner syndrome.

iii. **Differential diagnosis** includes a cerebral injury, which usually has other associated CNS symptoms. Injury of the clavicle, upper humerus, and lower cervical spine may mimic a brachial plexus injury.

iv. Radiographs of the shoulder and upper arm should be performed to rule out bony injury. The chest should be examined to detect diaphragm paralysis. Initial treatment is conservative. Physical therapy and passive range of motion exercises prevent contractures. Immobilization of the affected arm is not indicated and should be avoided. Wrist and digit splints may be useful.

v. The prognosis for full recovery varies with the extent of injury. If the nerve roots are intact and not avulsed, the prognosis for full recovery is excellent. If full recovery is not seen by 1 month of age, referral to a program specializing in brachial plexus injury is warranted. Surgery has most commonly been recommended when there is a lack of biceps function at 3 months of age. Current studies report persistent deficits in up to 20% to 30% of affected newborns.

C. Bone injuries

1. **Clavicular fracture** is the most commonly injured bone during delivery. Incidence has been reported between 2.7 and 5.7 per 1,000 live births.

Many clavicular fractures are not identified until after discharge from the hospital.

a. These fractures are seen in vertex presentations with shoulder dystocia or in breech deliveries when the arms are extended. Macrosomia is a risk factor.

b. A greenstick or incomplete fracture may be asymptomatic at birth. The first clinical sign may be a callus at 7 to 10 days of age. Signs of a complete fracture include crepitus, palpable bony irregularity, and spasm of the SCM. The affected arm may have a pseudoparalysis because motion causes pain.

c. Differential diagnosis includes fracture of the humerus or a brachial plexus palsy.

d. A **clavicular fracture** is confirmed by radiograph. If the arm movement is decreased, the cervical spine, brachial plexus, and humerus should be assessed. Therapy should be directed at decreasing pain with analgesics. The infant's sleeve may be pinned to the shirt to limit movement until the callus begins to form. Complete healing is expected.

2. Long bone injuries

a. Humeral fractures have a prevalence of 0.2 per 1,000 live births.

i. Humeral fractures typically occur during a difficult delivery of the arms in the breech presentation and/or of the shoulders in vertex. Direct pressure on the humerus may also result in fracture.

ii. A greenstick fracture may not be noted until the callus forms. The first sign is typically loss of spontaneous arm movement, followed by swelling and pain on passive motion. A complete fracture with displaced fragments presents as an obvious deformity. X-ray confirms the diagnosis.

iii. Differential diagnosis includes clavicular fracture and brachial plexus injury.

iv. The prognosis is excellent with complete healing expected. Pain should be treated with analgesics.

a) A fractured humerus usually requires splinting for up to 2 weeks. Displaced fractures may require closed reduction and casting. Radial nerve injury may be seen.

b) Epiphyseal displacement occurs when the humeral epiphysis separates at the hypertrophied cartilaginous layer of the growth plate. Severe displacement may result in significant compromise of growth. The diagnosis can be confirmed by ultrasonography because the epiphysis is not ossified at birth. Therapy includes immobilization of the limb.

b. Femoral fractures have a prevalence of 0.13 per 1,000 live births.

i. Femoral fractures usually follow a breech delivery. Infants with congenital hypotonia are at increased risk.

ii. Physical examination usually reveals an obvious deformity of the thigh. In some cases, the injury may not be noted for a few days until swelling, decreased movement, or pain with palpation develops. The diagnosis is confirmed by x-ray.

iii. Complete healing without limb shortening is expected.

a) Fractures, even if unilateral, should be treated with splinting and immobilization. In most circumstances, a Pavlik harness is used. A spica cast is less frequently used.

b) Femoral epiphyseal separation may be misinterpreted as developmental dysplasia of the hip because the epiphysis is not ossified at birth. Pain and tenderness with palpation are more likely with epiphyseal separation than dislocation. The diagnosis is confirmed by ultrasonography. Therapy includes limb immobilization for 10 to 14 days and analgesics for pain.

D. Intra-abdominal injuries. Intra-abdominal birth trauma is uncommon.

1. Hepatic injury

a. The liver is the most commonly injured solid organ during birth. Macrosomia, hepatomegaly, and breech presentation are risk factors for hepatic hematoma and/or rupture. The etiology is thought to be direct pressure on the liver.

b. Subcapsular hematomas are generally not symptomatic at birth. Nonspecific signs of blood loss such as poor feeding, pallor, tachypnea, tachycardia, and onset of jaundice develop during the first 1 to 3 days after birth. Serial hematocrits may suggest blood loss. Rupture of the hematoma through the capsule results in discoloration of the abdominal wall and circulatory collapse with shock.

c. Differential diagnosis includes trauma to other intra-abdominal organs.

d. Management includes restoration of blood volume, correction of coagulation disturbances, and surgical consultation for potential laparotomy. Early diagnosis and correction of volume loss increase survival.

2. Splenic injury

a. Risk factors for splenic injury include macrosomia, breech delivery, and splenomegaly (e.g., congenital syphilis, erythroblastosis fetalis).

b. Signs are similar to hepatic rupture. A mass is sometimes palpable in the left upper quadrant, and the stomach bubble may be displaced medially on an abdominal radiograph.

c. Differential diagnosis includes injury to other abdominal organs.

d. Management includes volume replacement and correction of coagulation disorders. Surgical consultation should be obtained. Expectant management with close observation is appropriate if the bleeding has stopped and the patient has stabilized. If laparotomy is necessary, salvage of the spleen is attempted to minimize the risk of sepsis.

3. Adrenal hemorrhage

a. The relatively large size of the adrenal gland at birth may contribute to injury. Risk factors are breech presentation and macrosomia. Ninety percent of adrenal hemorrhages are unilateral; 75% occur on the right.

b. Findings on physical examination depend on the extent of hemorrhage. Classic signs include fever, flank mass, purpura, and pallor. Adrenal insufficiency may present with poor feeding, vomiting, irritability, listlessness, and shock. The diagnosis is made with abdominal ultrasound.

c. Differential diagnosis includes other abdominal trauma. If a flank mass is palpable, neuroblastoma and Wilms tumor should be considered.
d. Treatment includes blood volume replacement. Adrenal insufficiency may require steroid therapy. Extensive bleeding that requires surgical intervention is rare.

E. Soft tissue injuries

1. **Petechiae and ecchymoses** are commonly seen in newborns. The birth history, location of lesions, their early appearance without development of new lesions, and the absence of bleeding from other sites help differentiate petechiae and ecchymoses secondary to birth trauma from those caused by a vasculitis or coagulation disorder. If the etiology is uncertain, studies to rule out coagulopathies and infection should be performed. Most petechiae and ecchymoses resolve within 1 week. If bruising is excessive, jaundice and anemia may develop. Treatment is supportive.
2. **Lacerations and abrasions** may be secondary to scalp electrodes and fetal scalp blood sampling or injury during birth. Deep wounds (e.g., scalpel injuries during cesarean section) may require sutures. Infection is a risk, particularly with scalp lesions and an underlying caput succedaneum or hematoma. Treatment includes cleansing the wound and close observation.
3. **Subcutaneous fat necrosis** is not usually recognized at birth. It usually presents during the first 2 weeks after birth as sharply demarcated, irregularly shaped, firm, nonpitting subcutaneous plaques or nodules on the extremities, face, trunk, or buttocks. The injury may be colorless or have a deep-red or purple discoloration. Calcification may occur. No treatment is necessary. Lesions typically resolve completely over several weeks to months. It is necessary, however, to monitor serum calcium levels in infants with extensive areas of subcutaneous fat necrosis as significant hypercalcemia may develop.

Suggested Readings

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7 The High-Risk Newborn: Anticipation, Evaluation, Management, and Outcome

Wendy Timpson and Alejandra Barrero-Castillero

KEY POINTS

- Providers should be prepared to identify and mitigate maternal, placental, and fetal conditions that pose immediate and long-term risks to newborns.
- Gestational age (GA) is a major driver of neonatal risk; accurate determination is essential to inform postnatal management.
- Both poor (small for gestational age [SGA]) and excessive (large for gestational age [LGA]) fetal growth incur additional risk for complications that should be addressed in the immediate postnatal period.
- Social determinants of health (SDoH) may amplify the risk for abnormal development perpetuating disparities. Identifying and addressing them may improve quality of care and outcomes.
- Placental pathology can inform future obstetrical and neonatal management and is recommended in all cases of high-risk delivery.

I. HIGH-RISK NEWBORNS are often born in the setting of certain maternal, placental, or fetal conditions; their presence should alert nursery staff to monitor and prepare for associated complications. Preserving the placenta is recommended in all cases of high-risk delivery, including those that result in transfer from the birth hospital. Placental evaluation can be helpful to identify challenging diagnoses, such as maternal side vascular phenomena, and pathology of the fetal side including malperfusion, sepsis, and viremia. The following factors are associated with high-risk newborns:

A. Maternal characteristics and associated risk for fetus or neonate

1. Age at delivery

a. Advanced maternal age (AMA) is traditionally defined as older than 35 years, although risks to fetus and mother increase significantly at older than 40 years. Chromosomal and congenital abnormalities, gestational diabetes, hypertension, intrauterine growth restriction (IUGR), stillbirth preterm delivery

b. Adolescence (younger than 18 years). IUGR, low birth weight (LBW), preterm delivery, gastroschisis

2. **Medical conditions**

a. Diabetes mellitus. Stillbirth, congenital anomalies, macrosomia, large for gestational age (LGA), birth trauma, respiratory distress syndrome (RDS), hypoglycemia, functional hypoparathyroidism (transient hypocalcemia, hyperphosphatemia and hypomagnesemia), polycythemia and hyperviscosity syndrome, hyperbilirubinemia, and neonatal mortality. Pregestational diabetes specifically is associated with IUGR secondary to vascular disease and accrues a higher risk for congenital anomalies (see Chapter 2).

b. Thyroid disease. Stillbirth, goiter, atrial septal defect, hypothyroidism, hyperthyroidism, neurodevelopmental disorders including attention deficit hyperactivity disorder and autism spectrum disorder (see Chapter 61)

c. Hypertension (chronic or pregnancy related). Stillbirth, IUGR, preterm birth, perinatal depression, hypoxic-ischemic encephalopathy (HIE), polycythemia, thrombocytopenia, leukopenia

d. Anemia. Stillbirth, IUGR, hydrops, preterm birth, perinatal depression, HIE

e. Isoimmunization (red cell antigens). Stillbirth, hydrops, anemia, jaundice

f. Thrombocytopenia, including alloimmunization (platelet antigens). Stillbirth, bleeding including intracranial hemorrhage (ICH)

g. Trauma (acute, chronic). Stillbirth, preterm birth, placental abruption

h. Tobacco/nicotine use. Congenital anomalies (heart, musculoskeletal, limb reduction, missing or extra digits, clubfoot, craniosynostosis, facial defects, gastrointestinal defects, anal atresia, hernia, undescended testicles), IUGR, LBW, preterm delivery, premature rupture of the membranes (PROM), placental abruption, sudden infant death syndrome (SIDS)

i. Substance abuse disorder (drugs and alcohol use). Structural abnormalities, preterm birth, IUGR, fetal alcohol syndrome, neonatal opioid withdrawal syndrome, SIDS, cognitive and behavioral impairments

j. Maternal (parental) mental health concerns (new onset and prior history exacerbated by neonatal intensive care unit [NICU] admission). NICU admission is a stressful and unexpected experience for parents that increases the risk for parental psychopathology during admission and after discharge (e.g., depression, postpartum depression, anxiety, posttraumatic stress disorder). This has been associated with altered parent–infant bonding (attachment impairment), lower breastfeeding rates, decreased quality of parenting, and adverse effects on the offspring including delayed growth and increased risk of socioemotional and behavioral impairment during childhood and adulthood. Parental mental health issues are often unrecognized and untreated; yet, early diagnosis, treatment, and support improve outcomes for both the affected parent and the child.

3. **Racial and ethnic disparities** confer additional risks, both secondary to increased rate of maternal medical (chronic diseases such as diabetes, obesity, hypertension) and pregnancy-related (e.g., preterm labor)

complications, as well as direct risks to the neonate (preterm birth, LBW, lower breastfeeding rate, higher infant mortality). Although exact mechanisms are unclear, evidence shows that racial and ethnic disparities result not from genetic differences but from societal, environmental, and psychosocial factors that differ by race/ethnicity and place these groups at disproportionally higher risk.

4. **Obstetric history**

a. Previous pregnancy complicated by anomalies, preterm birth, jaundice, RDS, or early-onset sepsis. Risk for recurrence of the same outcome in subsequent pregnancies

b. Short interpregnancy interval (<18 months). Small for gestational age (SGA), preterm delivery

c. Hyperthermia. Mild hyperthermia preimplantation or severe hyperthermia during embryonic and fetal periods of pregnancy increases risk for defects (of the neural tube, palate, skeleton, body wall, teeth, heart), as well as microphthalmia, cataract, microencephaly, neurodevelopmental disorders

d. Intrauterine infection. Postnatal syndrome varies based on specific diagnosis (toxoplasmosis, "other," rubella, cytomegalovirus [CMV], and herpes simplex [TORCH], HIV, Zika virus, bacterial infections), but all are at risk for IUGR (see Chapter 48).

e. Abnormal placentation. Abnormal position of the placenta (previa), vascular growth (accreta, increta, percreta), and vasa previa increase the risk for stillbirth, fetal growth restriction, preterm birth, and maternal and fetal hemorrhage.

f. Prolonged rupture of membranes. Early-onset sepsis, disseminated *Candida* infection

g. Preterm prolonged rupture of the membranes. Pulmonary hypoplasia, early-onset sepsis, disseminated *Candida* infection

B. Paternal characteristics. Age (older than 40 years) is associated with increased risk of stillbirth, preterm birth, LBW, musculoskeletal syndromes, cleft palate, retinoblastoma, and neurodevelopmental disorders including autism spectrum disorder.

C. Fetal characteristics and associated risk for fetus or neonate

1. **Multiple gestation.** Congenital anomalies and early malformations, IUGR, twin–twin transfusion syndrome, preterm birth, perinatal depression, HIE
2. **IUGR.** Stillbirth, chromosomal abnormalities, genetic syndromes, congenital anomalies, inborn errors of metabolism, intrauterine infection, perinatal depression, HIE, hypoglycemia, polycythemia, neonatal mortality (see section V)
3. **LGA and/or macrosomia.** Congenital anomalies, shoulder dystocia, brachial plexus injury, neonatal fractures, hypoglycemia (see section VI)
4. **Malposition/presentation.** Developmental dysplasia of the hip, birth trauma, hemorrhage
5. **Abnormality of fetal heart rate or rhythm.** Congestive heart failure, heart block, hydrops, perinatal depression, HIE

6. **Decreased activity.** Fetal demise, central nervous system (CNS) and neuromuscular disorders, perinatal depression, HIE
7. **Polyhydramnios.** Anencephaly, CNS and neuromuscular disorders, disordered swallowing (e.g., esophageal atresia, micrognathia, oropharyngeal mass), chylothorax, diaphragmatic hernia, omphalocele, gastroschisis, trisomy, tumors, hydrops, isoimmunization, anemia, cardiac failure, intrauterine infection, inability to concentrate urine, LGA, preterm delivery
8. **Oligohydramnios.** Stillbirth, SGA, IUGR, renal anomalies, pulmonary hypoplasia, deformations, nonreassuring fetal testing, neonatal death

D. Conditions of labor and delivery and associated risk for fetus or neonate

1. **Preterm delivery.** See section III.
2. **Postterm delivery.** See section IV.
3. **Maternal fever.** Early-onset sepsis
4. **Maternal hypotension.** Stillbirth, perinatal depression, HIE
5. **Rapid labor.** Birth trauma, ICH, transient tachypnea of the newborn (TTN)
6. **Prolonged labor.** Stillbirth, perinatal depression, HIE, birth trauma
7. **Uterine tetany.** Perinatal depression, HIE
8. **Meconium-stained amniotic fluid.** Perinatal depression, HIE, meconium aspiration syndrome, persistent pulmonary hypertension
9. **Prolapsed cord.** Stillbirth, perinatal depression, HIE
10. **Cesarean section.** RDS, TTN, laceration, abnormal microbiome colonization, hypothermia
11. **Systemic analgesia, anesthesia, or sedation.** Respiratory depression, hypotension, hypotonia

E. Social determinants of health (SDoH) include societal, environmental, psychosocial factors and stressors that perpetuate disparities and increase risk for infants and families. These have been associated with preterm birth, LBW, increased risk for infection, lower breastfeeding rates, poor follow-up, lower cognitive scores, higher rates of readmission, and lower satisfaction with medical care. Identifying risk and addressing adverse environmental and psychosocial stressors early in life (e.g., prenatally and during NICU stay) promotes child equity and may improve outcomes. Adverse environmental and psychosocial stressors include the following:

1. **Challenging caregiver environment and family context.** Living in poverty with unmet needs and financial burdens from housing insecurity, job insecurity, uninsured status, transportation issues (which may be exacerbated by the financial burden of hospitalization, e.g., bills, parking, meals), low maternal education, low literacy, and health literacy level, poor family support and social networks, domestic violence, and marital breakdown. Additional stressors associated with cultural/ethnic family context that may increase vulnerability include

immigration stress, language barriers (limited English proficiency [LEP] families), cultural and health beliefs, and variation in family structure and identity.

2. **Neighborhood environment (noise, pollution, and contaminants).** Neighborhood violence and crime, poor infrastructure and access to services, unhealthy work conditions
3. **Societal environment.** Systemic racism and implicit bias, discrimination, political determinants of health

II. GESTATIONAL AGE (GA) AND BIRTH WEIGHT CLASSIFICATION.

Neonates should be classified by GA, if at all possible, as this generally correlates more closely with outcomes than birth weight. Birth weight becomes significant in setting of abnormal growth (SGA or LGA).

A. GA evaluation

1. Assessment based on **obstetric information** is covered in Chapter 1. Note that GA estimates by first-trimester ultrasonography are accurate within 7 days. Later ultrasounds are accurate within approximately 11 to 14 (second trimester) and 21 days (third trimester).
2. Standardized postnatal examination tools can be useful to **confirm or supplement** obstetric dating. The Dubowitz examination for newborns is slightly more accurate (±2.6 weeks), whereas the Ballard (Fig. 7.1) is less so (±4.2 weeks), although significantly easier to use. There are limitations to this method, especially in the evaluation of the neuromuscular measures in sick newborns.
3. **Infant classification by GA**
   - **a. Preterm** infants are born at <37 completed weeks of gestation (258 days). Subgroups include the following:
     - **i. Extremely preterm** infants are born <28 weeks (195 days).
     - **ii. Early-preterm** infants are born <34 weeks (237 days).
     - **iii. Late-preterm** infants are born between 34 0/7 and 36 6/7 weeks of gestation (238 to 258 days).
   - **b. Term** infants are born between 37 0/7 and 41 6/7 weeks of gestation (259 to 293 days).
     - **i. Early-term** infants are subgroup of term infants born between 37 0/7 and 38 6/7 weeks of gestation (259 to 272 days).
   - **c. Postterm** infants are born after 42 weeks of gestation (294 days or more).
4. **Birth weight classification.** Although not universally agreed on, the commonly accepted definitions are as follows:
   - **a. Normal birth weight (NBW).** From 2,500 to 4,500 g
   - **b. LBW.** <2,500 g

     Note that, although most LBW infants are preterm, some are term but SGA. LBW infants can be further subclassified as follows:
     - **i. Very low birth weight (VLBW).** <1,500 g
     - **ii. Extremely low birth weight (ELBW).** <1,000 g
   - **c. Macrosomia.** Birth weight >4,500 g

MATURATIONAL ASSESSMENT OF GESTATIONAL AGE (New Ballard Score)

NAME _____ SEX _____
HOSPITAL NO. _____ BIRTH WEIGHT _____
RACE _____ LENGTH _____
DATE/TIME OF BIRTH _____ HEAD CIRC. _____
DATE/TIME OF EXAM _____ EXAMINER _____
AGE WHEN EXAMINED _____
APGAR SCORE: 1 MINUTE _____ 5 MINUTES _____ 10 MINUTES _____

NEUROMUSCULAR MATURITY

NEUROMUSCULAR MATURITY SIGN	SCORE							RECORD SCORE HERE
	-1	0	1	2	3	4	5	
POSTURE								
SQUARE WINDOW (Wrist)	>90°	90°	60°	45°	30°	0°		
ARM RECOIL		180°	140°–180°	110°–140°	90°–110°	<90°		
POPLITEAL ANGLE	180°	160°	140°	120°	100°	90°	<90°	
SCARF SIGN								
HEEL TO EAR								
							TOTAL NEUROMUSCULAR MATURITY SCORE	

SCORE
Neuromuscular ____
Physical _____
Total _____

MATURITY RATING

SCORE	WEEKS
-10	20
-5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

PHYSICAL MATURITY

PHYSICAL MATURITY SIGN	SCORE							RECORD SCORE HERE
	-1	0	1	2	3	4	5	
SKIN	sticky friable transparent	gelatinous red translucent	smooth pink visible veins	superficial peeling &/or rash, few veins	cracking pale areas rare veins	parchment deep cracking no vessels	leathery cracked wrinkled	
LANUGO	none	sparse	abundant	thinning	bald areas	mostly bald		
PLANTAR SURFACE	heel-toe 40–50 mm: -1 <40 mm: -2	>50 mm no crease	faint red marks	anterior transverse crease only	creases ant. 2/3	creases over entire sole		
BREAST	imperceptible	barely perceptible	flat areola no bud	stippled areola 1–2 mm bud	raised areola 3–4 mm bud	full areola 5–10 mm bud		
EYE / EAR	lids fused loosely: -1 tightly: -2	lids open pinna flat stays folded	sl. curved pinna; soft; slow recoil	well-curved pinna; soft but ready recoil	formed & firm instant recoil	thick cartilage ear shift		
GENITALS (Male)	scrotum flat, smooth	scrotum empty faint rugae	testes in upper canal rare rugae	testes descending few rugae	testes down good rugae	testes pendulous deep rugae		
GENITALS (Female)	clitoris prominent & labia flat	prominent clitoris & small labia minora	prominent clitoris & enlarging minora	majora & minora equally prominent	majora large minora small	majora cover clitoris & minora		
							TOTAL PHYSICAL MATURITY SCORE	

GESTATIONAL AGE (weeks)
By dates _____
By ultrasound _____
By exam _____

Figure 7.1. New Ballard Score. (Reprinted from Ballard JL, Khoury JC, Wedig K, et al. New Ballard Score, expanded to include extremely premature infants. *J Pediatr* 1991;119[3]: 417–423. Copyright © 1991 Elsevier. With permission.)

III. PRETERM BIRTH.

A preterm neonate is one who is born <37 weeks' gestation. See Chapter 13 for management of the ELBW neonate.

A. Incidence.

Approximately 10% of all births in the United States are preterm. In 2014, the National Center for Health Statistics officially completed the transition to a new method of quantifying GA, shifting from the

previous practice of counting from last menstrual period (LMP) to using best obstetric estimate (OE) of gestation at delivery. The 2014 preterm birth rate was 9.57%, following a steady decline since 2007 (10.44%), the first year for which national OE data are available for this measure. However, in each year since 2014, there has been a steady rise in prematurity rate to 10.02% in 2018. The rate of infants born early preterm (<34 weeks) has been roughly stable since 2014 at 2.75%. The late preterm birth rate (34 to 36 weeks) has however been slowly climbing since 2014, most recently at 7.28% in 2018.

B. Etiology is unknown in most cases. Preterm and/or LBW delivery is associated with the following conditions:

1. **Prior preterm birth** is the single strongest risk factor for subsequent preterm delivery. One preterm birth increases the risk for a subsequent preterm delivery fourfold.
2. **Low socioeconomic status** (SES) measured not only by family income/financial security and educational level but also by geographic area (zip codes and census tracts), perception of social status, and occupational vulnerability
3. **Non-Hispanic black** women are almost 3 times as likely to deliver a VLBW infant (<1,500 g) (2.9%) compared with non-Hispanic white (1%) and Hispanic women (1.2%). In 2018, the rate of preterm delivery for non-Hispanic black women was 14.1%. Although significantly higher than that of non-Hispanic white (9.1%) and Hispanic women (9.7%), the rate has dropped from its peak of 18.3% in 2007. Strong evidence suggests that observed racial disparities in preterm birth and other outcomes contributing to the black–white gap in infant mortality are due to the cumulative effects of racism, leading to socioeconomic disadvantage, environmental, and psychosocial factors.
4. **Tobacco/nicotine** use increases the risk of both maternal complications (placenta previa, placental abruption, PROM) and fetal complications, such as IUGR, that require early delivery.
5. **Women younger than 18 or older than 35 years** are more likely to deliver preterm or LBW infants; the association with age is more significant in whites than in African Americans.
6. **Short interpregnancy interval (<18 months)** increases risk of preterm delivery.
7. **Acute and chronic maternal illness** is associated with early delivery, whether onset of labor is spontaneous or, not infrequently, induced.
8. **Multiple-gestation births** frequently deliver preterm (19.5% of twins and 63.1% of triplets in the United States in 2018).
9. **Obstetric factors** such as uterine malformations, uterine trauma, placenta previa, placental abruption, hypertensive disorders, preterm cervical shortening, previous cervical surgery, premature rupture of membranes, and chorioamnionitis also contribute to preterm birth.

C. Problems associated with preterm birth are related to limited ability of immature organs to function in the extra uterine environment. Risk for all complications is inversely associated with GA.

1. **Respiratory.** Preterm infants may experience the following:
   a. RDS due to surfactant deficiency and pulmonary immaturity (see Chapter 33)
   b. Apnea due to immaturity in respiratory control mechanisms (see Chapter 31)
   c. Eventual development of bronchopulmonary dysplasia (BPD) (see Chapter 34)
2. **Neurologic.** Preterm infants have a higher risk of neurologic problems including the following:
   a. Perinatal depression and HIE (see Chapter 55)
   b. Intraventricular hemorrhage (IVH) and other ICH (see Chapter 54)
   c. Periventricular leukomalacia (see Chapter 54)
3. **Cardiovascular.** Preterm infants may present with cardiovascular problems including the following:
   a. Hypotension
      i. Hypovolemia
      ii. Cardiac dysfunction
   b. Patent ductus arteriosus (PDA) is common and may lead to pulmonary overcirculation and diastolic hypotension (see Chapter 41).
4. **Hematologic.** Conditions for which preterm infants are at higher risk include the following:
   a. Anemia (see Chapter 45)
   b. Hyperbilirubinemia (see Chapter 26)
5. **Fluid and nutrition.** Preterm infants are at increased risk for insensible water losses, hypoglycemia, excessive weight loss, poor weight gain, and muscle wasting due to catabolic demands (see Chapter 21).
6. **Gastrointestinal.** Premature infants are at increased risk for delayed gastric emptying, feeding intolerance, spontaneous intestinal perforation, and necrotizing enterocolitis (NEC) (see Chapter 27).
7. **Metabolic.** Imbalances, especially in glucose and calcium metabolism, are more common in preterm infants (see Chapters 24 and 25).
8. **Renal.** Immature kidneys are characterized by low glomerular filtration rate as well as an inability to process water, solute, and acid loads. This puts them at risk for significant electrolyte disturbances and metabolic acidosis (see Chapters 23 and 28).
9. **Temperature regulation.** Preterm infants are especially susceptible to hypothermia, although iatrogenic hyperthermia can also occur (see Chapter 15).
10. **Immunologic.** Because of deficiencies in both humoral and cellular response, in part due to the missed opportunity for transplacental passage of maternal antibodies, preterm infants are at greater risk for infection than are their term counterparts.

11. Ophthalmologic. Retinopathy of prematurity may develop in the immature retina, especially of infants born <30 weeks or with birth weight <1,500 g (see Chapter 67). Preterm infants are also at risk for myopia in childhood.

D. Management of the preterm infant (see Chapter 13)

1. Immediate postnatal management

a. Delivery in an appropriately equipped and staffed hospital is preferable. Very preterm or sick infants requiring transfer to higher level care experience delays in initiating necessary specialized care resulting in increased risk of short-term and long-term complications.

b. Resuscitation and stabilization require the immediate availability of qualified personnel and equipment. Resuscitation of the newborn at delivery should be in accordance with the American Academy of Pediatrics Neonatal Resuscitation Program (NRP). Anticipation and prevention are always preferred over reaction to problems already present. Provision of adequate respiratory support oxygen and maintenance of proper temperature are immediate postnatal goals (see Chapter 4).

2. Neonatal management

a. Thermal regulation should be directed toward achieving a neutral thermal zone; that is, environmental temperature sufficient to maintain body temperature with minimal oxygen consumption. For the small preterm infant, this will require either an overhead radiant warmer (with the advantages of infant accessibility and rapid temperature response) or a closed incubator (with the advantages of diminished insensible water loss) (see Chapter 15).

b. Oxygen therapy and assisted ventilation (see Chapter 29)

c. Fluid and electrolyte therapy must account for relatively high insensible water loss while avoiding overhydration and maintaining normal glucose and plasma electrolyte concentrations (see Chapter 23).

d. Nutrition may be complicated by the inability of many preterm infants to tolerate enteral feedings, necessitating treatment with parenteral nutrition. Human milk is associated with decreased risks for NEC in infants born <32 weeks' gestation. Providing lactation support to mothers of preterm infants is critical. Early initiation of low-volume enteral feeds is also associated with reduction in NEC risk. Immaturity in feeding skills and coordination of sucking, swallowing, and breathing requires gavage feeding and oral feeding support (see Chapter 21).

e. Hyperbilirubinemia, which is common in preterm infants, can usually be managed effectively by careful monitoring of bilirubin levels and early treatment with phototherapy. In severe cases, exchange transfusion may be necessary to prevent kernicterus (see Chapter 26).

f. Early-onset sepsis increases in frequency with decreasing GA, especially when maternal infection was a precipitant of preterm delivery. All preterm infants should be carefully evaluated for sepsis (physical exam, +/− blood culture, +/− complete blood count [CBC]) with a low threshold for starting broad-spectrum antibiotics (typically ampicillin for listeria coverage and gentamicin for broad gram-positive and gram-negative coverage) until sepsis can be ruled out. Risk for late-onset

sepsis (LOS) has a strong inverse correlation with GA, prompting vigilance in the very preterm infant. When evaluating a preterm infant for LOS, consider antistaphylococcal antibiotics for infants who have a central venous catheter, have undergone multiple procedures, and with prolonged hospitalization, incurring an increased risk for nosocomial infection (see Chapters 48 and 49).

g. PDA is a frequent phenomenon in preterm infants. Spontaneous closure is less frequent in those born <28 weeks and can be hemodynamically significant, putting infants at risk for ductal steal from the systemic circulation and pulmonary overcirculation. Defining hemodynamic significance and deciding between supportive care and intervention is challenging (see Chapter 41).

h. Immunizations. Diphtheria, tetanus toxoids, and acellular pertussis (DTaP) vaccine; inactivated poliovirus vaccine (IPV); multivalent pneumococcal conjugate vaccine (PCV); and *Haemophilus influenzae* type B (Hib) vaccine are given in full doses to preterm infants on the basis of their chronologic age (i.e., weeks after birth). Although the majority of preterm infants develop protective levels of antibodies, overall, they have reduced immune response to vaccines as compared to term infants and therefore develop the best protection if they receive a booster after 12 months. Hepatitis B (HepB) vaccine administration for medically stable preterm infants of hepatitis B surface antigen (HBsAg)-negative mothers may be given on a modified schedule. Respiratory syncytial virus (RSV) (for a subset of particularly high-risk preterm infants) and influenza prophylaxis (for infants older than 6 months) should be given as indicated. Because the rotavirus vaccine is a live oral vaccine, it is often deferred until after NICU discharge. All Centers for Disease Control and Prevention (CDC) and Advisory Committee on Immunization Practices (ACIP) recommendations can be found at http://www.cdc.gov/vaccines (see Chapters 48 and 49).

E. Survival of preterm infants. Although survival statistics vary by institution, geographic region, and country, the decades-old trend of improving survival of the highest risk, very preterm infants, continues. A National Institute of Child Health and Human Development Neonatal Research Network study demonstrated an increase in survival rate for infants born 22 to 24 weeks from 30% in the first epoch (2000 to 2003) to 36% in the last (2008 to 2011), driven mostly by improvements for 24-week infants. Survival of very preterm and VLBW populations varies significantly from 52% to 86% between large international cohort studies published in the last 15 years. Intercenter variation also contributes significantly to differences in outcome. It is therefore critical to use the most up-to-date and localized outcome data available when counselling families regarding outcomes.

F. Long-term sequelae of preterm birth. Preterm infants are vulnerable to a wide spectrum of morbidities. The risk of morbidity and mortality declines steadily with increasing GA.

1. Neurologic disability. Prediction of neurologic disability in the very preterm infant remains elusive; furthermore, there is evidence that some areas of impairment observed at 2- and 3-year follow-up may be

dynamic, whereas others are static and persist. Early intervention has been demonstrated to benefit motor and cognitive outcomes, with the latter extending into preschool age.

a. Cognitive impairment. Executive dysfunction, language disorders, low academic performance

b. Motor impairment. Cerebral palsy (most commonly bilateral spastic), developmental coordination disorder

c. Sensory impairment. Hearing loss, visual impairment, sensory processing issues (auditory, visual, tactile, vestibular, and oral) (see Chapters 67 and 68)

d. Behavioral and mental health disorders. Attention deficit hyperactivity disorder (fourfold increased risk for ELBW infants compared to term counterparts), autism spectrum disorder, generalized anxiety, depression

2. **Retinopathy of prematurity** (see Chapter 67)
3. **Chronic lung disease (CLD)** (see Chapter 34)
4. **Growth failure** (see Chapter 21)
5. **Health care utilization.** Increased rates of pediatric sick visits, emergency room utilization, and readmission to the hospital

IV. POSTTERM INFANTS

A. Definition. Approximately 6% of pregnancies extend beyond 40 weeks of gestation; however, only a fraction of birth occurs beyond 42 weeks and are considered postterm. This number has been declining from 0.46% in 2010 to 0.3% in 2018. This may be due to changes in obstetric practices.

B. Etiology. Although in some cases, postmaturity is the result of inaccurate pregnancy dating, in most, the cause of prolonged pregnancy is unknown. Risk factors for postterm pregnancies include the following:

1. **Maternal SES**
2. **Previous postterm pregnancy**
3. **Obesity**
4. **Male fetus**
5. **Anencephaly.** An intact fetal pituitary–adrenal axis appears to be involved in the initiation of labor.
6. **Placental sulfatase deficiency**

C. Risks associated with postterm pregnancy

1. Oligohydramnios
2. Macrosomia
3. Nonreassuring fetal heart tracing (NRFHT)
4. Meconium-stained amniotic fluid
5. Birth trauma
6. Low Apgar scores
7. Meconium aspiration syndrome

D. Postmaturity syndrome. Constellation of findings complicates 20% to 43% of postterm pregnancies. Postterm infants have begun to lose weight *in utero* but usually have normal length and head circumference. They may be classified as follows with increasing risk for morbidity and mortality with advancing stage:

1. **Stage 1**
   - **a.** Dry, cracked, peeling, loose, and wrinkled skin
   - **b.** Malnourished appearance (loss of subcutaneous fat and muscle mass)
   - **c.** Decreased subcutaneous tissue
2. **Stage 2**
   - **a.** All features of stage 1
   - **b.** NRFHT
   - **c.** Meconium staining of amniotic fluid (MSAF), fetal skin, placental membranes, and umbilical cord
3. **Stage 3**
   - **a.** The findings in stages 1 and 2
   - **b.** Meconium staining of cord and nails due to long-term exposure to MSAF, often transitioned from green/brown to yellow secondary to bile breakdown over time

E. Management. Infants with evidence of postmaturity syndrome should be evaluated for the frequently associated conditions, including the following:

1. Congenital anomalies
2. Perinatal depression
3. Hypoglycemia
4. Hypocalcemia
5. Polycythemia

V. SGA infants or those are affected by IUGR (see Chapter 1)

A. Definition. Although the terms *SGA* and *IUGR* are often used interchangeably, they refer to two subtly different populations. SGA describes a neonate whose birth weight or birth crown-heel length is <10th percentile for GA or <2 standard deviations (SDs) below the mean for the infant's GA (approximately the 3rd percentile for GA). Numerous standardized birth curves have been published based on large infant populations, each with advantages and disadvantages (see Chapter 21). IUGR describes diminished growth velocity in the fetus as documented by at least two intrauterine growth assessments (e.g., a fetus that is "falling off" its own growth curve). Babies who are constitutionally SGA are at overall lower risk compared to those who are IUGR due to some pathologic process. The etiology and management of SGA and IUGR fetuses overlaps considerably.

B. Etiology. Approximately 10% of pregnancies in high-income countries are impacted by IUGR. There is an association between the following factors and SGA/IUGR infants:

1. **Maternal factors** include constitutional (genetically small), demographics (adolescent pregnancy and AMA, race/ethnicity, SES, stress levels,

depression), chronic malnutrition, uterine anomalies, chronic disease, factors interfering with placental flow and oxygenation (cardiovascular disease, renal disease, hypertension), diabetes (primarily type 1), postterm delivery (IUGR more than SGA), exposure to teratogens including medications (e.g., valproic acid, antithrombotic drugs, radiation), tobacco (direct correlation between number of cigarettes consumed and degree of IUGR), and use and abuse of other substances like cocaine and opioids.

2. **Abnormal placentation, reduced uteroplacental perfusion, and associated maternal vascular disease** account for 25–30% of fetal growth restriction. These include obliterative vasculopathy of the placental bed, vascular malformations and preeclampsia, a major contributor to growth restrictions.
3. **Structural placental and umbilical anatomical factors** include bilobed placenta, low-insertion placenta, chorioangioma, velamentous umbilical cord insertion, and presence of a single umbilical artery.
4. **Fetal factors** include chromosomal abnormalities (trisomies 13, 18, and 21 contribute to 5% to 20% cases of early IUGR), genetic syndromes, malformations (e.g., abnormalities of CNS and skeletal system), congenital infection (e.g., rubella, CMV, toxoplasmosis) (see Chapter 48), inborn errors of metabolism, and multiple gestation.

C. Management. If unknown, the etiology of SGA/IUGR should be investigated. Early identification and treatment of SGA/IUGR may decrease risk for complications and long-term adverse outcomes.

1. **Evaluation.** Newborn examination may reveal signs of chromosomal, syndromic, or infectious findings to explain the infant's growth restriction or small size.

   a. Categorization. Growth restriction falls into two categories that distinguish etiology and stratify risk:

   i. **Asymmetric growth restriction** constitutes 70% to 80% of IUGR and results from complications that affect the later part of pregnancy. These infants have a relatively normal head circumference, some reduction in length, and a more profound reduction in weight. This is thought to be due to the redistribution of fetal blood flow preferentially to vital organs, mainly the brain; hence, the term "head-sparing IUGR." The ponderal index ([cube root of birth weight in grams $\times$ 100] / [length in centimeters]) or the weigh-to-length ratio is low (weight for GA disproportionately affected compared to length). These infants may have little subcutaneous tissue, peeling loose skin, a wasted appearance, and meconium staining.

   ii. **Symmetric IUGR** infants are more likely to have significant intrinsic fetal problems (e.g., chromosomal defects, malformations, and/or congenital infections acquired early in pregnancy). Infants have proportionally small head circumference, length, and weight, and their ponderal index may be normal. When compared to infants with "head-sparing" growth restriction, symmetric growth–restricted infants have higher risk for neurodevelopmental impairment.

b. Pathologic examination of the placenta for infarction, congenital infection, or other abnormalities may be helpful.

c. Laboratory evaluation may be helpful for infants without clear cause for IUGR. Given the association between CMV and long-term neurologic sequelae, it is reasonable to obtain CMV testing and consider treatment for infants who are CMV positive with CNS involvement (as evidenced by hearing loss, intracranial, or cerebrospinal findings). Maternal prenatal testing for infection (i.e., rubella, syphilis, HIV) should be reviewed, being mindful of timing (new infections may present after initial maternal testing) in addition to consideration for toxoplasmosis infection (included in many state newborn screening programs).

2. **Nutritional and glycemic support.** SGA infants are at risk for hypoglycemia due to poor fat and glycogen stores and should therefore undergo prefeed glucose surveillance in the hours after birth (see Chapter 24). They often require enhanced caloric density to achieve catch-up growth (see Chapter 21).
3. **Impaired thermoregulation** can result from heat loss secondary to reduced subcutaneous fat stores and limited heat production in setting of nutritional depletion.
4. **Thrombocytopenia, leukopenia/neutropenia.** There is a correlation between placental insufficiency and neonatal bone marrow suppression.
5. **Polycythemia and hyperviscosity syndrome** occur more frequently in IUGR infants than their average for gestational age (AGA) counterparts, possibly secondary to prolonged fetal hypoxia and increased erythropoietin production.
6. **Impaired immune function** may be present in the newborn period and persist through childhood, as evidenced by decreased numbers of T and peripheral B cell lymphocytes.
7. IUGR infants are also at risk for **transient direct hyperbilirubinemia**, often an incidental finding during routine screening for jaundice.

D. Long-term outcomes. Perinatal mortality is increased in both term and preterm growth-restricted infants. Mortality risk increases with degree of restriction, with a sharp increase at the 6th percentile. SGA/IUGR infants and children (especially those with other SDoH risk factors) are at higher risk for poor postnatal growth and neurodevelopmental abnormalities (lower cognitive, motor, and language function) than their AGA counterparts. There is also evidence that these infants are at higher risk for chronic adult disorders, including coronary artery disease, hypertension, and chronic kidney disease.

VI. LGA infants or those affected by fetal **macrosomia** (see Chapter 1)

A. Definition. LGA is generally defined as 2 SDs above the mean for GA or >90th percentile. Macrosomia refers to excessive fetal growth. Although there are specific GA-related thresholds, American College of Obstetricians and Gynecologists (ACOG) guidelines use birth weight >4,500 g, as this threshold accrues significantly higher morbidity.

B. Etiology. A number of factors for excessive fetal growth commonly complicated pregnancy.

1. **Genetic factors.** Constitutionally large size (large parents); genetic disorders associated with early, excessive growth (Beckwith-Wiedemann, Simpson-Golabi-Behmel, Sotos, and Weaver syndromes); and Berardinelli lipodystrophy. There is a growing body of evidence that suggests epigenetic factors may contribute to excessive fetal growth.

C. Maternal factors include racial and ethnic risks (Hispanic mothers are more likely to give birth to macrosomic infants than black mothers). AMA, multiparty, prior LGA pregnancy, and male fetus all incur risk for excessive growth. Metabolic syndrome is the leading causes of LGA/macrosomia, specific risk factors being prepregnancy obesity, excessive maternal weight gain during pregnancy, and diabetes.

D. Neonatal complications. The LGA/macrosomic infant is at increased risk for the following:

1. **Respiratory distress,** primarily due to increased risk for RDS in setting of maternal diabetes, although there is also an increased risk for MAS.
2. **Preterm birth** rate has been observed to be higher in the LGA population compared to their AGA counterparts in some cohort studies.
3. **Hypoglycemia.** In the setting of maternal hyperglycemia, the fetal pancreas produces compensatory insulin. Transient relative hyperinsulinemia persists in the neonate beyond disruption to the continuous placental glucose infusion.
4. **Polycythemia** is more common in both infants of diabetic mothers and euglycemic mothers. The presumed mechanism is via increased erythropoietin production due to oxidative stress induced by hyperglycemia and hyperinsulinemia.
5. **Perinatal depression, low Apgar scores, and HIE**
6. **Birth trauma** including shoulder dystocia
7. **Neonatal mortality** is higher in severely affected LGA infants than their AGA counterparts.

E. Long-term outcomes. There is evidence to suggest that LGA infants are at increased risk for long-term metabolic changes that can lead to the development of obesity and insulin resistance later in life.

Suggested Readings

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8 Assessment of the Newborn History and Physical Examination of the Newborn

Lise C. Johnson

KEY POINTS

- The initial examination of the newborn is an important opportunity to detect congenital anomalies and assess the infant's transition from fetal to extrauterine life.
- Problems uncovered in the initial newborn assessment must be discussed clearly and sensitively with parents, including any plans for further evaluation, monitoring, or treatment.
- All expectant parents dream of having a healthy child and worry about the possibility of abnormality or illness in their infant. Most newborns have normal physical examinations and smooth transitions from fetal to extrauterine life; this is a source of delight and reassurance to families.

I. HISTORY. The family, maternal, pregnancy, perinatal, and social history should be reviewed (Table 8.1).

II. ROUTINE PHYSICAL EXAMINATION OF THE NEONATE. Although no statistics are available, the first routine examination likely reveals more abnormalities than any other physical examination. Whenever possible, the examination should be performed in the presence of the parents to encourage them to ask questions regarding their newborn and allow for the shared observation of physical findings both normal and abnormal.

A. General examination. At the initial examination, attention should be directed to determine (i) whether any congenital anomalies are present; (ii) whether the infant has made a successful transition from fetal to extrauterine life; (iii) to what extent gestation, labor, delivery, analgesics, or anesthetics have affected the neonate; and (iv) whether the infant has any signs of infection or metabolic or other diseases.

1. The infant should be undressed for the examination, ideally in a well-lit room under warming lights to avoid hypothermia, which occurs easily in the neonatal period.

Table 8.1. Important Aspects of Maternal and Perinatal History

Family History	**Inherited diseases** (e.g., metabolic disorders, bleeding disorders, hemoglobinopathies, G6PD deficiency, polycystic kidneys, sensorineural hearing loss, Gilbert syndrome, genetic disorders or syndromes) **Developmental disorders including autism spectrum disorders** **Disorders requiring follow-up screening in family members** (e.g., developmental dysplasia of the hip, vesicoureteral reflux, congenital cardiac anomalies, familial arrhythmias)
Maternal History	**Age** **Gravidity and parity** **Infertility treatments required for pregnancy**, including source of egg and sperm (donor or parent) **Prior pregnancy outcomes** (terminations, spontaneous abortions, fetal demises, neonatal deaths, prematurity, malformations) **Blood type and blood group sensitizations** **Chronic maternal illness** (e.g., diabetes mellitus, hypertension, renal disease, cardiac disease, thyroid disease, systemic lupus erythematosus, myasthenia gravis, seizure disorders) **Maternal mental illness** (anxiety, depression, history of postpartum depression, other mental illness)
Inherited Disorder Carrier Screening	Hemoglobin electrophoresis, thalassemias, cystic fibrosis, fragile X, SMA, expanded carrier screening
Infectious Disease Screening in Pregnancy	Rubella immunity status; syphilis, gonorrhea, chlamydia, HIV, hepatitis C, and hepatitis B surface antigen screening, group B *Streptococcus* (GBS) culture; varicella, cytomegalovirus, and toxoplasmosis testing; tuberculin skin testing (TST) and/or interferon-γ release assay results and any past treatment for tuberculosis; history of herpes simplex infection; history of travel to Zika-endemic areas; any other recent infections or exposures; history of COVID-19 infection
Pregnancy Complications	For example, gestational diabetes mellitus, hypertension, preeclampsia, infections, bleeding, anemia, thrombocytopenia, trauma, surgery, acute illnesses, preterm labor with or without use of tocolytics or glucocorticoids

(continued)

Table 8.1. Table 8.1. Important Aspects of Maternal and Perinatal History *(Continued)*

Fetal Testing	**Genetic testing**, including preimplantation, chorionic villus sampling, amniocentesis **First- and/or second-trimester screens for aneuploidy** (serum markers, nuchal fold measurement, cell-free fetal DNA testing) **Ultrasound** (second trimester fetal survey, ultrasound monitoring of fetal well-being)
Fetal Exposures	**Maternal medications** Tobacco, alcohol, marijuana, and illegal substance use
Intrapartum History	**Gestational age at parturition** and method of calculation (e.g., ultrasound, artificial insemination or *in vitro* fertilization, last menstrual period) **Chief complaint at presentation** **Onset and duration of labor**, including cervical ripening, labor induction, and augmentation **Timing of rupture of membranes and appearance of amniotic fluid** (volume, presence of meconium, blood) **Results of fetal monitoring** **Intrapartum fever** **Intrapartum medications**, especially antibiotics, analgesics, anesthetics, magnesium sulfate, β-blockers, terbutaline **Complications** (e.g., excessive blood loss, chorioamnionitis, shoulder dystocia) **Method of delivery** **Timing of cord clamping** **Placental examination**
Infant Delivery Room Assessment	**Apgar scores** **Any resuscitation measures**
Postnatal Course Prior to Assessment	**Feeding** **Passage of first urine and stool** **Postnatal complications** (e.g., temperature instability, transient tachypnea of the newborn, sepsis evaluation) **Glucose monitoring**

(continued)

Table 8.1. ***(Continued)***

Social History	**Cultural background of family** **Marital status of mother** **Father of baby's involvement** **Household members** **Ages of prior children** **Identified social supports** **Social determinants of health**, including maternal and paternal occupations and planned parental work leaves, stability of housing, food security, adequacy of baby supplies, immigration status concerns, current or past domestic violence **Existing enrollment in social services**, including parent support programs, child protective services involvement

G6PD, glucose-6-phosphate dehydrogenase; SMA, spinal muscular atrophy.

2. Care providers should develop a consistent order to their physical examination, generally beginning with the cardiorespiratory system, which is best assessed when the infant is quiet. If the infant being examined is fussy, a gloved finger to suck on may be offered. The opportunity to perform the eye examination should be seized whenever the infant is noted to be awake and alert.

B. Vital signs and measurements. Vital signs should be taken when the infant is quiet, if possible.

1. **Temperature.** Temperature in the neonate is usually measured in the axilla. Rectal temperature can be measured to confirm an abnormal axillary temperature, although they tend to correlate quite closely. Normal axillary temperature is between 36.5° and 37.4°C (97.7° and 99.3°F).
2. **Heart rate.** Normal heart rate in a newborn is between 95 and 160 bpm. Vagal slowing may be noted and appreciated as a reassuring sign. Some infants, particularly those born postdates, may have resting heart rates as low as 80 bpm. Good acceleration with stimulation should be verified in these infants. A normal blood pressure is reassuring that cardiac output is adequate in the setting of marked sinus bradycardia.
3. **Respiratory rate.** Normal respiratory rate in a newborn is between 30 and 60 breaths per minute. Periodic breathing is common in newborns; short pauses (usually 5 to 10 seconds) are considered normal. Apneic spells (defined as 20 seconds or longer) associated with cyanosis and/or bradycardia are not normal in term infants and deserve further evaluation (see Chapter 31).
4. **Blood pressure.** Blood pressure is not routinely measured in otherwise well newborns. When measurement of blood pressure is clinically indicated, care should be taken that the proper neonatal cuff size is

chosen and the extremity used is documented in the blood pressure recording. A gradient between upper and lower extremity systolic pressure >10 mm Hg should be considered suspicious for coarctation or other anomalies of the aorta (see Chapter 41).

5. **Measurements.** All newborns should have their weight, length, and head circumference measured shortly after birth. These measurements should be plotted on standard growth curves such that the newborn may be determined to be appropriate for gestational age (AGA), small for gestational age (SGA), or large for gestational age (LGA). SGA or LGA newborns may require further evaluation of both the etiology and sequelae of these conditions (see Chapter 7). Newborns with extensive molding and/or caput may require a repeat head circumference measurement a few days after birth.

C. Cardiorespiratory system

1. **Color.** The healthy newborn should have a reddish pink hue underlying the skin's natural pigmentation except for the possible normal cyanosis of the hands and feet (acrocyanosis). Excessive paleness or ruddiness should prompt hematocrit measurement to detect relative anemia (hematocrit <42%) or polycythemia (hematocrit >65%), respectively (see Chapters 45 and 46).

2. **Respiratory pattern.** The majority of the neonatal respiratory examination may be performed visually without the use of a stethoscope. At rest, a newborn past initial transition should exhibit unlabored breathing without grunting (self-generated positive end-expiratory pressure [PEEP]), nasal flaring (decrease in airway resistance), or intercostal retractions (chest wall stabilization). Significant respiratory disease in the absence of tachypnea is rare unless the infant also has severe central nervous system depression. Rales, decreased breath sounds, decreased or displaced heart sounds, or asymmetry of breath sounds are occasionally found by auscultation in an asymptomatic infant and may reveal occult disease that should be confirmed by chest x-ray (e.g., pulmonary edema, neonatal pneumonia, pneumothorax, pneumomediastinum, dextrocardia).

3. **Heart.** The examiner should observe precordial activity; listen to the rate, rhythm, quality, and intensity of heart sounds and the presence or absence of murmurs; and palpate the femoral pulses.
   a. It should be determined whether the heart is on the left or right side of the chest by palpation of the point of maximum impulse (PMI) and auscultation.
   b. Arrhythmias, most often due to premature atrial contractions, are occasionally heard on the routine newborn examination. An electrocardiogram (ECG) with rhythm strip should be obtained to identify the etiology of the arrhythmia and screen for evidence of structural disease.
   c. The heart sounds should be auscultated, with attention paid to the reassuring presence of a split-second heart sound (evidence of the presence of two semilunar valves), detection of any gallops (an ominous finding that deserves further evaluation), and detection of ejection clicks, which may indicate pulmonary or aortic valve stenosis or a bicuspid aortic valve.

d. Murmurs in newborns can be misleading. Systolic murmurs are frequently heard transiently in neonates without significant structural heart disease, particularly as the ductus arteriosus is closing or in those with mild pulmonary branch stenosis. On the other hand, a newborn with serious, hemodynamically significant heart disease may have no murmur. Diastolic murmurs should always be considered abnormal. In an otherwise asymptomatic infant with a persistent or otherwise concerning murmur (e.g., loud, harsh, pansystolic, diastolic), investigation should include an ECG, preductal and postductal oxygen saturation measurement, and four extremity blood pressure measurement. A plain chest x-ray may also be considered. In consultation with a pediatric cardiologist, echocardiogram may also be obtained if available. Where echocardiography is not available, a hyperoxia test should be obtained to determine the presence of cyanotic heart disease and the potential need for institution of prostaglandin E1 (see Chapter 41).

e. Femoral pulses should be palpated, although often, they are weak in the first day or two after birth. Femoral pulses are most easily appreciated if the infant is calm. If there is doubt about the femoral pulses by the time of discharge, the blood pressure in the right upper extremity should be compared to that in either lower extremity to investigate the concern for coarctation of the aorta.

D. Thorax

1. The clavicles should be palpated. Crepitus or, less commonly, a "step off" may be appreciated in the presence of a clavicle fracture. Clavicle palpation should always be repeated on the discharge examination because some fractures may be more apparent on the second or third day of life. On follow-up examinations after hospital discharge, a healed clavicle fracture may leave a firm bump on the bone. No special care beyond gentle handling to avoid pain in the first neonatal days is required for clavicle fractures, which generally heal uneventfully and without sequelae. Undoubtedly, many fractured clavicles in the newborn period occur unnoticed.
2. The thorax should be inspected for shape and symmetry. One or more accessory nipples in the mammary line may be noted occasionally. Tiny periareolar skin tags which generally dry up and fall off in the first days of life may also be noted. Palpable breast buds due to the influence of maternal hormones are a normal finding in term newborns. Parents will sometimes need reassurance that the tip of the xiphoid process, which can be quite prominent in the newborn, is also a normal finding.

E. Abdomen. The abdominal examination of a newborn differs from that of older infants in that observation can again be used to greater advantage.

1. The anterior abdominal organs, particularly bowel, can sometimes be seen through the abdominal wall, especially in thin or premature infants. Diastasis rectus abdominis is frequently seen in neonates, most evident during crying. Asymmetry due to congenital anomalies or masses is often first appreciated by observation.
2. When palpating the abdomen, start with gentle pressure or stroking, moving from lower to upper quadrants to reveal edges of the liver or spleen.

The normal liver edge may extend up to 2.5 cm below the right costal margin. The spleen is usually not palpable. Remember there may be situs inversus.

3. After the abdomen has been gently palpated, deep palpation is possible, not only because of the lack of developed musculature but also because there is little food and air in the intestine. Kidneys may be palpated and abdominal masses may be appreciated, although the clinically meaningful yield of this portion of the examination may be low in the current age of fetal ultrasonography.
4. The umbilical stump should be inspected. The umbilical vein and one or two umbilical arteries should be identified. Discharge, odor, or periumbilical erythema should be noted, if present. Umbilical hernias are frequently seen in neonates and are generally benign and resolve spontaneously.

F. Genitalia and rectum

1. The anus should be checked carefully for patency, position, and size. Occasionally, a large fistula is mistaken for a normal anus; upon closer examination, it may be noted that the fistula is positioned either anterior or posterior to the usual location of a normal anus.
2. Anterior displacement of the anus, which may be associated with constipation, is determined using the **anal position index (API)**.

$$\text{API} = \frac{\text{anus to vaginal fourchette (scrotum) distance}}{\text{coccyx to vaginal fourchette (scrotum) distance}}$$

An API $\leq$0.34 in girls and 0.46 in boys is considered abnormal.

3. **Male**

a. It is normal and usual for the newborn's **foreskin** to be difficult to fully retract. Stretched penile length $<$2.5 cm is abnormal and requires evaluation (see Chapter 63). If present, the degree of hypospadias should be noted as well as the presence and degree of chordee. Circumcision should be deferred to a urologist whenever hypospadias is identified. Other common variants that also merit deferral of circumcision include penoscrotal webbing and 90 degree or greater torsion of the median raphe.

b. The **scrotum** is sometimes quite large because it is an embryonic analog of the female labia and responds to maternal hormones. Hyperpigmentation of the scrotum should raise suspicion for one of the adrenogenital syndromes (see Chapter 63). The scrotum may also be enlarged due to the presence of a **hydrocele**, which can be identified as a transilluminating mass in either or both sides of the scrotum. Hydroceles are collections of peritoneal fluid in the scrotum due to patency of the processus vaginalis in fetal life. They are common and require no immediate action, although they should be monitored to ensure resolution in the first year of life. The **testes** should be palpated. The testes should be the same size, and they should not appear blue (a sign of torsion) through the scrotal skin. Normal testicle size in a term newborn ranges from 1.6 (length) $\times$ 1.0 cm (width) up to 2.9 $\times$ 1.8 cm. Approximately 2% to 5% of term males will have an undescended testicle at birth, which should be followed for descent in the first months of life.

4. **Female**

   a. The **labia minora** and **labia majora** should be examined. The relative size of the labia majora and labia minora changes over the last weeks of gestation with labia minora receding in prominence as the fetus progresses to term. The labia majora of term newborn girls are frequently reddened and swollen due to the influence of maternal hormones, which are also responsible for a clear or white vaginal discharge in the first days of life. Occasionally, a small amount of blood (pseudomenses) accompanies the discharge after the first few days of life as maternal hormones in the neonate wane.

   b. The **vaginal introitus** should be examined and the hymen identified. The finding of an imperforate hymen, which can sometimes be difficult to distinguish from a paraurethral cyst, should prompt referral to a pediatric gynecologist for management. Hymeneal tags are commonly noted, and their presence is of no clinical significance.

   c. The **clitoris**, which recedes in prominence with increasing gestational age, should be noted. Mean clitoral length in term infants is 4.0 mm. Clitoral enlargement (>1 cm in length or 0.5 cm in width) particularly when there is accompanying hyperpigmentation should raise suspicion for androgen excess (see Chapter 63).

G. Skin. There are numerous, mostly benign, skin findings commonly seen in newborns (see Chapter 65).

1. **Dryness**, sometimes accompanied by cracking or peeling of the skin, is common, especially in the postmature newborn.
2. **Milia**, which are inclusion cysts filled with keratinous debris, are tiny, discrete, often solitary, white papules commonly seen on the face and scalp. Milia resolve spontaneously in the first weeks to months of life.
3. **Sebaceous hyperplasia** appears as tiny yellowish white follicular papules most commonly clustered on the nose. These papules self-resolve in the first weeks of life.
4. **Erythema toxicum neonatorum** occurs in approximately half of full-term newborns. Classically, the lesions of erythema toxicum are yellowish papules on an erythematous base, prompting the name "flea bite" dermatitis. Presentations may range from a few scattered isolated lesions to extensive, sometimes confluent, areas of pustules or papules with surrounding erythema. When unroofed and scraped, the contents of the papules and pustules will contain eosinophils on Wright or Giemsa stain. Erythema toxicum most typically appears on the second or third day of life, waxes and wanes for a few days, and resolves within the first week of life.
5. **Nevus simplex or salmon patch** refers to a frequently seen capillary malformation located on the forehead (typically V shaped), nape of the neck, eyelids, nose, or upper lip. Although most salmon patches on the face ("angel kisses") resolve in the first year or so, those on the nape of the neck ("stork bites") will sometimes persist.
6. **Transient pustular melanosis neonatorum (TPMN)**, most common in darker pigmented infants, consists of 2- to 10-mm fragile,

neutrophil-containing pustules that spontaneously break, leaving a collarette of scales and underlying hyperpigmented macules, which fade over weeks to months. Frequently, infants at birth will be found to have the hyperpigmented macules of TPMN with the pustular phase having presumably occurred *in utero*. TPMN may sometimes need to be distinguished from bacterial (usually staph) pustules, which are generally larger than TPMN, yield positive cultures, and are not associated with the typical hyperpigmented macules.

7. **Dermal melanocytosis**, commonly seen in darker skinned and Asian individuals, consists of dermal collections of melanocytes that appear as varying size macules or patches of black, gray, or slate blue skin, most often on the buttocks, although many other locations are also possible. It is prudent to make note of dermal melanocytosis on the newborn examination so that there is no confusion in the future with traumatic bruises.
8. **Sucking blisters** are occasionally on the hand or forearm of a newborn at birth. They resolve without incident and should not be a cause for concern.
9. The presence of **jaundice** on examination in the first 24 hours of life is not normal and should prompt further evaluation. Some degree of jaundice after the first day of life is common (see Chapter 26).

H. Lymph nodes. Palpable **lymph nodes** are found in approximately one-third of normal neonates. They are usually <12 mm in diameter and are often found in the inguinal, cervical, and, occasionally, the axillary area. Excess lymphadenopathy should prompt further evaluation.

I. Extremities, joints, and spine (see Chapter 58)

1. **Extremities.** Anomalies of the digits such as polydactyly (especially postaxial polydactyly, which is sometimes familial), clinodactyly, or some degree of webbing or syndactyly are seen relatively frequently. Palmar creases should be examined. Approximately 4% of individuals have a single palmar crease on one hand. Bilateral single palmar creases are less common but need not prompt concern unless associated with other dysmorphic features. Because of fetal positioning, many newborns have forefoot adduction, tibial bowing, or even tibial torsion. Forefoot adduction, also known as metatarsus adductus, will often correct itself within weeks and may be followed expectantly with stretching exercises. Mild degrees of tibial bowing or torsion are also normal. Talipes equinovarus, or clubfoot, always requires orthopedic intervention, which should be sought as soon as possible after birth (see Chapter 58).
2. **Joints.** All newborns should be examined for the presence of developmental dysplasia of the hips. Hip "clunks" can be sought by both the Barlow maneuver, which causes posterior dislocation of an unstable hip, and the Ortolani maneuver, which causes reduction of the dislocation. Hip "clicks," due to movement of the ligamentum teres in the acetabulum, are much more common than hip "clunks" and not a cause for concern.
3. **Spine.** The infant should be turned over and suspended face down with the examiner's hand supporting the chest. The back, especially the

lower lumbar and sacral areas, should be examined. Special care should be taken to look for pilonidal sinus tracts, skin findings, or small soft midline swellings that might indicate a small meningocele or other anomaly (see Chapter 57). Simple, blind-ending midline sacral dimples, a common finding, need no further evaluation unless they meet high-risk criteria for spinal dysraphism including being deep, >0.5 cm, are located >2.5 cm from the anal verge, or are associated with other cutaneous markers.

J. Head and neck

1. Head

a. Scalp. The scalp should be inspected for cuts, abrasions, or bruises from the birth process. Particular note should be made of puncture wounds from the application of fetal monitor leads because these may occasionally become infected and require further attention. Rarely, cutis aplasia congenita or a nevus sebaceous may also be identified.

b. Swelling. Swelling should be noted and identified, distinguishing between **caput succedaneum**, **cephalohematomas**, and **subgaleal hemorrhage**. Caput succedaneum, often boggy in texture, is simply soft tissue swelling from the birth process. Caput is most commonly located occipitally, although it may also have a "sausage" shape in the parietal area, may cross suture lines, and most often resolves within a day or two. Cephalohematomas, more common in the setting of an instrumented vaginal birth and most often involving one of the parietal bones, are the result of subperiosteal bleeding and, thus, do not cross suture lines. Cephalohematomas may initially be obscured by overlying caput and become increasingly apparent over the first 3 to 4 days of life. They are typically more tense to palpation than caput and may take weeks to even months to fully resolve. Cephalohematomas are a source of excess bilirubin, which may contribute to neonatal jaundice. Subgaleal hemorrhages, also associated with vacuum extractions but much rarer in incidence, result from bleeding underneath the aponeurosis of the occipitofrontalis muscle and, classically, result in very loose, soft swelling, which may flow freely from the nape of the neck to the forehead. It may even be possible to generate a fluid wave across the swelling from a subgaleal hemorrhage. If a subgaleal hemorrhage is suspected, the newborn should be carefully monitored for possible hemodynamically significant bleeding within the hemorrhage.

c. Skull bones. The skull bones (occipital, parietal, and frontal) and suture lines (sagittal, coronal, lambdoidal, and metopic) should be palpated. Mobility of the sutures will rule out craniosynostosis. Mobility can be appreciated by placing one's thumbs on opposite sides of the suture and then pushing in alternately while feeling for motion. Any molding of the skull bones, which resolves over the first days of life, should be noted. The skull should also be observed for deformational plagiocephaly, and when present, positioning instructions to aid in its resolution should be given. Occasionally, craniotabes may be found, with palpation of the skull bones (usually the parietal bones) resulting in an indenting similar to the effect of pressing on a ping pong ball. Craniotabes generally resolves in a matter of weeks with no further evaluation necessary if an isolated finding.

d. Fontanelles. The fontanelles should be palpated. As long as the head circumference is normal and there is motion of the suture lines, one need pay little attention to the size (large or small) of the fontanelles. Very large fontanelles reflect a delay in bone ossification and may be associated with hypothyroidism (see Chapter 61), trisomy syndromes, intrauterine malnutrition, hypophosphatasia, and osteogenesis imperfecta. Fontanelles should be soft, particularly when the infant is in an upright or sitting position. Tense or full fontanelles should raise concern for elevated intracranial pressure due to such causes as meningitis or acute intracranial bleeding.

2. **Eyes.** The eyes should be examined for the presence of scleral hemorrhages, icterus, conjunctival exudate, extraocular muscle movement, and pupillary size, equality, reactivity, and centering. The red reflex should be assessed, and cataracts ruled out. Of note, cataracts may cause photophobia resulting in difficulty obtaining cooperation from the infant in maintaining his or her eyes open for the examination. Puffy eyelids sometimes make examination of the eyes impossible. If so, this fact should be noted so that the eyes will be examined on follow-up.
3. **Ears.** Note the size, shape, position, and presence of auditory canals as well as preauricular pits or skin tags.
4. **Nose.** The nose should be inspected, noting any deformation from *in utero* position, patency of the nares, or evidence of septal injury.
5. **Mouth.** The mouth should be inspected for palatal clefts. **Epstein pearls** (small white inclusion cysts clustered about the midline at the juncture of the hard and soft palate) are a frequent and normal finding. Much less common findings include mucoceles of the oral mucosa, a sublingual ranula, alveolar cysts, and natal teeth. The lingual frenulum should also be inspected and any degree of ankyloglossia noted.
6. **Neck.** Because newborns have such short necks, the chin should be lifted to expose the neck for a thorough assessment. The neck should be checked for torticollis, goiter, and thyroglossal and branchial arch sinus tracts.

K. Neurologic examination. In approaching the neurologic examination of the neonate, the examiner must be at once humble and ambitious. On the one hand, severe neurologic anomalies may be inapparent on examination in the newborn. Also, good evidence of the prognostic significance of the neonatal neurologic examination is lacking. On the other hand, with a trained eye, a broad range of clinically relevant observations can be made of the newborn's neurologic system. Categorizing neurobehavioral observations into four systems—autonomic, motor, state, and responsiveness—allows the clinician to capture nuances of a newborn's competence or vulnerability, regulation or dysregulation, maturity or immaturity, as well as identify evidence of neurologic injury or impairment, if present.

1. Examination of the neonatal **autonomic system** includes evaluation of vital sign stability, neurocutaneous stability (even, appropriate color

for ethnicity vs. mottling or cyanosis), gastrointestinal stability, and the presence or absence of jitteriness or myoclonic jerks. Marked jitteriness should be investigated for etiologies including hypoglycemia, hypocalcemia, hypomagnesemia, or withdrawal from *in utero* exposure to drugs including opiates, cocaine, tobacco, or selective serotonin reuptake inhibitors (SSRIs) (see Chapter 12). Sneezes, hiccups, and frequent yawns may also be considered subtle expressions of autonomic stress in the neonate and are very commonly seen in normal term infants. Of note, many of the items on the Finnegan Neonatal Abstinence Score are signs and symptoms of autonomic dysregulation.

2. Assessment of the **motor system** begins with noting extremity and axial tone, particularly looking for asymmetries, such as those seen in brachial plexus injuries. An asymmetric grimace during crying may indicate injury to the seventh cranial nerve (especially if accompanied by incomplete ipsilateral eyelid closure) or congenital absence or hypoplasia of the depressor angularis oris muscle, a condition that becomes less noticeable over time. Self-regulatory motor activities, such as hand-to-mouth efforts, tucking, bracing, or grasping, or dysregulatory motor activities, such as arching, flailing, or hand splaying, should also be noted. The motor portion of the neurologic examination is completed by elicitation of the primitive reflexes, including palmar and plantar grasp, Babinski, Moro response, root, suck, Galant, tonic neck reflex, and stepping, and observation of the quality and quantity of the infant's motor activity.
3. The six behavioral states of the newborn are deep sleep, light sleep, drowsiness, quiet alertness, active alertness (or fussing), and crying. Aspects of the **state system** that can be observed include the clarity of the infant's states, the range of states displayed, the way in which the newborn moves between states, the ability to protect sleep from outside stimulation, and the quality of crying and ability to be consoled.
4. Finally, the newborn's **responsiveness** to the outside world can be observed. The ability to engage socially may be noted, including the ability to fix on and follow a face and voice. Response to inanimate stimuli such as the ability to fix on and follow a small, high-contrast object (such as a bright red ball) or respond to a sound such as a bell or rattle can also be observed.

L. Summary. All expectant parents hope for a healthy child and worry about the possibility of abnormality or illness in their infant. Whether the newborn examination is performed with the parents or alone in the nursery, the care provider should summarize the findings of the initial assessment for the parents. Most newborns have normal physical examinations and smooth transitions from fetal to extrauterine life; although perhaps mundane knowledge for care providers, this is a source of delight and reassurance to the family. When problems or abnormalities are uncovered in the initial newborn assessment, it is of critical importance that they are discussed clearly and sensitively with parents, including any plans for further evaluation, monitoring, or treatment.

Suggested Readings

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9 Care of the Well Newborn

Heena K. Lee and Elizabeth Oh

KEY POINTS

- Family-centered maternity care helps promote the initiation of breastfeeding and early bonding.
- Routine care of the well newborn includes important screening and prevention measures.
- The hospital stay of the mother and newborn allows identification of early problems, ensures that the mother is prepared to care for the infant at home, and reduces the risk of readmission.
- The birth of an infant is an exciting time for families, and the care of the well newborn is an opportunity to set the tone for a healthy lifestyle. The role of the pediatric provider is to encourage family-centered care, educate the family on best practices and routine screenings, and identify early problems.

I. ADMISSION TO THE NEWBORN NURSERY

A. Healthy newborns may room in with their mothers all or nearly all the time while they remain in the hospital. Every effort should be made to avoid separation of mother and infant especially during the first hour of life (the "golden hour") in order to promote immediate initiation of breastfeeding and early bonding through skin-to-skin contact. Delaying birth weight measurements is acceptable to allow the opportunity to breastfeed. These recommendations follow the global Baby-Friendly Hospital Initiative of the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) to strengthen maternity practices and improve exclusive breastfeeding. Family-centered maternity care, in which the nurse cares for the mother and baby together in the mother's room (couplet care), facilitates teaching and helps support this Baby-Friendly Hospital Initiative. Criteria for admission to the normal newborn nursery or couplet care with the mother vary among hospitals. The minimum requirement typically is a well-appearing infant of at least 35 weeks' gestational age, although some nurseries may specify a minimum birth weight, for example, 2 kg.

B. Security in the nursery and mother's room is necessary to protect the safety of families and to prevent the abduction of newborns.

1. Many nurseries use electronic security systems to track newborns.
2. Identification (ID) bands with matching identifiers are placed on the newborn, mother, and father/partner/support person as soon after birth as possible. Transport of infants between areas should not occur until ID banding has been confirmed.
3. All staff are required to wear a picture ID badge, and parents should be instructed to allow the infant to be taken only by someone wearing an appropriate ID badge.

II. TRANSITIONAL CARE

A. The transitional period is usually defined as the first 4 to 6 hours after birth. During this period, the infant's pulmonary vascular resistance decreases, blood flow to the lungs is greatly increased, overall oxygenation and perfusion improve, and the ductus arteriosus begins to constrict or close.

B. Interruption of normal transitioning, usually due to complications occurring in the peripartum period, will cause signs of distress in the newborn.

C. Common signs of disordered transitioning are the following:

1. Respiratory distress +/− cyanosis
2. Poor perfusion

D. Transitional care of the well-appearing newborn can take place in the mother's room or in the nursery.

1. Infants are evaluated for problems that may require a higher level of care, such as gross malformations and disorders of transition.
2. The infant should be evaluated every 30 minutes for the first 2 hours and then per nursery protocol for the remainder of the transition period. This evaluation includes the assessment of heart rate, respiratory rate, and temperature; assessment of color and tone; and observation for signs of withdrawal from maternal medications.
3. When disordered transitioning is suspected, a hemodynamically stable infant can be observed closely in the normal nursery setting for a brief period of time. Infants with persistent signs of disordered transitioning require transfer to a higher level of care.

III. ROUTINE CARE

A. Rooming-in should be encouraged during the infant's hospital stay. When possible, physical assessments, administration of medications, routine laboratory tests, and bathing should occur in the mother's room. For family-centered maternity care, nursing ratios should not exceed 1:4 mother–baby couplets.

1. Upon admission to the nursery, the infant's weight, head circumference, and length are recorded. On the basis of these measurements, the infant is classified as average for gestational age (AGA), small for gestational age (SGA), or large for gestational age (LGA) (see Chapter 7).

2. If the gestational age of the infant is uncertain, an assessment of gestational age can be performed using the expanded Ballard score (see Chapter 7).

B. The infant's temperature is stabilized with one of the following modalities:

1. Skin-to-skin contact with the mother
2. Open radiant warmer on servo control

C. Universal precautions should be used with all patient contact. In 2019, the global pandemic raised questions regarding the care of newborns born to mothers with suspected or confirmed COVID-19 infection. The American Academy of Pediatrics (AAP), Centers for Disease Control and Prevention, and the WHO have made recommendations on the care of these infants, which are outlined in Chapter 48.

D. The WHO recommends delaying the first bath until after 24 hours of age in order to prevent hypothermia and hypoglycemia, promote bonding and breastfeeding, and allow the infant to benefit from the antidrying and antibacterial properties of the vernix. After 24 hours, if the infant has demonstrated a stable axillary temperature >97.5°F (36.4°C), the first bath can be given with warm tap water and nonmedicated soap.

E. There are several acceptable practices for umbilical cord care. Dry cord care is generally sufficient and has not been shown to increase infection rates in high-income countries. However, antiseptics, such as alcohol, triple dye, or topical antibiotics can be considered if there is concern for infection (see Chapter 49 for treatment of omphalitis). Keeping the cord dry also promotes earlier detachment of the umbilical stump.

IV. ROUTINE MEDICATIONS

A. All newborns should receive prophylaxis against gonococcal ophthalmia neonatorum within 1 to 2 hours of birth, regardless of the mode of delivery. Prophylaxis is administered as a single ribbon of 0.5% erythromycin ointment bilaterally in the conjunctival sac (see Chapter 49). Although 1% tetracycline ointment is equally effective, it is not available in the United States.

B. A single, intramuscular dose of 0.5 to 1 mg of vitamin K (phytonadione) should be given to all newborns before 6 hours of age to prevent vitamin K deficiency bleeding (VKDB). The higher dose is generally indicated for newborns whose birth weight is ≥1,500 g, and the lower dose for those with birth weight <1,500 g. Currently available oral vitamin K preparations are not recommended because late VKDB (which occurs at 2 to 12 weeks of age) is best prevented by the administration of parenteral vitamin K (see Chapter 43).

C. Administration of the first dose of preservative-free, single-antigen hepatitis B vaccine is recommended within the first 24 hours for all medically stable infants with a birth weight of ≥2,000 g, even if the mother's hepatitis B surface antigen (HBsAg) test is negative (see Chapter 48). For infants whose birth weight is <2,000 g, the hepatitis B vaccine should be given at 1 month of age or at hospital discharge, whichever is first.

1. Hepatitis B vaccine is administered by 12 hours of age when the maternal HBsAg is positive or unknown. Infants of HBsAg-positive mothers also require hepatitis B immune globulin (see Chapter 48).

2. The vaccine is given after parental consent as a single intramuscular injection of 0.5 mL of either Recombivax HB (5 μg) (Merck & Co, Inc, Whitehouse Station, New Jersey) or Engerix-B (10 μg) (GlaxoSmithKline Biologicals, Rixensart, Belgium).
3. Parents must be given a vaccine information statement (VIS) at the time the vaccine is administered. Updated VIS, in English and in other languages, is available at http://www.cdc.gov/vaccines/hcp/vis.

V. SCREENING

A. Prenatal screening test results should be reviewed and documented on the infant's chart at the time of delivery. Maternal prenatal screening tests typically include the following:

1. Blood type, Rh, antibody screen
2. Hemoglobin or hematocrit
3. Rubella antibody
4. HBsAg
5. Serologic test for syphilis
6. Group B *Streptococcus* (GBS) culture
7. Human immunodeficiency virus (HIV)
8. Gonorrhea and *Chlamydia* cultures
9. Glucose tolerance test
10. Antenatal testing and ultrasonography results

B. Screening for neonatal sepsis risk

1. All mothers with a positive GBS culture should receive intrapartum antibiotics.
   a. Intravenous penicillin is the preferred intrapartum chemotherapeutic agent.
   b. Alternative intrapartum antibiotics include ampicillin, cefazolin (for penicillin-allergic women without history of anaphylaxis), clindamycin (for penicillin-allergic women with history of anaphylaxis), or vancomycin (for penicillin-allergic women with history of anaphylaxis colonized with GBS that is clindamycin resistant). Administration of antibiotics ≥4 hours before delivery provides adequate neonatal prophylaxis.
2. All newborns should be screened for the risk of perinatally acquired GBS disease (see Chapter 49). Risk factors for early-onset neonatal sepsis include maternal GBS colonization in the genitourinary or gastrointestinal tract, early gestational age, inadequate GBS prophylaxis, maternal intrapartum temperature ≥100.4°F (38°C), rupture of membranes >18 hours, and signs of chorioamnionitis.
3. The neonatal early-onset sepsis (EOS) calculator can be a useful tool to assess the probability of sepsis based on maternal risk factors and the infant's clinical presentation. The EOS calculator, recommendations, and references can be found at https://neonatalsepsiscalculator.kaiserpermanente.org.
4. The latest CDC guideline from 2019 can be found at http://www.cdc.gov/groupbstrep/guidelines.

C. Cord blood screening

1. Cord blood may be saved for up to 30 days, depending on blood bank policy.
2. A blood type and direct Coombs test (also known as direct antiglobulin test or DAT) should be performed on any infant born to a mother who is Rh negative, has a positive antibody screen, or who has had a previous infant with Coombs-positive hemolytic anemia.
3. A blood type and DAT should be obtained on any infant if jaundice is noted within the first 24 hours of age or there is unexplained hyperbilirubinemia (see Chapter 26).

D. Glucose screening

1. Infants should be fed early and frequently to prevent hypoglycemia.
2. Infants of diabetic mothers (see Chapter 2), infants who are SGA or LGA, and preterm infants should be screened for hypoglycemia in the immediate neonatal period (see Chapter 24).

E. Newborn metabolic screening

1. The AAP, March of Dimes, and American College of Medical Genetics recommend universal newborn screening for specific disorders for which there are demonstrated benefits of early detection and efficacious treatment of the condition being tested (see Chapter 60).
2. In the United States, newborn screening programs are operated at the state level in all 50 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands.
3. The U.S. Secretary of Health and Human Services has established the Recommended Uniform Screening Panel (RUSP), which lists the disorders that these state-based screening programs should universally include. Currently, the RUSP contains 35 core conditions and 26 secondary conditions, such as congenital hypothyroidism, phenylketonuria, galactosemia, hemoglobinopathies, cystic fibrosis, as well as amino acid, fatty acid, and organic acid disorders. An updated list of screened conditions in each state can be found at https://www.hrsa.gov/advisory-committees/heritable-disorders/.
4. Routine collection of the specimen is between 24 and 48 hours of life.
5. If an infant has an abnormal screening result, an action (ACT) sheet with an accompanying algorithm is available for each condition and provides information to clinicians about next steps to determine the final diagnosis: https://www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx

F. Bilirubin screening

1. Before discharge, all newborns should be screened for the risk of subsequent development of significant hyperbilirubinemia. A predischarge serum or transcutaneous bilirubin measurement combined with risk factor assessment best predicts subsequent hyperbilirubinemia requiring treatment. A total and direct serum bilirubin measurement can be obtained at the time of the newborn metabolic screen.

2. Risk factors for developing significant hyperbilirubinemia include hemolytic disease, prematurity, glucose-6-phosphate dehydrogenase (G6PD) deficiency, certain ethnicities (e.g., East Asian and Mediterranean), presence of cephalohematoma or significant bruising, exclusive breastfeeding with weight loss, and a sibling history of phototherapy treatment.
3. Jaundice during the first 24 hours of life is considered pathologic and warrants a total and direct serum bilirubin level.
4. The bilirubin result should be plotted and interpreted on an hour-specific nomogram to determine the need for phototherapy (see Chapter 26).
5. A direct bilirubin >1.0 if total serum bilirubin is <5.0 mg/dL, or >20% of total serum bilirubin if it is >5.0 mg/dL, is considered elevated, and the infant should be evaluated for cholestasis.
6. Parents should be given verbal and written information about newborn jaundice.

G. Hearing screening

1. Routine screening for hearing loss in newborns is mandated in most states (see Chapter 68) as outlined by the AAP and the Joint Committee on Infant Hearing.
2. Verbal and written documentation of the hearing screen results should be provided to the parents with referral information when needed.
3. Infants in the newborn nursery should also be assessed for risk factors for early childhood hearing loss which would warrant further audiology diagnostic evaluation regardless of hearing screen results. These risk factors include *in utero* infections (e.g., cytomegalovirus [CMV], herpes, rubella, syphilis, toxoplasmosis), trisomy 21, cleft lip/palate, craniofacial anomalies, syndromes associated with hearing loss, family history of permanent childhood hearing loss, and parental or clinician concern.

H. Critical congenital heart disease screening

1. In 2011, the U.S. Secretary of Health and Human Services recommended that screening for critical congenital heart disease (CCHD) using pulse oximetry be added to the uniform newborn screening panel. This has been endorsed by the AAP, the American Heart Association, and the American College of Cardiology Foundation (see Chapter 41).
2. CCHDs are congenital heart defects requiring surgery or catheter intervention within the first year of life. In combination with a physical examination, pulse oximetry has been demonstrated to increase the ability to identify certain CCHDs in newborns prior to discharge from the hospital and, in some newborns, before audible murmurs or other symptoms appear.
3. Pulse oximetry screening (of preductal and postductal oxygen saturations) is most likely to help diagnose the following seven CCHDs:
   a. Hypoplastic left heart syndrome
   b. Pulmonary atresia
   c. Tetralogy of Fallot
   d. Total anomalous pulmonary venous return

e. D-Transposition of the great arteries
f. Tricuspid atresia
g. Truncus arteriosus

4. Other CCHDs that may not be detected as consistently with pulse oximetry include coarctation of the aorta, double-outlet right ventricle, Ebstein anomaly, interrupted aortic arch, single ventricle, and L-transposition of the great arteries.
5. A normal pulse oximetry reading does not rule out all congenital heart diseases. Conversely, a low pulse oximetry reading does not always signify congenital heart disease; it may reflect a newborn's transitional postnatal circulation or a noncardiac disorder, such as sepsis or pulmonary process (transient tachypnea of the newborn, meconium aspiration syndrome, pneumonia, pulmonary hypertension of the newborn, pneumothorax).
6. Recommended strategies include screening between 24 and 48 hours of age, ensuring staff are properly trained in pulse oximetry measurement, and using later generation pulse oximeters that are less sensitive to motion artifact. If an infant is discharged before 24 hours of age, the screen should be completed as close to discharge as possible.
7. A pulse oximeter is used to obtain preductal oxygen saturation (right hand) and postductal oxygen saturation (either foot) simultaneously or one site immediately followed by the other.
8. AAP-defined criteria for a positive screening test that merits further clinical investigation for CCHD include any one of the following:
   a. Any oxygen saturation measure $<90\%$
   b. Oxygen saturation 90% to 94% in both sites on three measures, each separated by 1 hour
   c. $>3\%$ absolute difference in oxygen saturation between the two sites on three measures, each separated by 1 hour

VI. ROUTINE ASSESSMENTS

A. The physician should perform a complete physical examination within 24 hours of birth.

B. Vital signs, including respiratory rate, heart rate, and axillary temperature, are recorded every 8 to 12 hours.

C. Each urine and stool output is recorded in the infant's chart. The first urination should occur by 24 hours of age. The first passage of meconium is expected by 48 hours of age. Delayed urination or stooling is cause for concern and must be investigated.

D. Weights are recorded in the infant's chart. An online calculator is available at https://www.newbornweight.org/ to help plot these weights on hour-specific curves and assess adequacy of infant's intake. Weight loss in excess of 10% to 12% of birth weight, although common, should be investigated, especially for exclusively breastfed newborns. Lactation support is important to help determine further management inpatient and outpatient. If caloric intake is thought to be adequate, organic etiologies should be considered, such as infection or metabolic or thyroid disorders.

VII. FAMILY AND SOCIAL ISSUES

A. Sibling visitation is encouraged and is an important element of family-centered care. However, siblings with fever, signs of acute respiratory or gastrointestinal illness, or a history of recent exposure to communicable diseases are discouraged from visiting.

B. Social worker involvement is helpful in circumstances such as teenage mothers, limited or lack of prenatal care, history of domestic violence, maternal substance abuse, maternal mental health disorder or other increased risk for postpartum depression, and history of previous involvement with child protective services or similar agency.

VIII. FEEDINGS.

The frequency, duration, and volume of each feed will depend on whether the infant is feeding breast milk or formula. Details about each feeding session should be recorded in the infant's medical record.

A. Exclusive breastfeeding for the first 6 months of a newborn's life has long been the goal of the WHO, U.S. Department of Health and Human Services, AAP, and American College of Obstetricians and Gynecologists.

1. Mothers should initiate breastfeeding as soon as possible after delivery, preferably in the delivery room, and then feed on demand, 8 to 12 times per day during the newborn hospitalization (see Chapter 22).
2. Consultation with a lactation specialist during the postpartum hospitalization is strongly recommended for all breastfeeding mothers.

B. Standard 19 or 20 kcal/oz, iron-containing infant formula is offered to infants for whom breastfeeding is contraindicated or at the request of a mother who desires to formula feed. Unless contraindicated by a strong family history, lactose-containing formulas with milk protein (whey and casein) can be given to all newborns. Higher caloric density formula may be needed if infant is preterm or if medically indicated.

1. Formula-fed infants are fed at least every 3 to 4 hours.
2. During the first few days of life, the well newborn typically consumes at least 0.5 to 1 oz per feed.

IX. NEWBORN CIRCUMCISION

A. The AAP states that scientific evidence demonstrates potential medical benefits of newborn male circumcision; however, these data are not sufficient to recommend routine neonatal circumcision. Potential benefits are decreased incidence of urinary tract infection in the first year of life, decreased risk of penile cancer, and decreased risk of acquiring sexually transmitted diseases, particularly HIV infection.

B. Informed consent is obtained before performing the procedure. The potential risks and benefits of the procedure are explained to the parents.

1. The overall complication rate for newborn circumcision is approximately 0.5%.
2. The most common complication is bleeding (~0.1%) followed by infection. A family history of bleeding disorders, such as hemophilia

and von Willebrand disease, or maternal thrombocytopenia needs to be explored with the parents when consent is obtained. Appropriate testing to exclude a bleeding disorder must be completed before the procedure if the family history is positive.

3. The parents should understand that newborn circumcision is an elective procedure; the decision to have their son circumcised is voluntary and not medically necessary.

4. Contraindications to circumcision in the immediate newborn period that may require further consultation include the following:
   a. Sick or unstable clinical status
   b. Premature infants. Circumcision should be delayed until infant is of adequate size to perform the procedure safely.
   c. Diagnosis of a congenital bleeding disorder. Circumcision can be performed if the infant receives appropriate medical therapy before the procedure (i.e., infusion of factor VIII or IX).
   d. Inconspicuous or "buried" penis
   e. Anomalies of the penis, including hypospadias, ambiguity, chordee, or micropenis. Circumcision should be delayed until cleared by a pediatric urologist.
   f. Bilateral cryptorchidism. Circumcision should be delayed until infant is evaluated for ambiguous genital and gender issues.

C. Adequate analgesia must be provided for neonatal circumcision with dorsal penile nerve block techniques or topical anesthetic. In low birth weight or preterm infants, penile nerve block is preferred due to higher incidence of skin irritation and rare incidence of methemoglobinemia associated with topical analgesia creams.

D. In addition to analgesia, other methods of comfort are provided to the infant during circumcision.

1. Twenty-four percent sucrose on a pacifier, per nursery protocol, may be given as an adjunct to analgesia.
2. The infant's upper extremities should be swaddled, and the infant placed on a padded circumcision board with restraints on the lower extremities only.
3. Administration of acetaminophen after the procedure may alleviate postcircumcision discomfort.

E. Circumcision in the newborn can be performed using one of three different methods:

1. Gomco clamp
2. Mogen clamp
3. Plastibell device

F. Oral or written instructions explaining postcircumcision care should be given to all parents.

X. DISCHARGE PREPARATION

A. Parental education on routine newborn care should be initiated at birth and continued until discharge. Written information in addition to verbal

instruction may be helpful, and in some cases, it is mandated. The following newborn issues should be reviewed at discharge:

1. Adequacy of oral intake, particularly for breastfed infants. This includes a minimum of eight feeds per day; one wet diaper per day of age, constant at the sixth day of life; and at least one stool per day.
2. Routine cord and skin care
3. Routine postcircumcision care (when indicated)
4. Signs of infant illness including fever, irritability, lethargy, or a poor feeding pattern
5. Observation for neonatal jaundice
6. Safe sleep environment, such as supine positioning for sleep, using tight-fitting crib sheets, having no loose blankets or materials in the crib, and sleeping in proximity but not bed sharing
7. Appropriate installation and use of an infant car seat
8. Other infant safety matters, such as maintaining a smoke-free environment, checking smoke detectors, lowering the hot water temperature at home, and hand hygiene

B. Discharge readiness

1. Each mother–infant dyad should be evaluated to determine the optimal time of discharge.
2. The hospital stay of the newborn and mother should be long enough to identify early problems and to ensure that she is able and prepared to care for the infant at home.
3. All efforts should be made to promote the simultaneous discharge of a mother and infant.

C. The AAP recommends that the following minimum discharge criteria be met before any term newborn (37 0/7 to 41 6/7 weeks' gestation) is discharged from the hospital.

1. Clinical course and physical examination reveal no abnormalities that require continued hospitalization.
2. The infant's vital signs are documented to be within normal ranges (with appropriate physiologic variations) and stable for 12 hours preceding discharge.
3. The infant has urinated regularly and passed at least one stool spontaneously.
4. The infant has completed at least two successful feedings.
5. There is no excessive bleeding at the circumcision site for at least 2 hours.
6. The clinical significance of jaundice has been assessed and appropriate management and follow-up plans have been determined.
7. The infant has been adequately evaluated and monitored for sepsis based on maternal risk factors.
8. Maternal and infant laboratory tests have been reviewed.
9. The infant's initial hepatitis B vaccine has been administered if parent consents.

10. The mother's vaccine status has been updated, including influenza (during the flu season) and tetanus toxoid, reduced diphtheria toxoid, acellular pertussis (Tdap).
11. Newborn metabolic, hearing, and CCHD screenings have been completed per hospital protocol and state regulations.
12. Parental competency to care for the newborn has been demonstrated.
13. Appropriate car safety seat has been obtained, and the parent has demonstrated proper infant positioning and use.
14. Family members or other support persons are available to mother and infant after discharge.
15. A physician-directed source of continuing health care (medical home) has been identified.
16. Family, environmental, and social risk factors have been assessed.

D. Late-preterm infants who are 35 0/7 to 36 6/7 weeks' gestation are often eligible for admission to the well newborn nursery or couplet care. However, they are at greater risk for morbidity and mortality than term infants and are more likely to encounter problems in the neonatal period such as jaundice, temperature instability, feeding difficulties, and respiratory distress. Late-preterm infants are usually not expected to meet the necessary competencies for discharge before 48 hours of age. AAP discharge criteria for late-preterm infants are similar to criteria developed for healthy term infants with the following additions:

1. Best estimate of gestational age has been determined based on history and physical examination.
2. A physician-directed medical home has been identified, and a follow-up visit has been arranged within 48 hours of discharge.
3. A formal evaluation of breastfeeding has been documented in the chart by trained caregivers at least twice daily since birth.
4. The infant has demonstrated 24 hours of successful feeding with the ability to coordinate sucking, swallowing, and breathing while feeding.
5. A feeding plan has been developed and is understood by the family.
6. The infant has passed a car safety seat test to observe for apnea, bradycardia, or oxygen desaturation with results documented in the chart.

XI. FOLLOW-UP

A. For infants discharged before 48 hours of life, an appointment with a health care provider should be arranged within 48 hours of discharge. If early follow-up cannot be ensured, early discharge should be deferred.

B. For newborns discharged between 48 and 72 hours of age, outpatient follow-up should be within 2 to 3 days of discharge. Timing should be based on risk for subsequent hyperbilirubinemia, feeding issues, or other concerns.

C. The follow-up visit is designed to perform the following functions:

1. Establish a relationship with the medical home and verify the plan for health care maintenance.
2. Assess the infant's general state of health including weight, hydration, and degree of jaundice and identify any new problems.

3. Review feeding patterns; encourage and support breastfeeding.
4. Review adequacy of stool and urine patterns.
5. Provide referral for lactation support if feeding and elimination patterns are not reassuring.
6. Assess quality of mother–infant bonding.
7. Reinforce maternal or family education.
8. Review results of any outstanding laboratory tests.
9. Perform screening tests in accordance with state regulations.
10. Assess parental well-being and screen for maternal postpartum depression.

Suggested Readings

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10 Genetic Issues Presenting in the Nursery

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KEY POINTS

- Approximately 1 in 30 to 40 newborns has a congenital malformation.
- Evaluation for a suspected genetic disorder includes a comprehensive medical/family history and physical examination.
- Testing may be targeted to a suspected etiology if a specific phenotype is identified, although exome sequencing has emerged as an efficient diagnostic tool across a wide range of presenting features.

I. GENERAL PRINCIPLES

A. Approximately 3% of newborns have a major congenital malformation, which may be genetic, and others require genetic evaluation for reasons such as acidosis, liver failure, or other features suggestive of inborn errors of metabolism (IEM), unexplained seizures, extreme hypotonia, or feeding difficulties. Some children may have physical features consistent with a well-known syndrome, whereas others may have isolated anomalies detected prenatally or postnatally that appear to be nonsyndromic. A thorough clinical evaluation requires a detailed prenatal history, a family history, a comprehensive clinical exam including anthropometric measurements, and imaging studies such as echocardiography and abdominal ultrasound to identify associated structural malformations. Even if a hypothesis-free testing strategy is used, such as chromosomal microarray (CMA) or exome sequencing, defining the phenotype is critical to interpret genomic variations that are found.

B. Congenital anomalies are considered major or minor.

1. **Major malformations** are structural abnormalities that have medical and cosmetic consequence. They may require surgical intervention. Examples include cleft palate and congenital heart disease such as tetralogy of Fallot.
2. **Minor malformations** are anomalies with no medical or cosmetic significance. One example is a single transverse palmar crease, although most minor abnormalities are limited to the head and neck region.

Minor anomalies may aid in the diagnosis or recognition of a specific syndrome. Infants with three or more minor malformations are at high risk for having a major malformation (20% to 25%) and/or a syndrome.

C. Major and minor malformations are often part of patterns.

1. A **syndrome** consists of a group of anomalies that are associated due to single or similar etiologies, with known or unknown cause. Examples include conditions such as Down syndrome due to trisomy 21 or fetal hydantoin syndrome due to maternal use of phenytoin.
2. **Associations** are clusters of malformations that occur together more frequently than occur sporadically, such as VACTERL association (vertebral, anal, cardiac, tracheoesophageal fistula, renal, and limb—radial ray defects), where at least three anomalies are required for the diagnosis, or OEIS (omphalocele, exstrophy of the cloaca, imperforate anus, spinal defects) complex. The underlying genetic cause of such associations is not generally known, although these spectra of anomalies may occur in the context of a known genetic syndrome.
3. A **developmental field defect** consists of a group of anomalies resulting from defective development of a related group of cells (developmental field). In this case, the involved embryonic regions are usually spatially related but may not be contiguous in the infant. Holoprosencephaly affecting the forebrain and face is an example and secondary to an abnormality in a group of cells that form the rostral aspect of the prechordal mesoderm that will ultimately induce development of the forebrain and midface.
4. **Disruptions** are extrinsic events that occur during normal development. These events can compromise the fetal circulation and result in a major congenital anomaly. An example of a disruption is amniotic bands that may result in amputation of digits or limbs.
5. **Deformations** can occur when physical forces act on previously formed structures. Examples of deformations include uterine crowding or oligohydramnios that results in plagiocephaly or clubfeet.

II. INCIDENCE.

The Centers for Disease Control and Prevention (CDC) monitors rates of birth defects in the United States (http://www.cdc.gov/ncbddd/birthdefects/data.html). In the United States, approximately 1 of 33 children has a major congenital anomaly, and infants with congenital anomalies and genetic syndromes account for 20% of infant deaths.

III. ETIOLOGY.

The underlying etiology remains unknown for approximately 50% of infants with congenital anomalies. Of the remainder, the etiology has been attributed as follows: 10% chromosomal, 2% to 3% single-gene Mendelian disorders, 20% to 40% multifactorial, and 3% to 4% environmental exposures. The presence of multiple congenital anomalies or other syndromic features (e.g., dysmorphic facies, developmental delay, poor growth) makes an underlying genetic disorder more likely. Increased efforts at understanding these anomalies, including genomic sequencing, is likely to establish an underlying etiology in more cases.

IV. APPROACH TO THE INFANT WITH A CONGENITAL MALFORMATION OR OTHER SUSPECTED GENETIC DISORDER

A. A comprehensive history is an important first step in evaluating an infant with a birth defect.

1. Prenatal history should include the following:

a. Chronic maternal illnesses including diabetes (insulin and non–insulin dependent), seizures, hypertension, myotonic dystrophy, phenylketonuria, Graves disease (see Table 10.1 for prenatal exposures and effects).

b. Drug exposures should include prescribed drugs, such as antihypertensives (angiotensin-converting enzyme inhibitors), seizure medications, antineoplastic agents (methotrexate), abortifacients (misoprostol), and other substance use such as alcohol. The timing of the exposure is important, as teratogenic agents tend to have their maximum effect during the embryonal period, from the beginning of the fourth to the end of the seventh week postfertilization, with the exception of severe forms of holoprosencephaly when exposure may occur around or before 23 days.

c. Infections and immunizations

d. Social history

e. Other exposures may include physical agents such as x-rays, high temperature, chemical agents, and tobacco (see Table 10.1).

f. Nutritional status

g. Fertility issues and use of reproductive assistance (e.g., history of multiple miscarriages, *in vitro* fertilization [IVF], or medications to stimulate ovulation). Genetic disorders such as Beckwith-Wiedemann syndrome, Silver-Russell syndrome, and Angelman syndrome that can be caused by imprinting defects (epigenetic variants) occur with higher frequency in children conceived by assisted reproductive technology using intracytoplasmic sperm injection (ICSI).

h. Multiple gestations (see Chapter 11)

i. Results of prenatal studies should be obtained including ultrasonographic and magnetic resonance imaging (MRI) and chromosome or microarray studies done on samples obtained by amniocentesis, chorionic villi sampling (CVS), or percutaneous umbilical blood sampling. Many parents are now undergoing expanded carrier screening, and these results can be helpful in guiding a postnatal genetic evaluation.

j. Quality and frequency of fetal movements should be documented. Rapid and intense movements could be due to fetal seizures, whereas decreased movement can be seen with spinal muscular atrophy, Prader-Willi syndrome, and other congenital myopathies.

k. Results should be obtained from first- and second-trimester screening including triple and quad screens. First-trimester screening combines the use of nuchal translucency with serum levels of pregnancy-associated plasma protein A (PAPP-A) and human chorionic gonadotropin (hCG) measured as free β subunit (β-hCG) or total hCG. The second-trimester screen includes α-fetoprotein (AFP), unconjugated estriol (uE3), free β-hCG for the triple screen, plus inhibin A, as part of the quad screen. A low maternal serum α-fetoprotein (MSAFP) level can be seen in trisomies 21, 18, and 13. A high MSAFP may be a sign of multiple gestation,

Table 10.1. Well-Recognized Human Teratogens

Exposure Type	Fetal Effect
Drugs	
Aminopterin/methotrexate	Growth restriction, clefting, syndactyly, skeletal defects, craniosynostosis, dysmorphic features
Retinoic acid	CNS defects, microtia, ID, conotruncal defects: VSD, ASD, TOF
Lithium	Ebstein anomaly
Propylthiouracil, iodine	Hypothyroidism
Warfarin	Skeletal anomalies, stippled epiphyses, nasal hypoplasia
ACE inhibitors	Skull defects, renal hypoplasia/agenesis
Alcohol	Fetal alcohol syndrome or alcohol-related neurodevelopmental disorders
Thalidomide	Limb reduction defects
Valproic acid	Neural tube defects
Phenytoin	Dysmorphic features, nail hypoplasia, cleft lip and palate, ID, growth restriction
Diethylstilbestrol	Clear cell cervical cancer in female progeny
Cocaine	Vascular disruptions, CNS anomalies
Misoprostol (Cytotec)	Limb malformations, absent digits
Statins (HMG-CoA reductase inhibitor)	Limb defects, CNS abnormalities, congenital heart disease
Maternal conditions	
Maternal phenylketonuria	Microcephaly, ID
Myasthenia gravis	Neonatal myasthenia
Systemic lupus erythematosus	Cardiac conduction abnormalities
Diabetes	Neural tube defects, sacral agenesis, congenital heart disease, renal anomalies, skeletal anomalies

(continued)

Table 10.1. *(Continued)*

Exposure Type	Fetal Effect
Other exposures	
Radiation	Miscarriage, growth restriction
Prolonged heat exposure	Microcephaly
Smoking	Growth restriction
Lead	Low birth weight, neurobehavioral and neurologic deficits
Mercury	CNS anomalies, neurobehavioral and neurologic deficits
Infections	
Varicella	Limb scars
Cytomegalovirus	Microcephaly, chorioretinitis, ID
Toxoplasmosis	Microcephaly, brain calcifications, ID
Rubella	Microcephaly, deafness, congenital heart disease, ID

CNS, central nervous system; ID, intellectual disability; VSD, ventricular septal defect; ASD, atrial septal defect; TOF, tetralogy of Fallot; ACE, angiotensin-converting enzyme.

open neural tube defect, abdominal wall defect, impending fetal death, congenital nephrosis, or epidermolysis bullosa. A high hCG can be seen with trisomy 21, whereas low hCG may occur with trisomies 18 and 13. Low estriol can be seen in association with a fetus that has Smith-Lemli-Opitz syndrome, a congenital malformation syndrome caused by defective cholesterol metabolism.

l. Cell-free DNA testing, previously referred to as noninvasive prenatal testing (NIPT) or noninvasive prenatal screening (NIPS), involves the analysis of DNA fragments derived from trophoblastic tissue present in maternal serum. NIPT is increasingly used in both high- and low-risk pregnancies for the early and accurate detection of common aneuploidy syndromes such as Down syndrome (commonly caused by trisomy 21, sensitivity 99%), Edwards syndrome (commonly caused by trisomy 18, sensitivity 98%), and Patau syndrome (commonly caused by trisomy 13, 99%) in addition to sex chromosome aneuploidies such as Turner syndrome. The American College of Obstetricians and Gynecologists recommends cell-free DNA testing for any pregnancy as early as 9 to 10 weeks gestational age to screen for aneuploidy. Because this test does not distinguish differences in chromosomal structure, a karyotype would be required to detect trisomy 21 versus Down syndrome due to a Robertsonian translocation, important information for parental recurrence risk.

m. Cell-free DNA testing can also be used to detect common microdeletion syndromes, such as 22q11.2 deletion syndrome (DiGeorge/velocardiofacial syndrome [VCFS]) and Wolf-Hirschhorn syndrome. However, it is not formally recommended due to the lower prevalence of these conditions in the general population and thus the lower positive predictive value.

n. Cell-free DNA testing for monogenic disorders is commercially available, although due to technical limitations, this is generally limited to paternally inherited or *de novo* conditions. The ability of cell-free DNA to detect such conditions caused by single-nucleotide variants is likely to expand in the future.

2. **Family history** should include the following questions:

a. Are there any previous children with congenital anomalies or genetic diagnoses?

b. What is the parental ancestry? (Some conditions are more prevalent in specific populations.)

c. Is there consanguinity, or are the parents from the same geographic area? What is the population size of the parents' community? In cases of rare autosomal recessive disorders, the parents may be related.

d. Is there a history of infertility, multiple miscarriages, multiple congenital anomalies, neonatal deaths, or children with developmental delay? These can be secondary to a balanced chromosome rearrangement in one of the parents but unbalanced in the progeny.

3. **Prenatal and perinatal events** should be evaluated:

a. What was the fetal presentation, and how and for how long was the head engaged? Was there fetal crowding, such as might occur with multiple gestation? Are there uterine abnormalities (e.g., septate uterus, myomatosis)? Various deformations, sagittal synostosis, and clubfeet can be caused by fetal constraints.

b. What was the growth pattern throughout gestation? Was there proportionate or disproportionate growth restriction?

c. What was the mode of delivery? Was there fetal distress or any events potentially leading to hypoxemia?

d. Placenta appearance: Is there evidence of placental infarcts? Is the umbilical cord normal? Inspection of the cord may reveal severe narrowing, clots, or knots.

4. **Neonatal events**

a. What were the Apgar scores? Was resuscitation needed? Was intubation and ventilator assistance needed? Were there severe feeding difficulties necessitating parenteral nutrition or tube feedings? Were there neonatal seizures? Was there hypotonia or hypertonia?

B. Physical examination

1. **Anthropometric measurements.** The assessment of growth parameters is extremely valuable to determine growth patterns such as restriction, overgrowth, disproportion, macrocephaly, or microcephaly. In addition, precise measurements of anatomic structures and landmarks can aid the diagnostic evaluation process. Examples are ear length, eye measurements for hypertelorism or hypotelorism (widely or closely spaced eyes), finger length, and internipple distance. Extensive reference tables

for many of these measurements are available for children of all ages, including preterm infants starting at 27 weeks' gestation (see "Suggested Readings").

2. A thorough clinical evaluation is needed to document the presence of dysmorphic features: head shape (e.g., craniosynostosis, trigonocephaly, brachycephaly); ear shape (e.g., microtia, ear pits, or tags) and positioning; midface hypoplasia, clefting, micrognathia, short neck; and limb anomalies (e.g., asymmetry, clinodactyly, brachydactyly, polydactyly). Some physical findings can be obscured by aspects of clinical care such as endotracheal tube position and taping or intravenous arm board and tape over the limbs. In this case, the infant should be reexamined when these are no longer present.
3. Ancillary evaluations include a hearing screen (otoacoustic emissions testing) that is done typically before discharge from the nursery or neonatal intensive care unit (NICU) and an ophthalmologic evaluation, which usually requires a pediatric subspecialist and may not be available at every institution.

C. Laboratory studies (Table 10.2)

1. Chromosome studies are typically performed on whole blood drawn into sodium heparin tubes (green top). The T lymphocytes in the blood are stimulated with mitogens, cultured for 72 hours, placed on slides, and karyotyped through the help of banding techniques such as Giemsa trypsin G-banding (GTG). In extremely ill infants, those with immunosuppression, or who have low T-cell counts (as in DiGeorge syndrome), cell growth may be impaired and cell stimulation fails. In this case, a molecular-based assay such as a CMA may be performed (see following discussion). In the past, a punch skin biopsy would be performed to obtain chromosomes from skin fibroblasts, but this is no longer routinely done. The disadvantage of using skin fibroblasts is the delay of up to several weeks before a result is available in addition to the more invasive nature of this test; it can be helpful to detect mosaicism or if blood testing is not possible due to the aforementioned issues or after massive transfusion. In general, chromosome studies can detect up to 5% of abnormalities. Tables 10.3 and 10.4 list the main clinical findings of the most common chromosome aneuploidies.
2. Fluorescent *in situ* hybridization (FISH) studies can be useful for the rapid detection of aneuploidies. These studies are done on unstimulated interphase cells, and the results are typically available in a few hours or overnight. Rapid FISH is used for evaluation in trisomies 13 and 18 and for sex chromosome testing in infants with ambiguous genitalia. More specific studies, such as FISH for SRY (the sex-determining region on the Y chromosome), require more time and are done on stimulated metaphase cells.
3. CMA is a molecular technique performed on extracted DNA that allows detection of DNA copy number losses (deletions) and copy number gains (duplications, triplications) of small genomic regions, sometimes even at the level of an exon. This study is based on the comparison of a known genome from a normal individual against the test sample. CMA can detect

Table 10.2. Types of Genetic Testing

Test	Turnaround Time	Detection Type	Advantages	Disadvantages
Karyotype	4–5 days	Aneuploidy syndromes Large structural chromosomal variants, including deletions, duplications, inversions, and balanced translocations	Rapid detection of common chromosomal disorders such as Down syndrome, ability to detect large chromosomal events including balanced rearrangements	Unable to detect submicroscopic chromosomal CNVs or variants at the gene level
FISH	1–3 days	Aneuploidy syndromes Certain syndromes caused by chromosomal CNVs	Rapid detection of common chromosomal disorders, including microdeletion or duplication syndromes (areas larger than 200 kilobases)	Targeted test requiring high suspicion for a particular disorder, does not detect things that are not targeted
Chromosomal microarray	2–6 weeks	Chromosomal CNVs such as microdeletions and duplications	Able to detect chromosomal CNVs that cannot be visualized on karyotype	Unable to detect SNVs Many platforms unable to detect exon-level changes
Single gene sequencing	4–8 weeks	Monogenic disorders caused by SNVs and small insertions or deletions (~5–10 base pairs)	Able to diagnose common monogenic conditions in a low-cost, targeted fashion to decrease variants of uncertain significance	Unable to detect SVs in single genes and diagnosis is limited to the gene in question

Other single gene tests	4–8 weeks	Monogenic disorders caused by other types of variants such as triplet repeat expansions (e.g., myotonic dystrophy) or single exon deletions (e.g., spinal muscular atrophy)	Able to detect certain types of disorders that are not generally found by sequencing technology	Ability for diagnosis limited to the specific disease/variant in question
Gene panel testing	4–8 weeks	Monogenic disorders caused by SNVs and small insertions or deletions (~5–10 base pairs), occasionally include other types of variants	Ability to interrogate multiple genes at once; particularly helpful for disorders with locus heterogeneity such as epileptic encephalopathies	Analysis limited to the number of genes on the panel Not able to detect all types of SVs in single genes
Exome sequencing	1–2 weeks (rapid type, requires trios) 8–12 weeks (standard)	Monogenic disorders caused by SNVs and small insertions or deletions (indels, ~5–10 base pairs), occasionally larger copy number variants	Detects most pathogenic variants causing monogenic conditions (tend to lie in coding regions), rapid form can return results in 1–2 weeks	Cost may be prohibitive, especially for rapid form. Does not reliably detect all types of SVs; cannot detect deep noncoding variants
Genome sequencing	1–2 weeks (rapid) 8–12 weeks (standard)	Monogenic disorders caused by SNVs and indels Monogenic disorders caused by SVs (deletions, duplications, insertions, inversions) or deep noncoding and regulatory variants Structural chromosomal variants and CNVs	Able to detect many different types of pathogenic genomic variation, from SNVs/indels to SVs and CNVs in addition to deep noncoding variants (intronic and regulatory)	High cost and analytic burden

CNV, copy number variant; FISH, fluorescence *in situ* hybridization; SNV, single-nucleotide variant; SV, structural variant.

Table 10.3. Common Chromosome Anomalies (Aneuploidies)

	Trisomy 13/ Patau Syndrome	Trisomy 18/ Edward Syndrome	Trisomy 21/ Down Syndrome	Turner Syndrome
Growth	Growth restriction	Growth restriction	Normal	Mild growth restriction
Craniofacial	Hypotelorism, cleft lip and palate, small malformed ears, colobomas, microphthalmia	Triangular facies, micrognathia, pointy rotated low set ears	Upslanting palpebral fissures, epicanthal folds, midface hypoplasia, small round ears, tongue thrusting	Frontal prominence, low posterior hairline
Neck	Short		Short, redundant skin	Short, webbed, pterygium, cystic hygroma
Central nervous system	Holoprosencephaly, microcephaly	Microcephaly	Microcephaly	Normal
Neurologic	Hypertonia, seizures, apnea	Hypertonia, apnea	Hypotonia	Normal tone, mild developmental delay
Heart/chest	ASD, VSD	Multiple valvular anomalies Short sternum	AV canal, VSD, ASD	Aortic coarctation
Abdominal	Multicystic kidneys, horseshoe kidneys, double ureters	Omphalocele, renal anomalies	Duodenal atresia, Hirschsprung disease	Horseshoe kidneys
Limbs	Polydactyly, nail dysplasia	Overlapping fingers, nail hypoplasia, rocker-bottom feet	Brachydactyly, 5th finger clinodactyly, single transverse palmar crease	Hand and feet lymphedema, deep-set nails
Skin	Scalp defects (cutis aplasia)	Decreased subcutaneous tissue	Cutis marmorata	Multiple nevi

ASD, atrial septal defect; VSD, ventricular septal defect; AV, atrioventricular.

Table 10.4. Other Common Chromosome Abnormalities

	Cri-du-chat Syndrome	Wolf-Hirschhorn Syndrome	1p36.3 Deletion Syndrome	Killian/Teschler-Nicola Syndrome (Pallister Mosaic Syndrome)
Chromosomal defect	Deletion of 5p15.2	Deletion of 4p16.3	Deletion of distal short arm of chromosome 1 (1p36.3)	Tetrasomy 12p; mosaicism for isochromosome 12p
Growth	Growth restriction	Growth restriction, FTT	Growth restriction, FTT	Normal or increased weight, later growth deceleration, macrocephaly
Craniofacial	Hypertelorism, round face, low-set ears, epicanthal folds, micrognathia	Hypertelorism, cleft palate, prominent glabella with Greek helmet warrior appearance	Thin horizontal eyebrows, midface hypoplasia, pointy chin, cleft lip/palate, large anterior fontanel	Hypertelorism, sparse hair on lateral frontal region, eyebrows and eyelashes, prominent forehead, chubby cheeks, thick lips, coarse features
Skin		Posterior scalp defects		Linear hyper- and hypopigmented skin lesions
Central nervous system	Microcephaly	Microcephaly	Microcephaly	Polymicrogyria
Neurologic	High-pitched characteristic shrill cry (catlike), severe ID	Seizures that may improve with age, hypotonia, severe ID	Moderate-to-severe ID/absent speech, seizures	Seizures, hypotonia, contractures develop later, profound ID

(continued)

Table 10.4. Other Common Chromosome Abnormalities *(Continued)*

	Cri-du-chat Syndrome	Wolf-Hirschhorn Syndrome	1p36.3 Deletion Syndrome	Killian/Teschler-Nicola Syndrome (Pallister Mosaic Syndrome)
Heart		ASD, VSD	Cardiomyopathy	
Abdominal		Malrotation, absent gallbladder		Diaphragmatic hernia, imperforate anus
Limbs	Nail hypoplasia	Clubfeet, hyperconvex nails		Brachydactyly, broad digits
Genitourinary		Hypospadias, cryptorchidism, absent uterus		Hypospadias
Other			Sensorineural hearing loss	Mosaicism is often found in skin fibroblasts and rarely present in blood chromosomes.
Natural history	Severe ID, aggressive behavior, self-mutilation	Profound ID, major feeding difficulties sometimes require gastrostomy	Moderate-to-severe ID, seizures in 50% often improve, hearing loss leads to speech delays	Profound ID, no speech, seizures, joint contractures

FTT, failure to thrive; ID, intellectual disability; ASD, atrial septal defect; VSD, ventricular septal defect.

14% to 16% more abnormalities than conventional cytogenetic studies (regular karyotype). Disadvantages of microarray testing include failure to detect inversions, balanced chromosome translocations, and low-level mosaicism. CMA can be performed in blood and buccal brush samples (the latter can replace skin biopsy as it represents ectodermal tissue). Occasionally, parental studies are warranted after a copy number variant is found in order to determine if one parent is a carrier and to aid with the interpretation of the finding(s) in the case of a variant of uncertain significance. Consultation with a cytogeneticist or clinical genetics specialist is essential to interpret abnormal array results. The most common microdeletion syndromes detected in newborns are described in Table 10.5.

4. DNA sequencing studies or other specific DNA tests (such as evaluation for triplet repeats) are used to detect single-gene disorders and are usually performed on blood collected in an ethylenediaminetetraacetic acid (EDTA) tube or buccal swab/saliva samples. Single-gene disorders can be transmitted in a Mendelian fashion following autosomal recessive, autosomal dominant, and/or X-linked recessive/dominant patterns. Some can be the result of sporadic mutations. Many of them can present in newborns as life-threatening disorders. These include spinal muscular atrophy; congenital adrenal hyperplasia (most commonly due to 21-hydroxylase deficiency); congenital myotonic dystrophy (only when inherited from an affected mother); osteogenesis imperfecta; multiple malformation syndromes such as CHARGE syndrome (syndrome of coloboma, heart defects, atresia choanae, growth restriction, genital and ear abnormalities) (*CHD7* gene), Kabuki (*KMT2D* or *KDM6A* genes), or Noonan/RASopathy syndromes (*PTPN11* and others); and autosomal recessive polycystic kidney disease (*PKHD1*). A number of IEM are Mendelian disorders. Other non–life-threatening single-gene disorders that can present in the newborn period include achondroplasia, due to *FGFR3* mutations, and nonsyndromic deafness, due to pathogenic variants in *GJB2* or *GJB6* (also known as connexin 26 and connexin 30).
5. Exome sequencing involves sequencing of all the coding regions, or exons, of the genome in a single pass using massively parallel sequencing, a technique that reads small stretches of DNA multiple times, making the results more robust. Exonic DNA comprises approximately 2% to 3% of the genome and includes approximately 20,000 genes (although only about 6,000 are currently associated with known disorders). Multiple studies of exome sequencing used to diagnose infants, particularly those in the intensive care unit, have reported diagnostic yields of 30% if done as proband and up to 50% when done as a trio, using DNA from both parents to augment the interpretation of genomic sequence variation. This broad technique has particular appeal in the newborn period, where phenotypes may be more nonspecific than in older children. Exome consenting and results return should be aided by clinical geneticists and/or genetic counselors.
6. **Infection.** TORCH infections (toxoplasmosis, other, rubella, cytomegalovirus, herpes simplex) may be suspected in children with microcephaly, cataracts, deafness (cytomegalovirus, rubella, toxoplasmosis), and congenital heart disease (rubella). In that case, immunoglobulin G (IgG)

Table 10.5. Common Chromosome Microdeletions Ascertained in the Neonatal Period

	Prader-Willi Syndrome	DiGeorge Syndrome and Velocardiofacial Syndrome	Williams Syndrome	Miller-Dieker Syndrome
Chromosomal and genetic defect	15q11q13 deletion 70% UPD 20%–25% Imprinting center defect 5%	22q11.2 deletion	7q11.23 deletion	17p13.3 deletion
Critical gene(s) involved	*SNRPN*	*TBX1*	*ELN* (Elastin)	*LIS-1*
Growth	Normal birth weight, poor feeding, poor suck	Short stature	Short stature	IUGR
Craniofacial	Bitemporal narrowing, almond-shaped eyes	Prominent tubular nose, small ears, cleft palate, velopharyngeal incompetence (nasal regurgitation)	Supraorbital fullness, stellate pattern of the iris, long philtrum, everted lower lip	Microcephaly, bitemporal hollowing, furrow over mid-forehead, low-set ears
Abdomen		Absent/hypoplastic kidneys	Nephrocalcinosis, renal artery stenosis	Duodenal atresia, omphalocele
Central nervous system	Moderate-to-severe ID	Mild-to-moderate ID	Mild-to-moderate ID	Lissencephaly, agyria, pachygyria, heterotopias, absent corpus callosum, profound ID

Neurologic	Severe hypotonia in the first few weeks of life, poor feeding			Hypertonia, progressive spasticity, decerebrate posture, seizures
Heart	Normal	Conotruncal heart defects: VSD, ASD, tetralogy of Fallot, interrupted aortic arch	Supravalvular aortic stenosis,	Congenital heart defects
Limbs	Small hands and feet	Long digits	Normal	Normal
Skin	Lighter pigmentation than parents (in deletion cases)	Normal	Normal	Normal
Other		T-lymphocyte dysfunction: frequent infection	Hypercalcemia	
Natural history	Obesity and hyperphagia after 2–3 years	Normal life span	Normal life span	Death before age 2 years

UPD, uniparental disomy; IUGR, intrauterine growth restriction; ID, intellectual disability; VSD, ventricular septal defect; ASD, atrial septal defect.

and immunoglobulin M (IgM) antibodies or polymerase chain reaction (PCR)-based testing should be ordered. Brain imaging studies and fundoscopic exam may reveal brain calcifications and/or chorioretinitis. Parvovirus should be considered in cases of hydrops fetalis. The differential for nonimmune hydrops also includes several rare lysosomal storage disorders (see Chapter 60).

7. **Metabolic testing** for IEM is typically included in newborn screening programs. In most states, mandatory newborn screening is done initially between 24 and 48 hours of age. The March of Dimes and the American College of Medical Genetics and Genomics recommend 33 conditions for testing via dried blood spot testing (such as spinal muscular atrophy or cystic fibrosis, in addition to hearing screens and screening for critical congenital heart disease). Most of the genetic metabolic conditions can be managed by medications and/or special diets, and treatment in many can be lifesaving. Additional metabolic studies considered for the diagnosis of IEM include acylcarnitine profile for fatty acid oxidation disorders, urine organic acids for organic acidemias, very long chain fatty acids for peroxisomal disorders (Zellweger syndrome), sterol panel (Smith-Lemli-Opitz syndrome associated with low 7-dehydrocholesterol levels), and plasma amino acids for aminoacidopathies (e.g., phenylketonuria, tyrosinemia, nonketotic hyperglycinemia), plasma ammonia, and urine orotic acid (urea cycle disorders). The anion gap should be measured in cases of acidosis; if the anion gap is increased, measure lactic acid in whole plasma from a free-flowing blood sample (ideally arterial) and measure organic acids in urine. It is important to note that IEM may not manifest symptoms until the infant is receiving milk feedings (see Chapter 60). New studies available to the clinician allow detection of multiple IEM with a single detection in plasma and urine known as metabolomic studies.

D. Ancillary evaluations

1. **Imaging studies**

a. Ultrasonography. Brain imaging to detect major malformation and intracranial hemorrhage; abdominal ultrasound exam to detect major liver, kidney anomalies, presence and position of testicles/ovaries; and echocardiography to detect heart defects

b. Brain MRI, to delineate brain anatomy in greater detail

c. Magnetic resonance spectroscopy (MRS) in infants with lactic acidosis to evaluate for mitochondrial disorders

d. Magnetic resonance angiography (MRA) in infants with vascular malformations and to rule out further involvement such as arteriovenous fistulas, hemangiomas

e. Skeletal survey in children with intrauterine growth restriction (IUGR), poor linear growth, and especially with disproportionate growth, to evaluate for skeletal dysplasias. If fractures are present, a survey can be valuable to evaluate for osteogenesis imperfecta.

E. Anatomic pathology

1. Muscle biopsy in children with severe hypotonia can be considered in conjunction with nerve biopsy to assess for disorders such as congenital

muscular dystrophy, amyoplasia congenita, and hypomyelination syndromes. Sometimes, a muscle biopsy can be postponed until the infant is at least 6 months of age to gather better quality and more complete information, although as diagnoses are being increasingly made on a molecular basis (through exome and genome testing), muscle biopsies are rarely performed.

2. As certain genetic disorders occur due to somatic mutations, or genomic changes that occur in a certain cell line and are not present in the peripheral blood samples commonly used for genetic testing, it is worth considering saving frozen tissue for sequencing anytime a child with a suspected genetic disorder has a surgical procedure. For example, Pallister-Killian syndrome (tetrasomy 12p) is generally present in skin cells but not in peripheral blood samples, and Beckwith-Wiedemann and other overgrowth syndromes may also be mosaic. This could obviate the need for a separate skin biopsy for diagnosis.
3. Autopsy studies in stillbirths or infants who die in the neonatal period may provide a diagnosis and help with counseling and recurrence risks. Good documentation should be obtained and radiographs should be considered in addition to pathologic exam. The addition of DNA sequencing studies can augment diagnostic yield, although insurance coverage can be challenging; therefore, DNA banking is highly recommended.
4. Placental pathology can be useful in infants with growth restriction. A sample of the placenta can also be submitted for genetic studies such as karyotyping.

F. Follow-up

1. Infants with genetic disorders, suspected or confirmed, require close follow-up evaluation after hospital discharge either to aid in the diagnosis or to educate the family. Because approximately 50% of patients born with multiple congenital anomalies have no known diagnosis, the follow-up may reveal new findings that will contribute to the final diagnosis. This will help predict the natural history and allow a proper assessment of the recurrence risk.
2. Infants suspected to be at risk for developmental delay should be referred for therapy services and/or early childhood intervention programs.

Suggested Readings

Advisory Committee on Heritable Disorders in Newborns and Children. Recommended Uniform Screening Panel. https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html. Accessed October 6, 2020.

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11 Multiple Births

Melinda H. Markham

KEY POINTS

- Twin birth rates have been stable over the last decade, whereas higher order multiple gestation pregnancies are declining.
- Complication rates are higher in monozygous than dizygous twin pregnancies.
- Prematurity and low birth weight are the most common complications.
- Laser ablation is the intervention of choice for treatment of progressing twin-to-twin transfusion syndrome (TTTS).

I. CLASSIFICATION

A. Zygosity. Monozygotic (MZ) twins originate and develop from a single fertilized egg (zygote) as a result of division of the inner cell mass of the blastocyst. MZ twins are the same sex and genetically identical. Dizygotic (DZ) or fraternal twins originate and develop from two separately fertilized eggs. Triplets and higher order pregnancies (quadruplets, quintuplets, sextuplets, septuplets, etc.) can be multizygotic, MZ and identical, or, rarely, a combination of both.

B. Placenta and fetal membranes. A major portion of the placenta and the fetal membranes originate from the zygote. The placenta consists of two parts: (i) a larger fetal part derived from the villous chorion and (ii) a smaller maternal part derived from the decidua basalis. The chorionic and amniotic sacs surround the fetus. The chorion begins to form at day 3 after fertilization, and the amnion begins to form between days 6 and 8. The two membranes eventually fuse to form the amniochorionic membrane.

1. MZ twins commonly have one placenta with one chorion and two amnions (**monochorionic diamniotic**) or, rarely, one placenta with one chorion and one amnion (**monochorionic monoamniotic**).
2. If early splitting occurs before the formation of the chorion and amnion (days 0 to 3), MZ twins can have two placentas with two chorions and two amnions (**dichorionic diamniotic**).
3. DZ twins always have two placentas with two chorions and two amnions (dichorionic diamniotic); however, the two placentas and chorions may be fused.

II. EPIDEMIOLOGY

A. Incidence. The twin birth rate in 2019 was 32.1 per 1,000 live births, decreased 2% from 2018 and 5% from the peak in 2014. The rate of MZ twinning has remained relatively constant (3.5 per 1,000 births).

1. The rate of DZ twinning is approximately 1 in 100 births. This rate is influenced by factors such as ethnicity and maternal age. The frequency of DZ twinning has a genetic tendency that is affected by the genotype of the mother and not that of the father.
2. The birth rate of triplet and higher order multiples peaked in 1998 at 194 per 100,000 live births and has declined steadily to 87.7 per 100,000 live births in 2019.

B. Causative factors. Two main factors account for the increase in multiple births since the early 1990s: (i) increased use of fertility-enhancing therapies including assisted reproductive technologies (ARTs) such as *in vitro* fertilization (IVF) and non-ART therapies such as ovulation-inducing drugs and artificial insemination, and (ii) **older maternal age** at childbearing (peak at 35 to 39 years), which is associated with an increase in multiples. Due to the numerous maternal, fetal, and neonatal complications associated with multigestational pregnancies, the approach to infertility management has changed over the last 20 years.

III. ETIOLOGY

A. MZ pregnancies result from the splitting of a single egg between days 0 and 14 postfertilization. The type of placenta that forms depends on the day of embryo splitting.

1. A **dichorionic diamniotic** placenta results when early splitting occurs at days 0 to 3 before chorion formation (which usually occurs about day 3) and before implantation. A **monochorionic diamniotic** placenta results when splitting occurs about days 4 to 7 at which time the blastocyst cavity has developed and the chorion has formed. Amnion formation occurs at days 6 to 8, and splitting of the egg after this time (days 8 to 13) results in a **monochorionic monoamniotic** placenta. The frequency of placentation type is 30% dichorionic diamniotic, 70% monochorionic diamniotic, and <1% monochorionic monoamniotic. At day 14 and thereafter, the primitive streak begins to form and late splitting of the embryo at this time results in **conjoined twins**.
2. **DZ or multizygous pregnancies** result when more than one dominant follicle has matured during the same menstrual cycle and multiple ovulations occur. Increased levels of follicle-stimulating hormone (FSH) in the mother have been associated with spontaneous DZ twinning. FSH levels increase with advanced maternal age (peak at age ~37 years). A familial tendency toward twinning has also been shown to be associated with increased levels of FSH.

IV. DIAGNOSIS. Multiple gestational sacs can be detected by ultrasonography as early as 5 weeks, and cardiac activity can be detected from more than one fetus at 6 weeks.

A. Placentation. First-trimester or early second-trimester ultrasonography can best determine the chorionicity of a multiple gestation. From weeks 10 to 14, a fused dichorionic placenta can often be distinguished from a true monochorionic placenta by the presence of an internal dividing membrane or ridge at the placental surface (lambda sign). The dividing septum of a dichorionic placenta appears thicker and includes two amnions and two chorionic layers. In contrast, the dividing septum of a monochorionic placenta consists of two thin amnions. One placenta, same-sex fetuses, and absence of a dividing septum suggest monoamniotic twins, but absence of a dividing septum may also be due to septal disruption.

B. Zygosity. DNA typing can be used to determine zygosity in same-sex twins if this information is desired. Prenatally, DNA can be obtained by chorionic villus sampling (CVS) or amniocentesis. Postnatally, DNA typing should be performed on umbilical cord tissue, buccal smear, or a skin biopsy specimen rather than blood. There is evidence that DZ twins, even in the absence of vascular connections, can also carry hematopoietic stem cells (HSCs) derived from their twin. HSCs are most likely transferred from one fetus to the other through maternal circulation.

C. Pathologic examination of the placenta(s) at birth is important in establishing and verifying chorionicity.

V. PRENATAL SCREENING AND DIAGNOSIS

A. Zygosity determines the degree of risk of chromosomal abnormalities in each fetus of a multiple gestation. The risk of aneuploidy in each fetus of an MZ pregnancy is the same as a singleton pregnancy, and except for rare cases of genetic discordancy, both fetuses are affected. In a DZ pregnancy, each twin has an independent risk of aneuploidy; thus, the pregnancy has twice the risk of having a chromosomal abnormality compared with a singleton.

B. Second-trimester maternal serum screening for women with multiples is limited because each fetus contributes variable levels of these serum markers. When levels are abnormal, it is difficult to identify which fetus is affected using this information alone.

C. First-trimester ultrasonography to assess for **nuchal translucency** is a more sensitive and specific test to screen for chromosomal abnormalities. A **second-trimester ultrasonography exam** is important in surveying each fetus for **anatomic defects**. **First-trimester CVS and second-trimester amniocentesis** can be safely performed on multiples and are both accurate diagnostic procedures for determining aneuploidy. Cell-free fetal DNA testing on maternal blood to evaluate most common chromosomal abnormalities has not been validated in pregnancies with more than one fetus.

VI. MATERNAL COMPLICATIONS

A. Gestational diabetes has been shown in some studies to be more common in twin pregnancies.

B. Spontaneous abortion (fetal loss <20 weeks' gestation) occurs in up to 36% of twin pregnancies and more than 50% in higher order pregnancies with reduction to a lower order or singleton pregnancy by the end of the first trimester ("**vanishing twin**"). Possible causes include abnormal implantation, early cardiovascular developmental defects, and chromosomal abnormalities. Before fetal viability, the management of the surviving co-twin in a dichorionic pregnancy includes expectant management, in addition to close surveillance for preterm labor, fetal well-being, and fetal growth. The management of a single fetal demise in a monochorionic twin pregnancy is more complicated. The surviving co-twin is at high risk for ischemic multiorgan and neurologic injury that is thought to be secondary to hypotension or thromboembolic events. Fetal imaging by ultrasonography or magnetic resonance imaging (MRI) may demonstrate neurologic injury but would not exclude a poor outcome if normal.

C. Shortened cervix occurs more commonly in multigestational pregnancies.

D. Placental abruption risk rises as the number of fetuses per pregnancy increases. In a large retrospective cohort study, the incidence of placental abruption was 6.2, 12.2, and 15.6 per 1,000 pregnancies in singletons, twins, and triplets, respectively.

E. Preterm premature rupture of membranes complicates 7% to 10% of twin pregnancies compared with 2% to 4% of singleton pregnancies. **Preterm labor and birth** occur in approximately 57% of twin pregnancies and more than 90% of higher order multiple gestations.

F. Pregnancy-induced hypertension (PIH) and preeclampsia are 2.5 times more common in multifetal pregnancies compared with singleton pregnancies.

G. Cesarean delivery. Approximately 66% of patients with twins and 91% of patients with triplets have cesarean delivery. Breech position of one or more fetuses, cord prolapse, and placental abruption are factors that account for the increased frequency of cesarean deliveries for multiple gestations.

VII. FETAL AND NEONATAL COMPLICATIONS

A. Prematurity and low birth weight. The average duration of gestation is shorter in multifetal pregnancies and further shortens as the number of fetuses increases. The mean gestational age at birth is 39, 35, 32, and 30 weeks, respectively, for singletons, twins, triplets, and quadruplets. The likelihood of a birth weight <1,500 g is 8, 31, and more than 50 times greater in twins, triplets, and higher order multiples, respectively, compared with singletons.

B. Intrauterine growth restriction (IUGR). Fetal growth is independent of the number of fetuses until approximately 30 weeks' gestation, after which growth of multiples gradually falls off compared with singletons. IUGR is defined as an estimated fetal weight (EFW) less than either the 3rd percentile for gestational age or an EFW <10th percentile for gestational age with evidence

of fetal compromise. The mechanisms are likely uterine crowding, limitation of placental perfusion, anomalous umbilical cord insertion, infection, fetal anomalies, maternal complications (e.g., maternal hypertension), and monochorionicity. Monochorionic twins are more likely than dichorionic twins to have IUGR and have higher perinatal mortality.

C. Fetal growth discordance is typically defined as a difference in birth weight of more than 20% of the larger twin's weight. It can also be categorized as mild (<15%), moderate (15% to 30%), or severe (>30%). Risk factors for discordant growth include monochorionic placentation associated with velamentous cord insertion, placental dysfunction, preeclampsia, antepartum bleeding, twin-to-twin transfusion syndrome (TTTS), fetal infection, and fetal structural and chromosomal abnormalities. The smaller twin has an increased risk of fetal demise, perinatal death, and greater incidence of postnatal morbidities associated with prematurity.

D. Intrauterine fetal demise (IUFD) refers to fetal demise after 20 weeks' gestation but before delivery and is confirmed by ultrasonographic evidence of absent fetal cardiac activity. The death of one twin, which occurs in 9% of multiple pregnancies, is less common in the second and third trimesters. The risk of IUFD is 3 to 4 times greater in MZ pregnancies compared to DZ pregnancies. Because almost all MZ twins have placental vascular connections with resulting shared circulations, there is a significant risk (20% to 40%) of neurologic injury in the surviving co-twin as a result of associated severe hypotension or thromboembolic events upon death of the co-twin. Because their circulation is not shared, the death of one DZ twin usually has a lesser adverse effect on the surviving co-twin compared to MZ twin loss. The DZ co-twin is either completely resorbed if death occurs in the first trimester or is compressed between the amniotic sac of its co-twin and the uterine wall (fetus papyraceous). Other complications involving the surviving co-twin include stillbirth, preterm birth, placental abruption, and chorioamnionitis. The risk of fetal loss of the second twin is much higher in MZ twins (15%) when compared to DZ twins (3%). In the event of the demise of one monochorionic twin, decision regarding the timing of delivery of the co-twin is based on factors including gestational age, well-being of surviving twin, and maternal condition. Early delivery may not alter morbidity for the surviving twin as neurologic injury is thought to occur at the time of the co-twin's death.

E. Congenital malformations are more common in multifetal pregnancies. The risk in MZ twins is approximately threefold to fivefold greater than in DZ twins or singletons, and each DZ twin carries the same risk of congenital anomalies as a singleton. Structural defects specific to MZ twins include (i) early malformations that share a common origin with the twinning process, (ii) vascular disruption syndromes, and (iii) deformations.

1. **Early structural defects** include the following:
   - **a.** Caudal malformations (sirenomelia, sacrococcygeal teratoma)
   - **b.** Urologic malformations (cloacal or bladder exstrophy)
   - **c.** The vertebral anomalies, anal atresia, cardiac, tracheoesophageal, renal, and limb defects (VACTERL) spectrum
   - **d.** Neural tube defects (anencephaly, encephalocele, or holoprosencephaly)
   - **e.** Defects of laterality (situs inversus, polysplenia, or asplenia)

2. **Vascular disruption syndromes** may occur early or late in gestation.
   a. The presence of large vascular anastomoses between two embryos early in development may cause unequal arterial perfusion resulting in **acardiac twin or twin reversed arterial perfusion (TRAP) sequence**. In this condition, one embryo receives only low-pressure blood flow through the umbilical artery and preferentially perfuses its lower extremities. Profound malformations can result ranging from complete amorphism to severe upper body abnormalities such as anencephaly, holoprosencephaly, rudimentary facial features and limbs, and absent thoracic or abdominal organs. The co-twin is usually well formed. Acardia is rare, occurring in 1% monoamniotic twin pregnancies. Loss of pregnancy with TRAP sequence is 35% to 50%, and perinatal mortality in the pump twin is 50%, most often due to high output heart failure. Interruption of perfusion to the acardiac twin in the first half of the pregnancy can significantly improve survival of the pump twin. Multiple fetoscopic techniques are used, and survival rate of the pump twin is reported to be 70% to 85%. Both the best technique and the timing of the procedure (13 to 15 weeks vs. 16 weeks or after) are uncertain; the latter is the subject of an ongoing multicenter trial.
   b. Vascular disruptions that occur later in gestation are due to embolic events or the exchange of tissue between twins through placental anastomoses. Late vascular disruptions often occur after the demise of one fetus. Resulting malformations include cutis aplasia, limb interruption, intestinal atresia, gastroschisis, anorchia or gonadal dysgenesis, hemifacial microsomia, Goldenhar syndrome (facio-auriculo-vertebral defects), or Poland sequence (anomaly of chest wall and ipsilateral upper extremity). Cranial abnormalities include porencephalic cysts, hydranencephaly, microcephaly, and hydrocephalus.
3. **Deformations** such as clubfoot, dislocated hips, and cranial synostosis are more frequent in multiple pregnancies as a result of overcrowding of the intrauterine environment.
4. **Surveillance.** Twin pregnancies should be evaluated for anomalies by fetal ultrasonography; fetal echocardiography and/or fetal MRI may be considered if ultrasound is concerning. Congenital anomalies are concordant only in a minority of cases, even in MZ twins. Whether specific assisted reproductive techniques result in an increased incidence in congenital birth defects requires further study.

F. Chromosomal anomalies occur at a higher frequency in multifetal gestations. **Advanced maternal age** contributes to this increased risk. The risk in MZ twins is equivalent to that of a singleton. The risk in DZ twins is independent for each fetus.

G. Conjoined twins result when incomplete embryonic division occurs late after day 14 postconception. At this time, differentiation of the chorion and amnion has occurred, and therefore, conjoined twins are seen only in monochorionic monoamniotic twins. Conjoined twins are rare and occur in approximately 1 in 50,000 to 1 in 100,000 births. The most common sites of fusion are the chest and/or abdomen. Survival is rare when there is cardiac or cerebral fusion. Ultrasonography and/or fetal MRI can define the fetal anatomy and help determine management options. Polyhydramnios can affect as

many as 50% of cases of conjoined twins and may require amnioreduction. Elective cesarean delivery close to term is recommended. Decisions regarding separation are complex and depend on anatomic factors, associated anomalies, and parental wishes.

H. TTTS occurs only in monochorionic gestations.

1. The **pathophysiology** of TTTS is not completely understood, but placental vascular anastomoses and unequal placental sharing are required for the disease to develop. Abnormal umbilical cord insertions are also often found, particularly in the donor twin. Vascular connections occur in 85% of monochorionic placentas, but only 10% to 15% of MZ pregnancies are affected by TTTS. The vascular connections include superficial arterial-to-arterial (AA) and venous-to-venous (VV) anastomoses with bidirectional flow and deep interfetal artery-to-vein (AV) communications with unidirectional flow located in the placental cotyledons that are supplied by one fetus and drained by the other. The number and type of anastomoses affect whether the exchange of blood between the twins is balanced or unbalanced. AA connections are thought to be protective, associated with a reduction in the risk of developing chronic TTTS; AV anastomoses with unidirectional flow lead to shunting of blood from one twin to the other and are associated with worse perinatal outcome. One fetus (**the donor**) slowly pumps blood into the co-twin's circulation (**the recipient**). Complications in the donor include anemia, hypovolemia and resultant activation of the renin-angiotensin-aldosterone system, growth restriction, brain ischemia, renal hypoperfusion and insufficiency, oligohydramnios ("stuck twin"), lung hypoplasia, limb deformation, and high risk of fetal demise. Complications in the recipient include polycythemia, thrombosis, cerebral emboli, disseminated intravascular coagulation (DIC), polyhydramnios, progressive cardiomyopathy due to volume overload, and fetal hydrops.
2. **Diagnosis** is usually made between 16 and 26 weeks' gestation, but the process may occur as early as 13 weeks. Severe cases of TTTS have signs before 20 weeks' gestation and have a mortality rate in at least one fetus of 80% to 100% if left untreated. **Diagnostic criteria** for TTTS include monochorionicity, polyhydramnios in the sac of one twin (the recipient) and oligohydramnios in the sac of the other twin (the donor), umbilical cord size discrepancy, cardiac dysfunction in the polyhydramniotic twin, abnormal umbilical artery and/or ductus venosus Doppler velocimetry, and significant growth discordance (>20%). These findings are suggestive of TTTS, although not all are necessary for a diagnosis. Several staging systems have been used to classify disease severity and progression of disease and provide criteria for escalation of care to a specialty referral center and a framework to evaluate therapeutic trials. The most commonly used system is the Quintero staging system. This system is based on a series of ultrasonographic findings and does not include fetal echocardiographic findings. Staging criteria that include fetal echocardiography have been developed and are used in some centers.
3. **Fetal treatment** interventions depend on the gestational age and stage at the time TTTS is identified. Many pregnancies with stage 1 TTTS can be managed expectantly as some will stabilize or regress; however,

the risk of progression of disease makes management controversial. Most cases are detected in the second trimester at more advanced stages. Fetoscopic laser photocoagulation of placental anastomoses for stages 2 to 4 at <26 weeks' gestation has become standard of care. In the hallmark Eurofetus trial that included 142 women, laser treatment improved perinatal survival (76% vs. 56%) and decreased cystic periventricular leukomalacia (6% vs. 14%), and infants were more likely to have no neurologic complications at 6 months of age compared to serial amnioreduction. The success of laser ablation is dependent on identification of most, if not all, of the troublesome AV anastomoses. Failure to interrupt the pathologic connections can lead to TTTS recurrence or twin anemia polycythemia sequence (TAPS). To minimize recurrence, some centers use a Solomon method, which "connects the dots" of ablated anastomoses across the placenta from edge to edge to interrupt any anastomoses that were not seen. This technique has been associated with an increase in placental abruption, but survival rates in one or both twins is unchanged when compared to selective laser photocoagulation of anastomoses.

4. **Neonatal management** may include **resuscitation** at birth and need for ventilatory and cardiovascular support, rapid establishment of **intravascular access** for volume expansion to treat hypotension, correction of hypoglycemia, red blood cell transfusion to treat anemia, and **partial exchange transfusion** in the recipient to treat significant polycythemia. **Neuroimaging** should be performed to detect central nervous system (CNS) injury.

I. Velamentous cord insertion and vasa previa occur more often in twins than singletons and even more in higher order gestations. Contributing factors may include placental crowding and abnormal blastocyst implantation. All types of placentation can be affected. With velamentous cord insertion, vessels are unprotected by Wharton jelly and are more prone to compression, thrombosis, or disruption, leading to fetal distress or hemorrhage.

J. The perinatal mortality in monochorionic monoamniotic twins is reported to be as high as 40% due to umbilical cord entanglements and compression, congenital anomalies, preterm birth, and IUGR. The risk of fetal loss increases with gestational age, so most monochorionic monoamniotic twins are delivered electively at 32 to 34 weeks.

VIII. OUTCOMES

A. Neonatal mortality. Twin birth is associated with an increased risk of neonatal mortality compared to singleton births at all gestational ages. As with singleton births, preterm birth contributes substantially to mortality. In addition, the risk of stillbirth in twin pregnancies increases with advancing gestational age, so the American College of Obstetricians and Gynecologists recommends delivery of uncomplicated twins at 38 weeks' gestation if spontaneous labor/delivery has not occurred. Prematurity and low birth weight are the predominating factors that increase the rates of mortality and morbidity for multiple births.

B. Short-term morbidity. **Prematurity and growth restriction** are associated with increased risk of morbidities such as bronchopulmonary dysplasia, necrotizing enterocolitis, retinopathy of prematurity, and intraventricular hemorrhage (IVH) (see Chapters 27, 34, 54, and 67).

C. Long-term morbidity such as cerebral palsy (CP) and other neurologic handicaps affect more twins and higher order multiples than singletons. The risk of CP in multiples compared with singleton gestations is increased 5- to 10-fold. Twins account for 5% to 10% of all cases of CP in the United States. Death of a co-twin is considered an independent risk factor for CP in the surviving twin. Other risk factors for CP in twins include monochorionicity, severe birth weight discordance, TTTS, and artificial reproductive technology. Among extremely low birth weight (ELBW) infants, the frequency of CP is not significantly different between singletons and twins. In addition, the frequencies of chronic lung disease and IVH are not significantly different between singletons and twins ≤28 weeks' gestation. Twins have a greater risk of learning disabilities even after controlling for CP and low birth weight.

D. Impact of ART on outcomes. Adverse maternal and perinatal outcomes have been associated with ART. However, the extent to which the increased frequency of multiple births following ART (~44% with ART vs. ~3% with natural conception) contribute to this risk requires further study. Population-based studies in the United States demonstrate an increased risk of adverse perinatal outcomes in twin versus singleton ART births and non-ART twins, including prematurity, low birth weight, and very low birth weight. The rates of cesarean delivery are also increased in ART twins. Although multiple gestation overall is associated with an increased risk of neurodevelopmental abnormalities, this risk is similar in spontaneously conceived and ART multiples and is independent of the type of assisted reproduction. Studies evaluating the increased risk of birth defects among ART births have been inconsistent. However, a number of studies have demonstrated up to a twofold increased risk of congenital anomalies among ART births following either IVF or intracytoplasmic sperm injection (ICSI). Cardiac, urogenital, as well as ocular birth defects have been reported with ART. In addition, rare imprinting disorders have been reported with ART including Beckwith-Wiedemann syndrome (BWS) and Angelman syndrome.

E. Economic impact. Health care costs associated with twins and higher order multiples are substantially greater than singleton infants. Costs are largely influenced by preterm birth and the contribution of ART to multiple birth rates.

F. Social and family impact. Caring for twins or higher order multiples contributes to increased marital strain, financial stress, parental anxiety, and depression. Multiples are more likely to have medical complications (i.e., prematurity, congenital defects, IUGR) that result in prolonged hospital stays and contribute further to a family's emotional and financial stress. Social services and assistance from additional caregivers and family members can help parents cope with the increased amount of care required by multiples. Organizations of parents of multiples can provide advice and emotional support that can further help new parents of multiples cope.

Suggested Readings

American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Obstetrics, Society for Maternal–Fetal Medicine. Practice Bulletin No. 169: multifetal gestations: twin, triplet and higher-order multifetal pregnancies. *Obstet Gynecol* 2016;128(4):e131–e146.

Bliss JM, Carr SR, De Paepe ME, et al. What—and why—the neonatologist should know about twin-to-twin transfusion syndrome. *Neoreviews* 2017;18(1):e22–e32.

12 Maternal Substance Use, Infant Exposure, and Neonatal Opioid Withdrawal Syndrome

Lauren A. Sanlorenzo and Stephen W. Patrick

KEY POINTS

- Standardized verbal screening for substance use should occur in every pregnancy, ideally in the first trimester.
- Every birth hospital should have a protocol in place to screen, evaluate, and treat substance-exposed infants.
- The syndrome of drug withdrawal following opioid exposure during pregnancy is called neonatal opioid withdrawal syndrome (NOWS).
- An opioid (e.g., morphine, methadone, buprenorphine) should be the first choice for opioid withdrawal if pharmacotherapy is required for NOWS.

I. MATERNAL DRUG USE

A. Use of illicit substances. Data from the 2019 National Survey on Drug Use and Health (NSDUH) suggest that at least 5.8% of pregnant women use illicit drugs in pregnancy. Illicit drug use is highest among younger women, with the highest rate (12.7%) among 15- to 17-year-old girls. Overall, the rate of illicit drug use in pregnant women is nearly a third of the general population (16.6%), and women are less likely to use in the third trimester (3.3%). This suggests that, although illicit drug use in pregnancy is common, becoming pregnant may motivate some women to engage in treatment of substance use disorders. NSDUH reports the most common illicit substances used in the past month in the United States as a percentage of the population older than 12 years old are marijuana (11.5%), psychotherapeutics used illicitly (1.9%), opioids (1.1%), cocaine (0.7%), hallucinogens (0.7%), methamphetamine (0.4%), inhalants (0.3%), and heroin (0.2%).

B. Maternal use and misuse of legal substances. The use of prescription medicines in pregnancy grew by nearly 70% over the last three decades. Pregnant women use an average of 1.8 prescription medications, and data on risk of fetal effects are limited for many. Prescribed medications include atypical antipsychotics (e.g., risperidone), antidepressants (e.g., sertraline),

and opioid (e.g., hydrocodone). In addition, NSDUH reports high use (in last month) by pregnant women of alcohol (4.8%) and cigarettes (9.6%). The Centers for Disease Control and Prevention website Treating for Two (http://www.cdc.gov/pregnancy/meds/treatingfortwo/) provides information to support safer medication use in pregnancy.

II. DIAGNOSIS OF DRUG USE IN PREGNANCY. A comprehensive medical and social history should be obtained from the mother with every newborn evaluation and include use of illicit drugs, prescription drugs, tobacco, and alcohol. The American College of Obstetricians and Gynecologists recommends use of a validated screening tool for drug use such as the 4 *P*'s for adults or CRAFFT tool for adolescents (Table 12.1). This history can be augmented by communication with obstetric providers and, when available, the state's prescription drug monitoring program database.

A. Accurate information regarding illicit drug use may be difficult to obtain. Limited literature is available to inform the decision to test; however, many institutions are guided by nonspecific maternal and infant associations with illicit drug use that include the following:

1. Maternal
   - **a.** Poor or no prenatal care
   - **b.** Preterm labor
   - **c.** Placental abruption
   - **d.** Precipitous delivery
2. Infant
   - **a.** Small for gestational age
   - **b.** Intrauterine growth restriction
   - **c.** Microcephaly
   - **d.** Neonatal stroke

B. Toxicology testing can be useful to supplement standardized verbal screening tools. Testing should be considered when there is uncertainty in the diagnosis or if it will inform infant management. Pregnant women in treatment for substance use disorder have frequent toxicology testing. In this case, infant toxicology testing may not be necessary as it would not provide additional information. It is important to know state, local, and institutional reporting requirements to child welfare agencies for positive test results as laws may be interpreted differently among jurisdictions.

1. **Urine** testing is a quick, noninvasive way to test for recent drug exposure in the neonate. For example, cocaine will appear in the urine up to 3 days after the most recent use, marijuana for 7 to 30 days, methamphetamine for 3 to 5 days, and opiates (including methadone) 3 to 5 days. Drugs administered during labor may make results difficult to interpret.
2. **Meconium testing** provides information about drug use for a longer period in pregnancy. However, collection is time intensive for nursing staff, stools can be missed, and specimens can be contaminated.
3. **Umbilical cord testing** may provide data similar to meconium, although collection and storage of the umbilical cord at birth can be resource intensive.

Table 12.1. Clinical Screening Tools for Prenatal Substance Use

4 P's

Parents: Did any of your parents have a problem with alcohol or other drug use?

Partner: Does your partner have a problem with alcohol or drug use?

Past: In the past, have you had difficulties in your life because of alcohol or other drugs, including prescription medications?

Present: In the past month have you drunk any alcohol or used other drugs?

Scoring: Any "yes" should trigger further questions.

Ewing H. A practical guide to intervention in health and social services with pregnant and postpartum addicts and alcoholics: theoretical framework, brief screening tool, key interview questions, and strategies for referral to recovery resources. Martinez (CA): The Born Free Project, Contra Costa County Department of Health Services; 1990.

CRAFFT—Screening Tool for Adolescent and Young Adult Substance Use

C Have you ever ridden in a CAR driven by someone (including yourself) who was "high" or had been using alcohol or drugs?

R Do you ever use alcohol or drugs to RELAX, feel better about yourself, or fit in?

A Do you ever use alcohol or drugs while you are by yourself, or ALONE?

F Do you ever FORGET things you did while using alcohol or drugs?

F Do your FAMILY or FRIENDS ever tell you that you should cut down on your drinking or drug use?

T Have you ever gotten into TROUBLE while you were using alcohol or drugs?

Scoring: Two or more positive items indicate the need for further assessment.

NOTICE TO CLINIC STAFF AND MEDICAL RECORDS: The information on this page is protected by special federal confidentiality rules (42 CFR Part 2), which prohibit disclosure of this information unless authorized by specific written consent.

These questions are part of the larger CRAFFT 2.1 screen.

crafft@childrens.harvard.edu. http://www.crafft.org. For more information and versions in other languages, see http://www.crafft.org.

Source: Reprinted with permission from American College of Obstetricians and Gynecologists Committee on Health Care for Underserved Women. ACOG Committee Opinion No. 524: opioid abuse, dependence, and addiction in pregnancy. *Obstet Gynecol* 2012;119(5):1070–1076.

C. Risk of infection. Illicit drug use increases the risk of infections in the pregnant woman and her infant, especially when associated with intravenous drug use or other high-risk behaviors (e.g., prostitution). The mother's HIV, hepatitis B, hepatitis C, and syphilis status should be determined, and the infant should be managed accordingly (see Chapters 48 and 51).

III. NONOPIOID SUBSTANCE EXPOSURE.

Nonopioid substance use in pregnancy (Table 12.2) may result in abnormal psychomotor behavior in the newborn that is consistent with toxicity or withdrawal.

IV. NEONATAL OPIOID WITHDRAWAL SYNDROME FOLLOWING OPIOID EXPOSURE IN PREGNANCY

A. The American Academy of Pediatrics (AAP) recommends that all hospitals that care for infants at risk for withdrawal have policies in place for screening and treatment of infants that includes nonpharmacologic measures such as rooming-in and breastfeeding. Neonatal opioid withdrawal syndrome (NOWS) can result from a variety of opioids including prescription opioids (e.g., hydrocodone), illicit opioids (e.g., heroin), or medication for opioid use disorder (e.g., methadone, buprenorphine). Although medications for opioid use disorder in pregnancy increase an infant's risk of NOWS, the risk of preterm birth or low birth weight is less than with untreated opioid use disorder. As a result, the American College of Obstetricians and Gynecologists and the National Academy of Medicine recommend use of these medications for opioid use disorder.

B. An infant's risk of drug withdrawal and its severity varies by opioid type and the presence of additional exposures. Methadone has the greatest risk, followed by progressively less risk with buprenorphine, a long-acting opioid (morphine sulfate extended release), and then a short-acting opioid (hydrocodone). Adjunctive use of tobacco, selective serotonin reuptake inhibitors, atypical antipsychotics, and benzodiazepines increase the likelihood of NOWS or increase its severity.

C. Timing of presentation. The initial presentation of NOWS depends on when the woman last used the drug before delivery, infant metabolism, and half-life of the opioid used. In addition, for uncertain reasons, not all infants develop withdrawal. As a result, the AAP recommends that all opioid-exposed infants be observed in the hospital for signs of withdrawal for 3 to 7 days after birth, depending on exposure half-life.

D. Site of care. Increasing evidence shows that processes of care that keep mother and infant together (e.g., rooming-in), promote bonding, and encourage breastfeeding may reduce infant symptomatology and decrease NOWS severity. Where possible, infants should not be separated from their mothers. Care in a mother–baby unit is preferable to neonatal intensive care unit (NICU) admission.

E. Assessment. Infants at risk for drug withdrawal should be assessed using an available scoring tool. Commonly used tools include the modified Finnegan Neonatal Abstinence Score Tool (NAST) and a modification of the Finnegan scale created from the Maternal Opioid Treatment: Human Experimental

Table 12.2. Onset and Duration of Clinical Signs Consistent with Neonatal Withdrawal after Intrauterine Substance Exposure (Excluding Narcotics)

Drug	Signs	Onset of Signs	Duration of Signs*
Alcohol	Hyperactivity, crying, irritability, poor suck, tremors, seizures; onset of signs at birth, poor sleeping pattern, hyperphagia, diaphoresis	3–12 hours	18 months
Barbiturates	Irritability, severe tremors, hyperacusis, excessive crying, vasomotor instability, diarrhea, restlessness, increased tone, hyperphagia, vomiting, disturbed sleep; onset first 24 hours of life or as late as 10–14 days of age	1–14 days	4–6 months with prescription
Caffeine	Jitteriness, vomiting, bradycardia, tachypnea	At birth	1–7 days
Chlordiazepoxide	Irritability, tremors; signs may start at 21 days	Days–weeks	9 months; 1 1/2 months with prescription
Clomipramine	Hypothermia, cyanosis, tremors; onset 12 hours of age		4 days with prescription
Diazepam	Hypotonia, poor suck, hypothermia, apnea, hypertonia, hyperreflexia, tremors, vomiting, hyperactivity, tachypnea (mother receiving multiple drug therapy)	Hours–weeks	8 months; 10–66 days with prescription
Ethchlorvynol	Lethargy, jitteriness, hyperphagia, irritability, poor suck, hypotonia (mother receiving multiple drug therapy)		Possibly 10 days with prescription

(continued)

Table 12.2. Onset and Duration of Clinical Signs Consistent with Neonatal Withdrawal after Intrauterine Substance Exposure (Excluding Narcotics) ***(Continued)***

Drug	Signs	Onset of Signs	Duration of Signs*
Glutethimide	Increased tone, tremors, opisthotonos, high-pitched cry, hyperactivity, irritability, colic		6 months
Hydroxyzine	Tremors, irritability, hyperactivity, jitteriness, shrill cry, myoclonic jerks, hypotonia, increased respiratory and heart rates, feeding problems, clonic movements (mother receiving multiple drug therapy)		5 weeks with prescription
Meprobamate	Irritability, tremors, poor sleep patterns, abdominal pain		9 months; 3 months with prescription
SSRIs	Crying, irritability, tremors, poor suck, feeding difficulty, hypertonia, tachypnea, sleep disturbance, hypoglycemia, seizures	Hours–days	1–4 weeks

*Prescription indicates the infant was treated with pharmacologic agents, and the natural course of the signs may have been shortened.

SSRIs, selective serotonin reuptake inhibitors.

Source: Reproduced with permission from Hudak ML, Tan RC. Neonatal drug withdrawal. *Pediatrics* 2012;129(2):e540–e560. Copyright © 2012 by the American Academy of Pediatrics.

Research (MOTHER) study. The MOTHER modification tool directs assessment of common clinical signs that are weighted to reflect severity. This score is used for initiation, advancement, and weaning of pharmacotherapy for NOWS. Eat, Sleep, Console (ESC) is another scoring tool that tracks clinical signs of withdrawal by evaluating the infant's ability to eat ≥1 oz of breast milk/formula or breastfeed well, sleep undisturbed ≥1 hour, and be consoled. If these criteria are not met, the clinical team meets, assesses the

environment and nonpharmacologic approaches, and considers initiating or escalating pharmacotherapy. ESC is appealing because it is simple and easy to use but has not been studied outside of quality improvement initiatives.

1. Signs of NOWS include the following:
   a. Central nervous system/neurologic excitability: tremors, irritability, increased wakefulness/sleep disturbance, frequent yawning and sneezing, high-pitched cry, increased muscle tone, hyperactive reflexes (e.g., Moro), seizures
   b. Gastrointestinal dysfunction: poor feeding, uncoordinated and constant sucking, vomiting, diarrhea, dehydration, and poor weight gain
   c. Autonomic signs: sweating, nasal stuffiness, fever/temperature instability, and mottling

F. Management. Infants with signs of withdrawal are treated based on NAST/MOTHER/ESC scores. Treatment begins with nonpharmacologic measures. Engaging caregivers in nonpharmacologic care promotes bonding and is a foundational component of care. Nonpharmacologic treatment should be individualized to address the behavioral and physiologic needs of the infant. For example, an infant experiencing overreactivity to visual stimulation may benefit from a dimly lit room, whereas an infant with hypertonia may benefit from swaddling. Infants with severe withdrawal are treated with an opioid (morphine or methadone) as a first-line agent. An example of how to use the MOTHER scoring tool is outlined below and shown in Table 12.3.

1. Nonpharmacologic interventions are implemented for MOTHER scores <8.
   a. Decrease stimulation by reducing lights, noise, and touch.
   b. Promote infant self-regulation by encouraging pacifier use, nonnutritive sucking, and swaddling.
   c. Room in with mother if possible.
   d. Encourage holding, especially skin to skin.
   e. Encourage breastfeeding.

2. Pharmacologic interventions are implemented based on MOTHER scores >8. Infants are scored every 3 to 4 hours before feeds. Reassessment and "rescore" occurs immediately after a feed or within 1 hour after feeding. Pharmacotherapy is initiated for a MOTHER score ≥ 13 on initial assessment or if the neonate scores 9 to 12 on the rescore. Infants treated with an opioid should have continuous cardiac and respiratory monitoring, particularly in the initial period, to detect any signs of respiratory depression.
   a. Morphine is used as the first-line drug. Dosing interval is 3 to 4 hours depending on the care and feeding schedule of the infant (e.g., a baby feeding every 4 hours could be dosed every 4 hours). However, dosing interval should not exceed 4 hours once treatment has been initiated.
      i. Morphine dose is adjusted based on the MOTHER score as shown in Table 12.3.
   b. Weaning begins after an infant is stable on maintenance morphine dose for 48 hours.
      i. If the MOTHER score is 0 to 8, wean by 0.02-mg morphine every day. Weaning is deferred for scores 9 to 12. If infant has

Table 12.3. Morphine Initiation, Maintenance, Weaning, and Reescalation from the MOTHER Trial Modification of the Finnegan Score

Morphine Initiation Process	
If initial score is 9–12, rescore after feeding or within the hour.	If rescore is 9–12, start treatment based on highest score. If rescore is 0–8, do not start treatment.
If initial score is ≥13	Start treatment without rescore.
Morphine Initiation Dosing: Dose is given every 3–4 hours with feeds.	
Score	**Morphine Dose for Initiation**
0–8	0
9–12	0.04 mg per dose
13–16	0.08 mg per dose
17–20	0.12 mg per dose
21–24	0.16 mg per dose
25 or above	0.20 mg per dose
Morphine Maintenance	
Score	**Morphine Dose**
0–8	Maintain dose, no change.
9–12 (rescore before changing dose)	0.02 mg
13–16	0.04 mg
17–20	0.06 mg
Morphine Weaning: Maintain on dose 48 hours before starting to wean.	
Score	**Morphine Wean per Day**
0–8	0.02 mg
9–12	Defer wean.
Reescalation: If neonate scores 9–12, rescore after a feed or within the hour.	
If rescore 9–12	Increase morphine 0.01 mg per dose
If 2 consecutive scores 13–16	Increase morphine 0.02 mg per dose
If 2 consecutive scores 17–20	Increase morphine 0.04 mg per dose

MOTHER, Maternal Opioid Treatment: Human Experimental Research.

Source: Adapted from Jones HE, Kaltenbach K, Heil SH, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med* 2010;363(24):2320–2331.

a score >9 during the weaning process, the team should assess whether reescalation is needed.

ii. Reescalation

a) If infant scores 9 to 12, repeat score.

b) If second score is 9 to 12, increase morphine by 0.01 mg per dose.

c) If two consecutive scores are 13 to 16, increase morphine does by 0.02 mg per dose.

d) If two consecutive scores are 17 to 20, increase morphine dose by 0.04 mg per dose.

3. Educational interventions

a. Caregivers and families should be provided verbal and written education about NOWS.

b. Families should receive communication about the plan of care, a safety plan and referral to social service, and the appropriate state agency when indicated.

V. BREASTFEEDING OF SUBSTANCE-EXPOSED INFANTS.

In addition to its advantages in nonexposed infants (see Chapter 22), breastfeeding of substance-exposed infants can enhance maternal–infant bonding and can reduce withdrawal severity and duration in infants with NOWS.

A. We encourage breastfeeding in the following circumstances:

1. Mother is in treatment for substance use and allows newborn providers to discuss progress in treatment and plans for postpartum treatment with her substance abuse provider.
2. Substance use disorder treatment provider endorses that mother has been able to achieve and maintain sobriety prenatally.
3. Mother plans to continue in treatment in the postpartum period.
4. Mother has abstained from illicit drug use or licit substance misuse for 90 days prior to delivery and demonstrates the ability to maintain sobriety in an outpatient setting as follows:

a. Negative maternal urine toxicology testing at delivery except for prescribed medications

b. Received consistent prenatal care

c. No medical contraindication to breastfeeding (such as HIV)

d. Not taking a psychiatric medication that is contraindicated during lactation

e. Stable on methadone or buprenorphine (regardless of dose)

B. We discourage breastfeeding in the following circumstances:

1. Illicit drug use or licit substance misuse in the 30-day period prior to delivery. In some cases, breastfeeding may be permissible for mothers with illicit drug use in the previous 30 days if the mother is not currently using and has engaged in treatment and the provider team, including the infant's provider and the mother's substance use treatment provider, deem it appropriate.

2. Active substance use while not in substance use disorder treatment or refusal to allow communication with substance use treatment provider
3. Positive maternal urine toxicology testing for misuse of licit or use of illicit substances at delivery
4. No confirmed plans for postpartum substance use treatment or pediatric care
5. Erratic behavioral or other indicators of active drug use
6. No prenatal care

C. We evaluate for breastfeeding in the following circumstances:

1. Relapse to illicit substance use or licit substance misuse in the 90- to 30-day period prior to delivery but abstinent for the 30 days prior to delivery
2. Concomitant use of other prescription (i.e., psychotropic) medications
3. Sobriety obtained in an inpatient setting
4. Isolated marijuana use: The literature to support breastfeeding in the context of marijuana use is limited; some data suggest long-term cognitive/developmental delays for exposed infants. We, therefore, inform the mother that the effects of marijuana use are not well understood and may cause cognitive/developmental delays in her infant. If the mother is aware of this risk and wishes to breastfeed, she is allowed and is encouraged to discontinue marijuana use.

VI. DISCHARGE.

Clinical signs of NOWS may last for months, and infants with NOWS are 2.5 times as likely as uncomplicated term infants to be readmitted to the hospital within 30 days of discharge. The following interventions help ensure a safe discharge home:

A. Pediatrician follow-up within a few days of discharge

B. Home nurse visitation where available

C. Communication with child protective services when applicable

D. Referral to early intervention services

E. Parental education

1. Clinical signs of NOWS
2. How to seek help
3. Relevant community resources

F. Ideally, infant care would be coordinated with maternal care (e.g., addiction medicine, obstetrics).

VII. LONG-TERM OUTCOMES.

Data for long-term infant outcomes of substance use in pregnancy are limited but are summarized in Table 12.4.

Table 12.4. Short- and Long-Term Effects of Substance Use in Pregnancy

	Nicotine	Alcohol	Marijuana	Opiates	Cocaine	Methamphetamine
Short-term effects/birth outcome						
Fetal growth	Effect	Strong effect	No effect	Effect	Effect	Effect
Anomalies	No consensus on effect	Strong effect	No effect	No effect	No effect	No effect
Withdrawal	No effect	No effect	No effect	Strong effect	No effect	*
Neurobehavior	Effect	Effect	Effect	Effect	Effect	Effect
Long-term effects						
Growth	No consensus on effect	Strong effect	No effect	No effect	No consensus on effect	*
Behavior	Effect	Strong effect	Effect	Effect	Effect	*
Cognition	Effect	Strong effect	Effect	No consensus on effect	Effect	*
Language	Effect	Effect	No effect	*	Effect	*
Achievement	Effect	Strong effect	Effect	*	No consensus on effect	*

*Limited or no data available.

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Suggested Readings

American College of Obstetricians and Gynecologists Committee on Health Care for Underserved Women. ACOG Committee Opinion No. 524: opioid abuse, dependence, and addiction in pregnancy. *Obstet Gynecol* 2012;119(5):1070–1076.

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13 Initial Care of the Extremely Low Birth Weight Infant

Lori A. Christ

KEY POINTS

- If possible, extremely premature infants should be delivered in a facility with a high-risk obstetrical service and a level 3 or 4 neonatal intensive care unit (NICU).
- Uniformity of approach within an institution and a commitment to provide and evaluate care in a collaborative manner across professional disciplines may be the most important aspects of protocols for the care of extremely low birth weight (ELBW) infants.
- Careful attention to detail and frequent monitoring are the basic components of care of the ELBW infant because critical changes can occur rapidly.

I. INTRODUCTION. Extremely low birth weight (ELBW; birth weight <1,000 g) infants are a unique group of patients in the neonatal intensive care unit (NICU). Because these infants are so physiologically immature, they are extremely sensitive to small changes in respiratory management, blood pressure, fluid administration, nutrition, and virtually all other aspects of care. The optimal way to care for these infants continues to be determined by ongoing research. However, the most effective care based on currently available evidence is best ensured through the implementation of standardized protocols for the care of the ELBW infant within individual NICUs. One approach is outlined in Table 13.1. Uniformity of approach within an institution and a commitment to provide and evaluate care in a collaborative manner across professional disciplines may be the most important aspects of such protocols.

II. PRENATAL CONSIDERATIONS. Whenever possible, ELBW infants should be delivered in a facility with a high-risk obstetrical service and a level 3 or 4 NICU; the value of this practice in preventing mortality and morbidity in ELBW infants has been demonstrated in several studies. The safety of maternal transport must of course be weighed against the risks of infant transport (see Chapter 17). Prenatal administration of corticosteroids to the mother, even if there is not time for a full course, reduces the risk of respiratory

Table 13.1. Elements of a Protocol for Standardizing Care of the Extremely Low Birth Weight Infant

Prenatal Consultation
Parental education
Determining parental goals of care when viability is questionable
Defining limits of parental choice; need for caregiver–parent teamwork
Delivery Room Care
Define limits of resuscitative efforts.
Respiratory support
Low tidal volume ventilation strategy
Prevention of heat and water loss
Ventilation Strategy
Low tidal volume, short inspiratory time
Avoid hyperoxia and hypocapnia.
Surfactant therapy as indicated
Define indications for high-frequency ventilation.
Fluids
Early use of humidified, double-walled isolette to aid in thermoregulation
Judicious use of fluid bolus therapy for hypotension
Careful monitoring of fluid and electrolyte status
Use of CVL to optimize nutritional and fluid support
Nutrition
Initiation of parenteral nutrition shortly after birth
Early initiation of trophic feeding with human milk
Advancement of feeding density to provide adequate calories for growth
Cardiovascular Support
Maintenance of blood pressure within standard range
Use of dopamine for support as indicated
Corticosteroids for unresponsive hypotension

(continued)

Table 13.1. *(Continued)*
PDA
Avoidance of excess fluid administration
Consider medical therapy when hemodynamically significant PDA is present.
Consider surgical intervention after failed medical therapy.
Infection Control
Meticulous hand hygiene and attention to infection prevention protocols
Limiting blood drawing, skin punctures
Protocol for CVL insertion and care, minimize dwell time
Minimal entry into CVLs
Family Support
Communication and education
Postpartum depression screening
Promote kangaroo and developmentally appropriate care
CVL, central venous line; PDA, patent ductus arteriosus.

distress syndrome (RDS) and other sequelae of prematurity and is strongly recommended.

A. Neonatology consultation. If delivery of an extremely premature infant is threatened, a neonatologist should consult with the parents, preferably in collaboration with the obstetrics team. There are no reliable prognostic scores that allow definitive predictions about short- and long-term outcomes, in part because outcomes are also affected by variable approaches to active resuscitation of these infants. The most useful current data is based on analysis of ELBW infants born in NICUs participating in the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network. In this cohort, survival free from neurodevelopmental disability for infants born between 22 and 25 weeks of gestation was dependent not only on completed weeks of gestation but also on (i) sex, (ii) birth weight, (iii) exposure to antenatal steroids, and (iv) singleton or multiple gestation. Using this model, which was subsequently validated using data from the Vermont Oxford Network (VON), the NICHD published a web-based tool to *estimate* the likelihood of survival with and without severe neurosensory disability (https://www.nichd.nih.gov/about/org/der/branches/ppb/programs/epbo/Pages/epbo_case.aspx). To use the tool, data are entered in each of the five categories

(estimated gestational age, birth weight, sex, exposure to antenatal steroids, and singleton or multiple birth). The tool calculates outcome estimates for survival and survival with moderate or severe disabilities. It is helpful to use this estimator tool as a guide, combine with the experience in the individual institution, during antenatal discussions with parents. A general approach to consultation is as follows:

1. **Survival.** To most parents, the impending delivery of an extremely premature infant is frightening, and their initial concern almost always focuses on the likelihood of infant survival. Recent studies have reported that survival is possible at a gestational age as low as 22 weeks. The NICHD network reported survival rates of 6% at 22 completed weeks, 26% at 23 weeks, and 55% and 72% at 24 and 25 weeks, respectively. Other studies have reported even higher survival rates, even at 22 weeks. Assessments based solely on best obstetrical estimate of gestational age do not allow for the impact of other factors, whereas those based on birth weight (a more accurately determined parameter), don't fully account for the impact of growth restriction. The use of the NICHD estimator allows the consultant to estimate the impact and interaction between gestational maturity, weight, and the other identified critical factors. Although extremely helpful as a starting point, at least two important cautions should be considered in individual cases. First, birth weight has to be estimated for purposes of antenatal discussion, although reliable estimates are often available from ultrasonographic examinations, assuming a technically adequate examination can be performed. Second, there may be important additional information in individual cases that will significantly impact prognosis, such as the presence of congenital anomalies, infection, chronic growth restriction, or evidence of deteriorating status before birth. Clinical experience and up-to-date evidence, when available, must be used to guide interpretation of the impact of such factors.
2. **Institutional approach to periviability.** Many institutions have come to consensus, based on data that continues to emerge, on an approach to obstetric and neonatal care at a given gestational age. Consensus between the neonatal and obstetric teams should include antenatal interventions as well as delivery room resuscitation, and these interventions should be considered individually and not necessarily bundled. A sample approach is presented in Table 13.2.

   In discussions with parents, it is important to attempt to reach a collaborative decision about what course of treatment would be best for their baby. Although an attempt at initial resuscitation and stabilization of a newborn who is periviable is reasonable, the personal views of parents regarding an acceptable outcome for their child will vary and thereby impact decisions about resuscitation. Resuscitation at birth has been technically feasible at gestational ages as low as about 22 weeks and a birth weight as low as about 400 g. In an individual case, the superimposition of medical problems other than prematurity may make survival extremely unlikely or impossible even at higher gestational ages. In counseling parents, it is important to note that delivery room resuscitation alone has a high (but not absolute) chance of success, but that this

Table 13.2. Sample Approach to Obstetric and Delivery Room Intervention by Gestational Age

	<22 weeks	22 0/7–22 6/7	23 0/7–23 6/7	24 0/7–24 6/7	≥25 weeks
Antenatal steroids	Not recommended	Consider	Consider	Recommend	Recommend
Tocolysis to allow ACS administration	Not recommended	Not recommended	Consider	Recommend	Recommend
Magnesium for neuroprotection	Not recommended	Not recommended	Consider	Recommend	Recommend
Cesarean delivery	Not recommended	Not recommended	Consider	Consider	Recommend
Antibiotics for latency in PPROM when delivery not imminent	Consider after counseling, if delivery is declined	Consider after counseling, if delivery is declined	Consider after counseling, if delivery is declined	Recommend	Recommend
Offer resuscitation/ comfort care	Comfort care only	Comfort care encouraged; resuscitation considered if family desired	Resuscitation and comfort care offered	Resuscitation offered; comfort care considered if family desires	Recommend, unless other circumstances present

ACS, antenatal corticosteroids; PPROM, preterm premature rupture of membranes.

in no way guarantees survival beyond these early minutes. Studies show that decisions based on the apparent condition at birth are unreliable in terms of viability or long-term outcome. It is also important to note that the initiation of intensive care in no way mandates that it be continued if it is later determined to be futile or very likely to result in a poor long-term outcome. Parents should be assured that initial resuscitation is always followed by frequent reassessment in the NICU. In future discussions with parents, the goals of care may be redirected if the degree of immaturity results in no response to therapy or if catastrophic and irreversible complications occur. Parents are counseled that the period of highest vulnerability may last several weeks in extremely premature infants. Once these considerations are discussed, a recommendation can be made regarding an approach to initial resuscitation.

3. **Neonatal morbidity and NICU stay.** Care decisions and parental expectations must be based not only on estimates of survival but also on information about likely short- and long-term prognosis. Before delivery, particular attention is paid to the problems that might appear at birth or shortly thereafter, including the need for respiratory support. Increasingly, support includes continuous positive airway pressure (CPAP) alone, but mechanical ventilation, at least for a short period, is still required for a significant percentage of infants at the lowest gestational ages. Parents should also be informed of the likelihood of infection at birth depending on perinatal risk factors as well as any plan to screen for it and begin empiric antibiotic therapy while final culture results are pending.

   During prenatal consultation, a detailed discussion about every potential sequela of extreme prematurity is typically not feasible. However, an overview of morbidities that are most likely to occur in ELBW infants or will be screened for during hospitalization should be offered. These include apnea of prematurity, intraventricular hemorrhage (IVH), nosocomial sepsis and necrotizing enterocolitis, feeding difficulties, long-term neurodevelopmental outcomes, the risk of retinopathy of prematurity and subsequent visual deficits, and the need for hearing screening and the potential for hearing loss. Some complications are not diagnosed until late in the hospital course, but perspective on the entire hospitalization, including a very rough estimation of length of stay, can be helpful to some families.

4. **Shared decision making.** Parents are the best surrogate decision makers for their child. As discussed earlier, a uniform approach to parental requests for attempting or withholding resuscitation at very low gestational ages is recommended. The best practice is to formulate decisions in concert with parents, after providing them with clear, realistic, and factual information about the possibilities for success of therapy and its long-term outcome.

   During the consultation, the neonatologist should try to understand parental wishes about resuscitative efforts and subsequent support especially when chances for infant survival are slim. Parents should be encouraged to voice their understanding of the planned approach and their expectations for their soon-to-be born child because the strength

of their wishes can help guide caregivers in determining whether, and how long to continue resuscitation attempts. Through this approach, the parents' role in decision making as well as the limitations of that role is clarified. In practice, parents' wishes about resuscitation are central to decision making when the gestational age is <24 completed weeks. At 25 weeks and older, in the absence of other factors, most centers strongly advocate for a full trial of neonatal intensive care.

III. DELIVERY ROOM CARE. The delivery room team should include an experienced pediatrician or neonatologist, particularly when the fetus is of <26 weeks' gestational age. The approach to resuscitation is similar to that in more mature infants (see Chapter 4) in accordance with the recommendations of the Neonatal Resuscitation Program (NRP). However, special attention should be paid to the following:

A. Thermoregulation. The ELBW neonate is at high risk for hypothermia, which can lead to cold stress. The use of the following may optimize thermoregulation in the ELBW neonate: (i) wrapping the neonate in an occlusive polyethylene wrap or bag, (ii) the use of an exothermic mattress, (iii) setting the delivery room temperature at 25°C, and (iv) use of an overhead radiant warmer or open top isolette. Care must be taken to avoid overheating the neonate, especially when more than one of these modalities is employed.

B. Respiratory support. ELBW infants require some degree of ventilatory support because of pulmonary immaturity and respiratory muscle insufficiency. Blended oxygen and air should be available to help avoid prolonged hyperoxia after the initial resuscitation. Oxygenation should be monitored using a pulse oximeter probe placed on the right upper ("preductal") extremity during the resuscitation. It is recommended that resuscitation starts with 21% to 30% oxygen; oxygen saturation should be targeted per NRP guidelines over the first several minutes after birth (see Table 4.2), and thereafter, oxygen concentration should be adjusted to keep the saturation level the same as that used during NICU care for all babies <32 weeks. Electrocardiography leads should be placed as soon as possible during the resuscitation to accurately measure heart rate and guide resuscitative efforts.

Noninvasive respiratory support should be initiated immediately after birth. If the infant is breathing spontaneously, initial respiratory support can be provided via CPAP. If the infant is not breathing spontaneously, positive pressure ventilation (PPV) must be initiated and optimized per NRP guidelines. During PPV, care should be taken to use the smallest tidal volumes and peak pressure possible while still adequately ventilating the infant. Use of a T-piece device (Neopuff Infant T-Piece Resuscitator, Fisher & Paykel Healthcare, Irvine, California) is recommended in lieu of bag-and-mask ventilation or providing CPAP via bag and mask because it ensures adequate and regulated positive end-expiratory pressure and regulated inflation pressures. Administration of exogenous surfactant therapy before the first breath has not been proven to be more beneficial than administration after initial stabilization of the infant. However, if intubation is necessary, exogenous surfactant may be safely administered in the delivery room once correct

endotracheal tube position has been confirmed. Intravenous (IV) access should be obtained, and IV fluids should be administered as soon as possible after the respiratory status has been stabilized.

If the infant fails to respond to resuscitative efforts per NRP guidelines, the team should recheck that all support measures are being effectively administered and mitigating factors have been addressed as able. If there is no positive response to resuscitation after a reasonable length of time, a redirection of care to comfort measures should be offered. In all cases, communication with the parents should be maintained through a designated member of the care team.

C. Care after resuscitation. Immediately after resuscitation, the infant should be transported to the NICU in a warmed isolette. Within practical limits, parent–infant interaction should be encouraged prior to transfer to facilitate parent–infant bonding. In the NICU, the infant should remain in a heated, humidified, double-walled isolette. The infant's temperature should be rechecked and closely monitored. As soon as possible, the isolette unit should be closed. Heat and humidity should be maintained per institutional protocol to support thermoregulation and reduce insensible fluid losses.

IV. CARE IN THE INTENSIVE CARE UNIT.

Careful attention to detail and frequent monitoring are the basic components of care of the ELBW infant because critical changes occur rapidly. Insensible fluid loss, immature glucose regulation, tenuous pulmonary status, and the immaturity and increased sensitivity of all organ systems require close monitoring. Monitoring itself, however, may pose increased risks because each laboratory test requires a significant percentage of the baby's total blood volume, tiny-caliber vessels may be hard to cannulate without several attempts, and limited skin integrity increases susceptibility to injury or infection. Issues in routine care that require special attention during the first few weeks of life include the following:

A. Survival. The first several days after birth, and in particular the first 24 to 48 hours, are the most critical for survival. Infants who require significant respiratory, cardiovascular, and/or fluid support are assessed continuously, and their chances for ongoing survival are evaluated as part of this process. If caregivers and parents determine that death is imminent, continued treatment is futile, or treatment is likely to result in survival of a child with profound neurologic impairment, it is appropriate to recommend redirection of care to comfort measures.

B. Respiratory support. Most ELBW infants require respiratory support in the first days to weeks of life.

1. Noninvasive support. Many ELBW infants can achieve respiratory stability with noninvasive CPAP. It is generally initiated at 5– to 6–cm H_2O pressure, and the pressure increased in 1-cm increments to a maximum of 8 cm if the oxygen requirement remains elevated. One key to successful CPAP therapy and the prevention of atelectasis is to ensure that the CPAP is not interrupted, even briefly. There is no conclusive evidence that one mode of CPAP delivery is superior to another. If the oxygen requirement rises even after the maximal pressure has been

reached, or if there is recurrent apnea, surfactant and/or mechanical ventilation is indicated.

2. **Conventional ventilation.** Many centers use conventional pressure-limited synchronized intermittent mandatory ventilation (SIMV), usually in a volume guarantee mode, as the primary mode of mechanical ventilation (see Chapter 29). The lowest possible tidal volume to provide adequate ventilation and oxygenation and a short inspiratory time should be used. Special effort should be made to avoid hyperoxia by targeting specific oxygen saturations. Several reports have demonstrated that oxygen saturation limits for babies <32 weeks' gestation who require supplemental oxygen should be lower than those used in more mature babies, in order to limit the number of hypoxia–hyperoxia fluctuations and reduce the incidence and severity of retinopathy of prematurity. It is hypothesized that limiting hyperoxia may also reduce the incidence or severity of chronic lung disease. However, the optimal oxygen saturation target range remains uncertain. A recent report found that a target range of 85% to 89% decreased retinopathy but may be associated with an increase in mortality, compared to a range of 90% to 94%. It is important as well to avoid dramatic shifts in carbon dioxide and hypocapnia, although the potential benefit of permissive hypercapnia as a ventilatory strategy remains a subject of debate.
3. **Surfactant therapy** (see Chapter 33). Surfactant administration should be strongly considered if the neonate requires a mean airway pressure of at least 7 cm H_2O with an inspired oxygen concentration (FiO_2) of 0.4 or higher in the first 2 hours after birth. The first dose should be given as soon as possible after intubation, preferably within the first 2 hours after birth, although with increased use of CPAP as initial therapy, the timing of surfactant therapy may be delayed. Many infants treated with surfactant can be rapidly transitioned to support with CPAP shortly after surfactant administration. For larger, more mature infants, the INtubation-SURfactant-Extubation (INSURE) procedure, or minimally invasive surfactant administration (MIST), can be considered.
4. **High-frequency oscillatory ventilation (HFOV)** can be used in infants who require high mean airway pressures and/or fail to ventilate with an SIMV approach after surfactant administration. For infants with air leak syndromes, especially pulmonary interstitial emphysema (see Chapter 38), high-frequency jet ventilation may be the preferred mode of ventilation.
5. **Caffeine citrate** administered within the first 3 days after birth at standard doses has been associated with a reduced risk of developing bronchopulmonary dysplasia (BPD).
6. **Vitamin A** injections during the first 28 days of life has also been demonstrated to reduce the risk of BPD in ELBW infants.

C. **Fluids and electrolytes** (see Chapters 23 and 28). Fluid requirements increase as gestational age decreases <28 weeks. Preterm infants have both an increased surface area–body weight ratio and immaturity of the stratum corneum resulting in significant transepidermal water loss. Renal immaturity may result in large urinary losses of fluid and electrolytes that must also

be replaced. Early use of humidified isolettes significantly reduces insensible fluid losses and therefore the total administered volume necessary to maintain fluid balance, especially when care interventions are coordinated to ensure that the isolette top is only rarely opened.

1. **Route of administration.** Whenever possible, an umbilical venous line should be placed shortly after birth, along with an umbilical arterial line for infants requiring higher levels of support or those with blood pressure instability. Arterial lines generally are maintained for a maximum of 7 days and then replaced by peripheral arterial lines if needed. Because of an increased risk of infection, the dwell time for umbilical venous catheters (UVCs) in most cases is limited to 7 to 10 days. These are often replaced by percutaneously inserted central venous catheters (PICCs) if continued long-term IV access is required.
2. **Rate of administration.** Table 13.3 presents suggested initial rates of fluid administration for different gestational ages and birth weights when humidified isolettes are used. Weight, blood pressure, urine output, and serum electrolyte levels should be monitored frequently. Fluid rate is adjusted to avoid dehydration or hypernatremia. Serum electrolytes should generally be measured before the age of 12 hours (6 hours for infants <800 g) and repeat as often as every 6 hours until the levels are stable. By the second to third day, many infants have a marked diuresis and natriuresis and require continued frequent assessment and adjustment of fluids and electrolytes. Insensible water loss diminishes as the skin develops over the first few days of life.
3. **Fluid composition**

   a. Dextrose. Initial IV fluids should consist of dextrose solution in a concentration sufficient to maintain serum glucose levels >50 mg/dL. Often, immature infants do not tolerate the elevated glucose infusion rates (GIRs) that can result from high IV fluid rates with dextrose concentrations of >10%, Usually, a GIR of 4 to 6 mg/kg/minute is sufficient initially and can be advanced as blood sugar levels tolerate to 10 mg/kg/minute to provide sufficient caloric intake over the first week

Table 13.3. Suggested Initial Fluid Administration Rates and Laboratory Monitoring*

Birth Weight (g)	Gestational Age (weeks)	Fluid Rate (mL/kg/day)	Frequency of Electrolyte Testing
400–600	<24	100–120	q6h
601–800	24–25	100	q8h
801–1,000	>25	80–100	q12h

*Urine output and serum electrolytes should be closely monitored to determine optimal adjustments on an individual basis.

of life. If hyperglycemia results, lower dextrose concentrations should be administered to lower the GIR to no >4 mg/kg/minute; hypoosmolar solutions (dextrose <5%) should be avoided. If hyperglycemia persists at levels higher than 180 to 220 mg/dL with glycosuria, an insulin infusion at a dose of 0.05 to 0.1 unit/kg/hour may be initiated and adjusted as needed to maintain serum glucose levels at acceptable levels (see Chapter 24).

b. Protein. ELBW infants begin to develop a negative nitrogen balance almost immediately after birth. To avoid this, parenteral nutrition should be started immediately upon admission to the NICU for all ELBW infants using a premixed stock solution of amino acids and trace elements in dextrose. Many "starter total parenteral nutrition (TPN)" formulations also include calcium gluconate. Multivitamin solutions are not included in this initial parenteral nutrition because of shelf-life issues but are added within 24 hours after delivery. The solution is designed so that the administration of 60 mL/kg/day (the maximum infusion rate used) provides 2.5 g of protein/kg/day. Additional fluid needs are met by the solutions described earlier. Customized parenteral nutrition, including lipid infusion, is begun as soon as it is available, generally within the first day.

4. **Skin care.** Immaturity of skin and susceptibility to damage requires close attention to maintenance of skin integrity (see Chapter 65). Topical emollients or petroleum-based products are not used except under extreme situations, but semipermeable coverings (Tegaderm and Vigilon) may be used over areas of skin breakdown.

D. Cardiovascular support

1. **Blood pressure.** There is discussion over acceptable values for blood pressure in extremely premature infants and some suggestion that cerebral perfusion may be adversely affected at levels below a mean blood pressure of 30 mm Hg. In the absence of data demonstrating an impact on long-term neurologic outcome, slightly lower values (mean arterial consistent with gestational age) for infants of <26 weeks' gestational age in the transitional period after birth can be accepted if the infant appears well perfused without evidence of end-organ compromise. Early hypotension is more commonly due to altered vasoreactivity than hypovolemia, so therapy with fluid boluses are generally limited to 10 to 20 mL/kg, after which pressor support should be initiated. Hydrocortisone may be useful in infants with hypotension refractory to this strategy (see Chapter 40).

   If the infant is breathing spontaneously at birth, clamping of the umbilical cord should be delayed until 30 to 60 seconds have elapsed. This practice has been shown to decrease the incidence of early hypotension in premature infants.

2. **Patent ductus arteriosus (PDA).** The incidence of symptomatic PDA is as high as 70% in infants with a birth weight <1,000 g. A murmur may be absent or difficult to hear, and the physical signs of increased pulses or an active precordium may be difficult to discern. Most importantly, it remains a matter of controversy whether a patent ductus

is always harmful or requires treatment. Infants with a symptomatic PDA have a higher risk of BPD, but early closure does not decrease this risk. Recent studies suggest that a large percentage of PDAs will ultimately close spontaneously, and the risks of either medical or surgical therapy may have an adverse effect on both acute and long-term outcome. This suggests that some of the outcomes attributed to the PDA might be related to the impact of the therapies employed in an effort to close it. Many practitioners remain vigilant for the presence of a PDA but delay pharmacologic therapy until an echocardiogram has been performed and the PDA is noted to be large (PDA:pulmonary artery ratio >1), unrestrictive to flow (<1.5 m/second), and/or shown to be causing a diminution in left ventricular function and distal flow in the descending aorta. If initial medical therapy fails to eliminate the hemodynamic impact of the PDA, a second course of pharmacologic therapy (indomethacin, ibuprofen, or acetaminophen) can be considered. Prophylactic treatment with indomethacin has been demonstrated to reduce the incidence and severity of PDA and the need for subsequent ligation. However, it has not been shown to result in a change in long-term neurologic or respiratory outcome. Surgical ligation (or percutaneous ductal occlusion in certain centers) is infrequently necessary and should only be considered if there is clear evidence of a significant left to right shunt after medical management.

E. Blood transfusions. Transfusions of packed red blood cells are often necessary in small infants because of large obligatory phlebotomy losses. Infants who weigh <1,000 g at birth and are moderately or severely ill may receive as many as eight or nine transfusions in the first few weeks of life. Donor exposure can be successfully limited by reducing laboratory testing to the minimum necessary level, employing strict uniform criteria for transfusion, and by identifying a specific unit of blood for each patient likely to need several transfusions (see Chapter 45). Each such unit can be split to provide as many as eight transfusions for a single patient over a period of 21 days with only a single donor exposure. Erythropoietin therapy in conjunction with adequate iron therapy will result in accelerated erythropoiesis, but it has not been shown to reduce the need for transfusion and is not routinely used in these patients.

F. Infection and infection control (see Chapter 49). In general, premature birth is associated with an increased incidence of early-onset sepsis, with an incidence of 1.5% in infants having birth weight <1,500 g. Group B *Streptococcus* (GBS) remains an important pathogen, but gram-negative organisms now account for most of early-onset sepsis in infants weighing <1,500 g. Screening for infection immediately after birth is recommended in cases in which there are perinatal risk factors for infection. ELBW infants are particularly susceptible to hospital-acquired infections (occurring at >72 hours after birth), with about half due to coagulase-negative *Staphylococcus*. Mortality, as well as long-term morbidity, is higher among infants who develop these late-onset infections, particularly in those with gram-negative or fungal infections. Risk factors for late-onset infection include longer duration of mechanical ventilation, presence of central catheters, and parenteral nutrition support.

The risk of these late-onset infections (particularly central line–associated infections) can be decreased by improvements in care practices. Foremost among these is meticulous attention to hand hygiene. Alcohol-based gel for hand hygiene should be available at every bedside and prominently in other locations throughout the NICU. Periodic anonymous observation to monitor and report on hand hygiene practices before any caregiver–patient contact may help maintain compliance. In-line suctioning is used in respiratory circuits to minimize disruption, and every effort is made to minimize the duration of mechanical ventilation. The early introduction of feedings, preferably with human milk, minimizes the need for central lines and provides the benefits of milk-borne immune factors. When central lines are necessary, an observer to monitor the PICC insertion technique and immediately identify deviation or omission from a standard checklist can be considered. Dedicated central line insertion teams are employed in many units and help standardize insertion techniques to reduce the risk of infection. After insertion, attention to scrupulous central line care to avoid line hub bacterial colonization, as well as sterile line changes, have also has been shown to reduce the risk of central line–associated bacterial infection. The need for the line should be reassessed daily to reduce line dwell time to a minimum. Minimal laboratory testing as allowed by the infant's condition and clustering blood draws whenever possible help reduce the number of skin punctures and reduce patient handling. These practices are part of a standardized protocol for skin care for all neonates born with weight of <1,000 g. Ideally, the establishment of a uniform NICU culture that rejects the idea that these infections are inevitable and fosters pride in care and cooperation has helped create an environment of blameless questioning between practitioners.

G. Nutritional support (see Chapter 21)

1. **Initial management.** For ELBW infants, parenteral nutrition is initiated shortly after birth using a standard parenteral solution administered at a rate of 60 mL/kg/day (see section IV.C), resulting in protein administration of approximately 2.5 g/kg/day. On subsequent days, customized parenteral solutions are formulated to increase the protein administration rate to 4 g/kg/day. Parenteral lipids are begun on day 2 and advanced each day to a maximum of 3 g/kg/day as allowed by triglyceride levels. A goal of 90 to 110 kcal/kg/day is optimal to promote growth while receiving the majority of nutrition via TPN. Enteral feeding is begun as soon as the patient is clinically stable without evidence of significant end-organ dysfunction.
2. **Enteral feeding.** The safe initiation of enteral feeds begins with the introduction of small amounts of human milk (20 mL/kg/day), with the goal of priming the gut by inducing local factors necessary for normal function. In many units, donor breast milk is used for the highest risk infants if expressed breast milk is not available; in units without availability of donor breast milk, options include use of preterm formula or delay in initiation of enteral feedings for 3 to 4 days until expressed breast milk or colostrum is available. These small amounts of enteral feedings may be started even in the presence of an umbilical arterial line and continued for 3 to 5 days before advancement. A standardized approach to feeding

advancement may reduce the risk of feeding intolerance or necrotizing enterocolitis (see Chapters 21 and 27). As feedings are advanced, signs of feeding intolerance such as abdominal distention and/or emesis should be monitored closely. Of note, many units have discontinued routine monitoring of gastric residuals; in isolation, the ability of residuals to predict an evolving abdominal process is minimal and often leads to interruption in feeding. It is important but often difficult to differentiate the characteristically poor gastrointestinal motility of ELBW infants from signs of a more serious gastrointestinal disorder such as necrotizing enterocolitis (see Chapter 27). Mounting evidence suggests that a more rapid feed advance (30 mL/kg/day) and fortification at lower enteral volumes (40 to 60 mL/kg/day) is safe while also minimizing the time needed for a central line. Enteral caloric density can be increased using human milk fortifier (either bovine or human derived) (see Chapter 21). This eliminates a drop in caloric intake as parenteral nutrition is weaned while feedings advance. Multivitamin supplementation with vitamin D and iron should be initiated once on full volume feeds to achieve a minimum of 120 kcal/kg/day. Electrolytes, specifically sodium, should be monitored while infants are receiving breast milk feeding as many infants require supplemental sodium chloride to prevent hyponatremia and maintain adequate rates of growth.

H. Family support and developmental care

1. **Communication strategies.** The birth of an extremely premature, ELBW infant creates a significant amount of stress on the family unit. An introduction to the care of ELBW infants and the NICU should be provided as early as possible after admission. Family communication preferences should be determined and should include frequent touch-points for medical updates, opportunities for questions to be answered, and NICU "anticipatory guidance" regarding upcoming screenings and testing. Many units have a suggested schedule of updates that can be customized to each family's need. In addition, parental presence during rounds, in person and/or virtually, should be encouraged. The use of technology to provide daily updates and interaction with ELBW infants when families cannot be physically present can be considered.

2. **Postpartum depression (PPD).** The impact of PPD on family well-being is increasingly appreciated. Collaboration between the obstetric and neonatal teams to ensure that PPD screening is ongoing is encouraged. Additional resources for families affected by PPD should be provided.

3. **Kangaroo care.** Kangaroo care, or skin-to-skin contact between infant and caregivers, should be encouraged as soon as medically appropriate. Benefits to the ELBW neonate include improved vital sign stability, thermoregulation, and parent–infant bonding. Kangaroo care may also promote lactation. A unit protocol to address eligibility for kangaroo care is recommended to maximize opportunities for skin-to-skin contact.

4. **Developmentally appropriate care.** The proper use of positioning aids, containment, and therapeutic touch can aid in parent–infant bonding and vital sign stability, even during procedures in the NICU.

V. SUMMARY. The care of ELBW infants in the intensive care unit requires constant surveillance, adjustment, and collaboration between families and all members of the health care team. A program of continuous quality improvement, standardization of care, and consensus can optimize outcomes for the smallest infants.

Suggested Readings

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14 Developmentally Supportive Care

Lu-Ann Papile and Carol Turnage Spruill

KEY POINTS

- Infant cues form the basis for all handling and caregiving.
- Environments are modified to meet individual infants' requirements based on age, current abilities, and vulnerability.
- Parents are encouraged to provide care and nurturing for their infant in the neonatal intensive care unit (NICU).

I. INTRODUCTION. Individualized developmentally supportive care (IDSC) promotes a culture that respects the personhood of preterm and medically fragile term infants and optimizes the care and environment in which health care is delivered to this neurodevelopmentally vulnerable population. Implementing the principles of family-focused IDSC in a neonatal intensive care unit (NICU) environment facilitates family adaptation and may improve neurodevelopmental outcomes.

Preterm infants have a substantially higher incidence of cognitive, neuromotor, neurosensory, and feeding problems than infants born at full term. Fluctuations in the cerebral circulation that occur even during routine care and smaller than expected brain volumes at 36 to 40 weeks' postmenstrual age (PMA) may contribute to this increased morbidity. Changes in cerebral oxygenation and blood volume measured with near-infrared spectroscopy (NIRS) that occur during diaper changes with elevation of legs and buttocks, endotracheal tube (ET) suctioning, repositioning, routine physical assessment, and gavage feedings have been associated with early parenchymal brain abnormalities. IDSC helps to minimize these disturbances.

II. ASSESSMENT. Identification of an infant's stress responses and self-regulating behaviors at rest, as well as during routine care and procedures, is essential for the creation of care plans that support and promote optimal neurodevelopment (Table 14.1). Ideally, an infant's cues are continuously monitored, and care is modified as needed to lower stress and promote stability. Acutely ill term infants have responses to stress and pain like those of preterm infants; however, their cues are often easier to read because they have more mature behaviors.

A. Stress responses. A baseline profile of an infant's overall tolerance to various stimuli includes a combination of autonomic, motoric, state organizational behavior, and attentional/interactive signs of stress. Autonomic signs

Table 14.1. Neurobehavioral Organization and Facilitation

System	Signs of Stress	Signs of Stability	Interventions
Autonomic			
Respiratory	Tachypnea, pauses, irregular breathing pattern, slow respirations, sighing, or gasping	Smooth, unlabored breathing; regular rate and pattern	Reduce light, noise, and activity at bedside (place pagers/phone on vibrate, lower conversation levels at bedside).
Color	Pale, mottled, red, dusky, or cyanotic	Stable, overall pink color	Use hand containment and pacifier during exams, procedures, or care.
			Slowly awaken with soft voice before touch including all procedures, exams, and care unless hearing impaired; use slow movement transitions.
Visceral	Several coughs, sneezes, yawns, hiccups, gagging, grunting and straining associated with defecation, spitting up	Visceral stability, smooth digestion, tolerates feeding	Pace feedings by infant's ability and cues in appropriately modified environment.
Autonomic-related motor patterns	Tremors, startles, twitches of face and/or body, extremities	Tremors, startles, twitching not observed	Gently reposition while containing extremities close to body if premature.
			Avoid sleep disruption.

(continued)

Table 14.1. Neurobehavioral Organization and Facilitation *(Continued)*

System	Signs of Stress	Signs of Stability	Interventions
			Position appropriately for neuromotor development and comfort; use nesting/boundaries or swaddling as needed to reduce tremors, startles.
			Manage pain appropriately.
Motor			
Tone	Either hypertonia or hypotonia; limp/flaccid body, extremities, and/or face; hyperflexion	Consistent, reliable tone for post-menstrual age (PMA); controlled or more control of movement, activity, and posture	Support rest periods/reduce sleep disruption, minimize stress, contain or swaddle.
Posture	Unable to maintain flexed, aligned, comfortable posture	Improved or well-maintained posture, with maturation posture sustainable without supportive aids	Provide boundaries, positioning aids, or swaddling for flexion, containment, alignment, and comfort as appropriate.
Level of activity	Frequent squirming, frantic flailing activity, or little to no movement	Activity consistent with environment, situation, and PMA	Intervene as needed for pain management, environmental modification, less stimulation; encourage skin-to-skin holding; containment

State			
Sleep	Restless, facial twitching, movement, irregular respirations, fussing, grimacing, whimpers, or makes sounds; responsive to environment	Quiet, restful sleep periods; less body/facial movement; little response to environment	Comfortable and age-appropriate positioning for sleep with a quiet, dim environment and no interruptions except medical necessity
			Position with hands to face or mouth or so they can learn to achieve this on their own.
Awake	Low-level arousal with unfocused eyes; hyperalert expression of worry/panic; cry face or crying; actively avoids eye contact by averting gaze or closing eyes; irritability, prolonged awake periods; difficult to console or inconsolable	Alert, bright, shiny eyes with focused attention on an object or person; robust crying; calms quickly with intervention, consolable in 2–5 minutes	Encourage parent holding as desired either traditional or skin to skin.
			May be ready for brief eye contact around 30–32 weeks without displaying stress cues
			Support awake moments with PMA-appropriate activity based on stress and stability data for individual infant.

(continued)

Table 14.1. Neurobehavioral Organization and Facilitation *(Continued)*

System	Signs of Stress	Signs of Stability	Interventions
Self-regulation			
Motor	Little attempt to flex or tuck body, few attempts to push feet against boundaries, unable to maintain hands to face or mouth, sucking a pacifier may be more stressful than soothing	Strategies for self-regulation include foot bracing against boundaries or own feet/leg; hands grasped together; hand to mouth or face, grasping blanket or tubes, tucking body/truck; sucking; position changes	Examine using blanket swaddle or nest to support infant regulation by removing only a small part of the body at a time while keeping most of body contained during exam.
			Ask a parent or nurse to provide support during exams, tests, or procedures; swaddle or contain as needed to keep limbs close to body during care or exams and to provide boundaries for grasping or foot bracing.
			Position for sleep with hands to face or mouth.
			Provide pacifier intermittently when awake and at times other than exams, care, or procedures.
			Give older infants something to hold (maybe a finger or blanket).

			Encourage parent to support parenting skill; teach parents communication cues and behaviors; model appropriate responses to cues.
State	Rapid state transitions, unable to move to drowsy or sleep state when stressed, states are not clear to observers	Transitions smoothly from high arousal states to quiet alert or sleep state; focused attention on an object or person; maintains quiet alert state without stress or with some facilitation	Consistently avoid rapid disruption of state behavior (e.g., starting an exam without preparing the baby for the intrusion) by awakening slowly with soft speech or touch; use indirect lighting or shield eyes depending on PMA during exams or care.
			Assist return to sleep or quiet alert state after handling.
			Provide auditory and facial visual stimulation for quietly alert infants based on cues; premature infants may need to start with only one mode of stimulation initially, adding others based on cues.
			Swaddling or containment to facilitate state control or maintenance

Source: Modified from Als H. Toward a synactive theory of development: promise for the assessment and support of infant individuality. *Infant Ment Health J* 1982;3(4):229–243; Als H. A synactive model of neonatal behavioral organization: framework for the assessment of neurobehavioral development of the premature infant and his parents in the environment of the neonatal intensive care unit. *Phys Occup Ther Pediatr* 1986;6(3–4):3–55; Hunter JG. The neonatal intensive care unit. In: Case-Smith J, Allen AS, Pratt PN, eds. *Occupational Therapy for Children*. St. Louis, MO: Mosby; 2001:593; Carrier CT, Walden M, Wilson D. The high-risk newborn and family. In: Hockenberry MJ, ed. *Wong's Nursing Care of Infants and Children*. 7th ed. St. Louis, MO: Mosby; 2003.

of stress include changes in color, heart rate, and respiratory patterns as well as visceral changes such as such as gagging, hiccupping, vomiting, and stooling. Motoric signs of stress include facial grimacing, gaping mouth, twitching, hyperextension of limbs, finger splaying, back arching, flailing, and generalized hypertonia or hypotonia. State alterations suggesting stress include rapid state transitions, diffuse sleep states, irritability, and lethargy. Changes in attention or interactional availability, exhibited by covering eyes/face, gaze aversion, frowning, and hyperalert or panicky facial presentation, represent signs of stress in preterm infants.

B. Self-regulating behavior. Preterm infants employ a number of self-consoling behaviors to cope with stress including hand and/or foot bracing against an object such as a bed; sucking; bringing hands to face; flexed positioning; cooing; and grasping of linens, tubing, or own body parts. Because painful environmental stressors or procedures, whether painful or not, may overwhelm an infant's ability to self-console, support of the infant by parents or staff during these activities is needed.

III. GOALS OF DEVELOPMENTAL SUPPORT.

Developmental support necessitates attention by caregivers to observe cues (autonomic, motor, state) and respond to them. Infant cues provide clues to the type of intervention that may be most effective in decreasing stress and the subsequent physiologic cost. The individual caregiver must learn to recognize and appropriately respond when an infant communicates stress, pain, or the need for attention. A priority of IDSC is for infants to experience auditory, visual, and social input without disrupting autonomic, motor, or state function and integration. Once this objective is achieved, infants can begin to explore their world and relate to their parents during meaningful and reciprocal exchanges.

A. Supporting autonomic system (ANS) stability. Because the autonomic and visceral systems cannot be impacted directly, interventions are used to maintain or assist an infant's return to a state that supports autonomic stability. Swaddling, hand containment (facilitated tuck), and nesting with boundaries are supportive interventions that have been shown to be efficacious. Anticipatory planning for a quiet, calm environment, swaddling to reduce motor arousal, and letting the infant's behaviors guide the pace of caregiving will elicit less stress behaviors during assessment, provision of daily care and some procedures resulting in better autonomic, motor, and state tolerance. Autonomic stability is especially important during handling not only to assist the infant with coping but also to allow the clinician to perform a physical exam or diagnostic test that reflects an infant's true condition.

Heart rate variability (HRV) has been used to evaluate ANS maturation. In a study of infants divided into three gestational age groups and cared for in a NICU that supported state stability, including single-bed rooms, avoidance of long-term intubation, less invasive respiratory support, less noise, early skin-to-skin contact, and minimal early handling, infants had improved ANS as measured by decreased HRV regardless of gestational age at birth.

B. Intervening through the motor system. Support of the motor system is focused first on development and function and second on the prevention of acquired positioning deformities or functional limitations. Containment or

"facilitated tuck" is useful for calming or support during care and/or procedures. Repositioning can be extremely stressful for preterm infants and can be supported by using hands to maintain flexion during movement or swaddling while slowly changing positions. Positioning aids may be needed when an infant cannot sustain a flexed, aligned posture with midline orientation that is also comfortable. Term infants who cannot maintain age-appropriate posture and/or movement due to neuromuscular disease, congenital anomalies, severity of illness, or medications can develop musculoskeletal problems or loss of skin integrity necessitating positioning support. Movement is necessary for musculoskeletal growth and development. Thus, it is imperative that boundaries or swaddling provide containment without being restrictive. It is necessary to remove positioning supports as infants mature (around 32 weeks) in preparation for safe sleep at home. Parents can observe safe sleep practices being modeled in the NICU prior to infant discharge. If therapeutic positioning or a medically necessary device is required for an infant approaching discharge, the NICU team (including neonatal therapists [NTs]) should collaborate with the family to create a plan that ensures safe sleep in the home.

C. Creating environments that cultivate state organization. Preterm infants have less ability to maintain state and have more variable transition between states compared to term infants. Environmental modifications are made to promote quiet, focused attentional states and foster periods of well-defined, restful sleep with regular respirations and little movement. To promote the development of state organization, it is important to avoid activities that cause abrupt state transitions, such as rousing an infant from sleep by suddenly repositioning for an examination. Letting an infant know when a caregiver approaches to perform care at the bedside by using soft speech (infant's name), gentle touch, and containment while slowly repositioning can alleviate abrupt state disruption. Staff, parents, and others need to be consistent in their approach sharing what works best with individual infants. Restful environments without disturbance for specific periods of time are essential for developing sleep states.

IV. DEVELOPMENTALLY SUPPORTIVE ENVIRONMENT.

By providing a developmentally supportive NICU environment, neonatal caregivers can support neurologic and sensory development and potentially minimize later developmental issues in preterm infants. The acutely ill term infant also requires environmental modifications that reduce stress and promote sleep and recovery. Environments may be modified at the bedside to meet each infant's current and ongoing requirements. When possible, anticipation of an infant's environmental needs prior to admission is ideal.

Environments on a larger, more complex scale occur when NICUs are remodeled or newly designed. Health care professionals, architects, interior design consultants, health care facility regulators, and acoustic designers have revolutionized the NICU environment with continuously evolving standards of design based on research findings and clinical experience. The influence of the environment, such as light and sound, is of practical concern for short- and long-term development.

A. Sound. Increased noise levels in the NICU are associated with physiologic stress and autonomic instability. Intense noise levels at 55 to 60 dBA and higher disrupt sleep and may impact brain development occurring during

both active/light sleep and quiet/deep sleep. The development of sleep state organization may also be altered. Infants cared for in incubators may be exposed to increased ambient noise from personnel tapping on the incubator walls or using the top of the incubator as a shelf. Music or recording devices placed within the incubator also increase ambient sound levels.

The Committee for New NICU Design Standards recommends not exceeding a combination of continuous background sound and operational sound of 45 dB A-weighted, slow response levels for 50% of the measured time and 65 dB A-weighted, slow response levels for 10% of the measured time from a distance 3 ft away from an infant bed or visitor.

An acoustical engineer involved in all phases of planning, design, construction, and sound level verification of new buildings or renovation can assure criteria for sound abatement are met and attain desired noise control. An IDSC program includes systematic efforts to manage continuous background sound (e.g., ice machines, heating, ventilation and air conditioning systems, plumbing, refrigerators) and operational sound (e.g., low conversational tones, rounding away from the bedside, placing pagers and phones in vibrate mode, care in opening and closing portholes). Background sound levels should be measured occasionally along with an evaluation of operational or daily work noise sources contributing to noise intensity or sudden loud sounds. Random monitoring of sound levels is helpful to promote awareness and sustain noise abatement efforts.

Limited information is available on the impact of sound frequencies on infants in the NICU. Early investigations reported frequencies ranging from <500 Hz to 16,000 Hz or more over 50% of the measured time in the NICU. Inside the womb, the fetus is exposed to frequencies of <500 Hz until later in gestation when the uterine wall thins. Around 33 weeks, fetuses can respond to high-frequency sounds; however, the effects of repeated exposure over time are unknown. Without the natural protection of mother's womb, the developing architecture and functional organization of cortical auditory connections may be affected.

The most natural source of sound for the infant is mother's voice, and auditory development may be altered from the natural evolution that occurs in the womb. For optimal development, an infant must be able to distinguish the maternal voice from ambient noise. Encouraging mothers to read, talk, or sing to their infants at the bedside has been shown to soothe, lessen pain, enhance awake states, promote continued sleeping after loud sounds, and increase language exposure by presenting a natural, familiar sound as opposed to NICU noise.

B. Light. The relationship between ambient light and neurodevelopment is less clear. Reduced illumination is associated with increased autonomic stability in preterm infants and more frequent eye opening by both preterm and term infants. An additional developmental benefit of reducing environmental light is often the concurrent reduction in environmental noise and handling of infants. Early preterm infants may experience discomfort when exposed to intense light due to very thin eyelids that cannot block light and an immature pupillary reflex. Visual stimulation before 30 to 32 weeks' PMA is often accompanied by stress responses.

Use of thick, quilted covers with dark material on the side facing the incubator can protect the early preterm infant from light while providing sufficient lighting for staff to allow safe and efficient functioning. During procedures, using blanket tents or other methods that do not require tactile input should be used to protect the infant's eyes from direct light. Eye covers should only be used during phototherapy. Reduction of light in the NICU does not appear to affect the incidence or progression of retinopathy of prematurity or alter visually evoked potentials measured in early childhood, both relatively short-term outcomes. The long-term effects of early, atypical lighting and visual stimulation are unknown.

The American Academy of Pediatrics (AAP) *Guidelines for Perinatal Care* recommends adjustable ambient light levels from 10 to 600 lux (1 to 60 foot-candles) in infant areas. Procedure lighting that can be controlled or reduced as needed is recommended for each NICU bed, and infant's eyes should be shielded when illuminated. Procedure lights need to be focused, so they do not alter the light intensity around other infants. The AAP also supports the recommendations of both the Illuminating Engineering Society and the 2019 Consensus Committee on NICU design.

New or renovated NICUs typically provide ambient lighting of 10 to 20 lux. The light levels used in cycled lighting research for the nighttime cycle are within this range and can be used for light variation in the development of circadian rhythms. Cycled lighting may be beneficial for preterm infants, but the gestational age at which light intensity, day/night pattern, and light duration is safe and beneficial is not known. Preterm infants who have been exposed to cycled lighting at 30 weeks' gestational age and beyond have greater weight gain, earlier oral feeding, and more regulated patterns of rest/activity after discharge than control groups. However, atypical stimulation to one sensory system may adversely affect the function of another sensory system. Until more is understood about light exposure, a conservative approach is best.

C. NICU design. Single family rooms (SFRs) support the infant and family bond and create an environment that is readily adapted to meet an individual infant's requirements. Whether SFRs are more beneficial than the traditional open-bay design is not certain. A systematic review and meta-analysis of SFRs versus open-bay units found that the incidence of sepsis is reduced and exclusive breastfeeding is higher in SFRs but detected no difference in long-term neurodevelopment. Another systematic review and meta-analysis of SFRs versus open-bay units showed that SFRs facilitated parental presence, skin-to-skin care, and lower NICU-related stress levels at discharge. Regardless of design, thoughtful consideration of the needs of an individual infant must be considered to provide an environment that supports optimal outcomes.

V. DEVELOPMENTALLY SUPPORTIVE CARE PRACTICES.

Developmental support in the NICU requires collaboration and teamwork to integrate the developmental needs of infants within the context of medical treatment and nursing care. This entails a coordinated, primary team that includes the family and is designed to work in partnership around the infant's state of alertness,

sleep cycles, communication cues, medical condition, and family presence. The goal is to maximize rest, minimize stress, and optimize healing and growth in a framework that supports family participation.

A. Positioning. The goals of positioning are to facilitate flexed and midline positioning of extremities, stabilize respiratory patterns, and lessen physiologic stress. Interventions include flexion, containment, midline alignment, and comfort. The use of "nesting materials" (e.g., soft blanket rolls, commercially available positioning devices) or swaddling is useful in minimizing the upper/lower extremity abduction, scapular retraction, and cervical hyperextension typical of preterm infants. More mature infants with congenital neuromuscular or skeletal disorders may also need positioning support.

Nesting needs to allow sufficient room for the infant to push against boundaries, to facilitate continuing development of the neuromotor and skeletal systems.

B. Feeding. Oral feeding is a complex task requiring physiologic maturation, coordination of suck–swallow–breathe mechanics, and development of oral motor skills. Breastfeeding is the preferred method, and breast milk is recommended for both preterm and term infants (see Chapter 22). The transition to oral feeding from tube feeding requires skilled assessment and judgment on the part of the caregiver. An infant who is successful in learning to nipple feed is less likely to develop feeding problems after discharge. It is important that the infant learns to feed properly and that family members can feed their infant.

Progression to oral feeds is highly contingent on elements of IDSC and occurs predictably in several phases. Pre-nonnutritive suck (pre-NNS) is characterized by weak suck and instability of motor, autonomic, and state regulation systems; NNS is characterized by more optimal suck patterns and should be encouraged during gavage feeds. Nutritive suck typically begins at approximately 33 weeks' PMA and progresses to full oral intake as autonomic stability and oral motor coordination improve. Strategies to promote successful progression through these phases include identifying and minimizing signs of physiologic stress; environmental modification to promote autonomic stability; feeding in a flexed, midline position; pacing techniques; and use of slow-flow nipples.

Considerations for a feeding plan include the infant's opportunities to practice, environmental preparation to minimize stressors, and using the infant's feeding readiness cues to start feedings rather than strict adherence to a specific PMA, specific time intervals, and feeding duration. Infants fed using feeding readiness cues experience significantly fewer adverse events during feedings, reach full oral feeding sooner, are discharged earlier, gain the same amount of weight as controls, and demonstrate about three cues per feeding. In addition, experiential feeding, that is, feeding frequently during the day without regard for duration, also results in less time to full oral feeding. Leaving a gavage tube in place during initial feeding attempts or repeated insertions may cause discomfort and interfere with feeding progression or generate oral aversion and later feeding disorders. Research is needed to understand more about the risk factors for feeding behavior disorders associated with aversive or repeated noxious stimulation of the oropharynx and gastrointestinal tract.

C. Touch

1. **Hand containment or facilitated tuck** can be taught to parents soon after admission as a gentle, nurturing way to connect with their infant. This technique reduces pain responses during painful and nonpainful events. Parents can be taught how to touch their infant in ways that are nurturing and won't create stress.

2. **Kangaroo care**, sometimes referred to as **skin-to-skin holding**, is a technique consistently associated with improved infant outcomes (i.e., fewer respiratory complications, improved weight gain, and temperature regulation) and maternal outcomes (i.e., improved maternal competence and longer breastfeeding duration). Mothers who use kangaroo holding produce a greater volume of breast milk than mothers who hold in the traditional way. Kangaroo care can be initiated as soon as infants are medically stable. Infants are held on their mother or father's chest wearing only a diaper and are covered with a blanket and hat as needed. A minimum of 1 hour is recommended for kangaroo holding. A NICU protocol for kangaroo holding ensures safety and minimizes an infant's stress response to handling/positioning. Cardiorespiratory monitoring needs to be ongoing with frequent observation to make sure head position facilitates an open airway. Two people are often needed to make the infant transfer to the chest less stressful and safe especially with tubing, respiratory equipment, venous access devices, and other apparatus necessary in the NICU.

   Kangaroo holding impacts several developing sensory systems including tactile (skin), olfactory, and vestibular (rise/fall of chest). Soft speech by the parent will be audible to their infant if ambient noise is minimized. The preterm infant's visual capacity is not challenged because eye-to-eye contact is not a necessary component for kangaroo care. Parents can be with their infant earlier in a way that is satisfying for them and supportive for their baby.

3. **Massage**, either whole body or abdominal, is another type of tactile stimulation that can be taught to parents with support from a certified infant massage therapist who has training specific to preterm and term infants. Massage is often considered for stable infants at approximately 32 weeks' PMA, although individual differences may determine when it is most beneficial. Infant massage has been associated with improved weight gain and sleep, less fussiness, and decreased hospital days. Caretaker benefits include increased confidence in caretaking ability, a positive effect on caregiver–infant attachment, and less maternal postnatal depression. Adverse effects of massage therapy are more likely to occur in infants who are unable to tolerate added stimulation or who are clinically unstable.

D. Team collaboration and consistency of care. Developmental care should be considered as part of routine care. The developmental plan is complementary to the medical plan and uses developmental principles, techniques, and environmental modifications to reduce stressors that challenge an infant's physiologic stability through behavioral instability. The unpredictable nature of care in the NICU can be diminished by consistent caregivers who

are familiar with an infant's clinical and behavioral baseline, provide care in a similar manner, respond quickly to cues, and provide relevant information to all members of the infant's team including the family to create an individualized plan of care.

An infant's team consists of multiple disciplines including licensed NTs. Occupational therapists (OTs), physical therapists (PTs), and speech-language pathologists (SLPs) provide valuable neuroprotective and habilitative services in the NICU. These NTs require advanced knowledge and skills in gestational age–appropriate assessment (stability and stress cues) and interventions, medical conditions and procedures, family-centered care, and the neurodevelopmental systems needed for development. Assessments with formalized clinical instruments assist NTs to evaluate oral motor function, feeding skills, neurobehavioral, and sensory and motor skills and provide a baseline to measure progress and make plan adjustments.

NTs promote neonatal functionality in neurobehavioral, neuromotor, neuroendocrine, musculoskeletal, and sensory and psychosocial skills to support a foundation for optimal outcomes. Assessments and plans are individually based and may begin on admission with environmental and positional support, family teaching and encouragement to discharge teaching, and developmental follow-up appointments.

VI. PAIN AND STRESS.

Effective nonpharmacologic interventions should incorporate developmental principles (see Chapter 70).

VII. PARENT SUPPORT/EDUCATION

A. Effective IDSC is dependent on implementation of the principles of family-centered care during NICU stay as well as upon transition to home. Likewise, parent education is critical to ongoing understanding of their infant's cues and how to respond in an appropriate, nurturing manner.

B. In the NICU. Preterm birth and NICU hospitalization negatively impact parent–infant interactions, which, in turn, is associated with long-term adverse developmental sequelae. Individual family-centered interactions (i.e., family-based developmental evaluations, support, and education) have been associated with reduced parent stress and more positive parent–infant interactions. Family-centered NICU policies include welcoming families 24 hours per day; encouraging family participation in infant care; and creating parent advisory boards, parent support groups, and comfortable rooming-in accommodations for parents.

C. Discharge teaching. Because brain growth and maturation may occur at a slower rate in the extrauterine environment, parents must understand that their baby may not behave as a term baby would when he or she has reached 40 weeks' PMA. Many parents report being ill-prepared for discharge from the NICU with respect to recognizing signs of illness, employing effective calming strategies, being aware of typical and delayed development, and using strategies to promote infant development. Teaching that begins well before discharge can help parents be better prepared to assume their role as the primary caregiver.

D. Postdischarge family supports. Parents report feeling frightened and alone following discharge of their preterm infant from the NICU, even when services are provided by a visiting nurse and early intervention (EI) specialists. Support groups for parents of preterm infants designed to provide long-term emotional and educational support are available in many communities. In addition, magazines, books, and web-based materials related to parenting preterm infants are available. A promising approach to facilitating seamless transition to community-based services includes referral to the federally mandated EI program before the infant's discharge and collaboration between NICU and EI professionals to create a developmentally supportive transition plan.

E. Infant follow-up and EI programs. The focus of a follow-up program is to prevent or minimize developmental delay through early identification of risk factors and referral to appropriate treatment programs. Close follow-up is paramount to maximizing developmental outcome. Every center that cares for medically fragile and preterm neonates needs to have a follow-up program available. Which group of infants to follow and the frequency of follow-up assessments are dependent on state and medical center resources. Emphasizing the importance of follow-up appointments before leaving NICU may motivate parents to attend and participate in their infant's developmental outcome.

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15 Temperature Control

Kimberlee E. Chatson

KEY POINTS

- Immediate postnatal hypothermia is a worldwide issue with a significant morbidity and mortality burden.
- The preterm infant is especially vulnerable, and extra measures need to be taken to provide a neutral thermal environment.
- Induced hypothermia is a new modality that can reduce neuronal loss and subsequent brain injury after hypoxic-ischemic insult. Recognition and timely treatment of infants is needed to be effective.

I. BACKGROUND. Neonatal hypothermia after delivery is a worldwide issue, occurs in all climates, and if prolonged can cause harm and affect survival. Thermoregulation in adults is achieved by both metabolic and muscular activity (e.g., shivering). During pregnancy, maternal mechanisms maintain intrauterine temperature. After birth, newborns must adapt to their relatively cold environment by the metabolic production of heat because they are not able to generate an adequate shivering response. Brown fat is a source for thermogenesis in term newborns. It is highly vascularized; composed of many mitochondria, lipid molecules, and numerous capillaries; and innervated by sympathetic neurons. Norepinephrine is released in response to cold, causing vasoconstriction and increased metabolism. The stimulation of the sympathetic pathways also causes a surge in thyrotropin which leads to the release of thyroxine (T_4) and triiodothyronine (T_3). T_3 causes upregulation of thermogenin which, like norepinephrine, acts on brown fat to initiate chemical thermogenesis; heat is produced by fatty acid oxidation and uncoupling of adenosine triphosphate. When brown fat is metabolized, the heat produced warms the organs and blood directly leading to an elevation in body temperature. Factors that increase risk for hypothermia include prematurity, intrauterine growth restriction, asphyxia, and certain congenital anomalies (e.g., abdominal wall defects, central nervous system [CNS] anomalies). Infants with persistent, unexplained hypothermia should be evaluated for hypothyroidism.

II. TEMPERATURE MAINTENANCE

A. Premature infants experience increased mechanisms of heat loss combined with decreased heat production capabilities. These special problems in temperature maintenance put them at a disadvantage. Compared with term infants, premature infants have the following:

1. A higher ratio of skin surface area to weight and a relatively large head which is a prominent source of heat loss if not covered by a hat
2. Highly permeable skin which leads to increased transepidermal water loss and therefore increased evaporative heat loss
3. Decreased subcutaneous fat, an effective source of insulation
4. Decreased ability to maintain a flexed posture to minimize heat loss
5. Less-developed stores of brown fat (1% to 2% of body weight of preterm infant vs. 4% of body weight of term) and decreased glycogen stores
6. Poor vasomotor control
7. Low levels of thermogenin and 5′3′ monodeiodinase
8. Lower surge of thyrotropin (especially infants <30 weeks)
9. Challenges with adequate caloric intake to provide nutrients for thermogenesis and growth

B. Cold stress. In the setting of resuscitation, newborn infants can be subject to acute hypothermia and respond with a cycle of peripheral vasoconstriction, causing anaerobic metabolism, metabolic acidosis, and pulmonary vasoconstriction. Hypoxemia further compromises the infant's response to cold. Premature infants are at the highest risk for hypothermia and its sequelae (i.e., hypoglycemia, metabolic acidosis, increased oxygen consumption). After the immediate newborn period, the more common and chronic problem facing premature infants than actual hypothermia is caloric loss from unrecognized chronic cold stress, resulting in excess oxygen consumption and inability to gain weight. The use of low-reading thermometers (from 29.4°C [85.0°F]) is recommended because temperature readings <34.4°C (94.0°F) can go undetected with routine thermometers.

C. Neonatal cold injury is a rare, extreme form of hypothermia that may be seen in low birth weight (LBW) infants and term infants with CNS disorders. Core temperature can fall below 32.2°C (90°F). It occurs more often in home deliveries, emergency deliveries, and settings where there is inadequate thermoregulatory support including equipment and care practices. These infants may have a bright red color because of the failure of oxyhemoglobin to dissociate at low temperature. They may have central pallor or cyanosis. The skin may show edema and sclerema. Signs may include hypotension; bradycardia; slow, shallow, irregular respiration; poor sucking reflex; abdominal distention or vomiting; decreased activity; decreased response to stimulus; and decreased reflexes. Metabolic acidosis, hypoglycemia, hyperkalemia, azotemia, and oliguria can be present. Sometimes, there is generalized bleeding, including pulmonary hemorrhage. It is controversial whether warming should be rapid or slow. Setting the abdominal skin temperature to 1°C (33.8°F) higher than the core temperature or setting it to 36.5°C (97.7°F)

on a radiant warmer will produce slow rewarming. In addition to rewarming, hypoglycemia should be corrected. The infant may benefit from a normal saline bolus (10 to 20 mL/kg), supplemental oxygen, and correction of metabolic acidosis. These infants should not be fed until euthermic and should be carefully evaluated and treated for possible infection, bleeding, or injury.

D. Hyperthermia, defined as an elevated core body temperature, may be caused by a relatively hot environment, infection, dehydration, CNS dysfunction, or medications. Although the issue of infection is of clinical concern, awareness of environmental contributors such as phototherapy, incubators or warming table settings, or proximity to sunlight should be considered. If environmental temperature is the cause of hyperthermia, the trunk and extremities are the same temperature and the infant appears vasodilated. In contrast, infants with sepsis are often vasoconstricted and the extremities are cooler than the trunk.

E. Induced hypothermia. Due to both experimental and clinical evidence that induction of controlled hypothermia can reduce neuronal loss and subsequent brain injury after a hypoxic-ischemic insult, therapeutic hypothermia is now standard of care for these infants. It is a time-sensitive therapy and needs to be instituted within the first 6 hours after birth to be most effective. Passive cooling in the delivery room and during stabilization, followed by transfer to a center that performs the treatment, should be considered when there is a history of an acute perinatal event (nonreassuring fetal heart tracings, cord prolapse, placental abruption), pH $\leq$7.0/base deficit $\geq$16 on cord gas or gas obtained within 1 hour of life, 10-minute Apgar score $\leq$5, or assisted ventilation initiated at birth and continued for at least 10 minutes. Target temperature range is 32.5° to 34.5°C or 90.5 to 94.1°F. Core temperature should be monitored every 15 minutes (see Chapter 55).

III. MECHANISMS OF HEAT LOSS.

There are **four major** mechanisms of heat loss in neonates.

A. Evaporation. This is the most common route, occurring immediately after birth in both term and preterm infants and in the first few weeks after birth in preterm infants <28 weeks' gestation. Heat is lost through conversion of water to gas. This tends to occur with wet skin and hair after birth or during a bath, wet clothes, linens or diapers, or insensible water loss from skin or lungs. Preventive strategies include drying the infant immediately after delivery, the use of plastic bag or wrap, keeping the infant and clothing dry, delaying the first bath, and placing the infant in a humidified isolette.

B. Radiation. This mode occurs when infants are near but not in direct contact with cold surfaces such as cold surrounding walls/windows or sides of incubator. This is the predominant route of heat loss in preterm infants >28 weeks and term infants. Preventive strategies include increasing the environmental temperature, placing a hat on infant's head, using a plastic bag/wrap, using double-walled incubators, and avoiding placement of incubator or bassinets near cold windows or air conditioning vents.

C. Conduction. This occurs when infants are in direct contact with cold surfaces such as a cold scale, mattress, or blankets. Preventive strategies include using

an exothermic mattress, using skin-to-skin care, placing infant on prewarmed bed at time of delivery, and placing a warm blanket between the infant and any cold surfaces.

D. Convection. Heat loss occurs when there is draft of air from open doors or air conditioners. Preventive strategies include keeping the porthole doors of incubators closed, placing preterm infant in an incubator, warming inspired air, and using servo control for skin temperature.

IV. THERMONEUTRAL ENVIRONMENT.

This describes an environment that minimizes heat loss. Thermoneutral conditions exist when heat production (measured by oxygen consumption) is minimal and core temperature is within the normal range (Table 15.1).

V. MANAGEMENT TO PREVENT HEAT LOSS

A. Healthy term infant

1. Standard thermal care guidelines include maintaining the delivery room temperature at 23° to 25°C or 73° to 77°F (Neonatal Resuscitation Program)/25°C or 77°F (World Health Organization), immediately drying the infant (especially the head) and applying a hat if available to prevent significant heat loss through the scalp, removing wet blankets, and wrapping the newborn in prewarmed blankets. It is also important to prewarm contact surfaces and minimize drafts.
2. Examination in the delivery room should be performed with the infant under a radiant warmer. A skin probe with servo control to keep skin temperature at 37°C (98.6°F) should be used for prolonged examinations.
3. Skin-to-skin care during the first 1 to 2 hours of life offers a practical and effective approach to achieving a neutral thermal environment. This method has the added benefit of promoting early breastfeeding.

B. Premature infant

1. Standard thermal care guidelines should be followed. Of note, the practice of delayed cord clamping has not been found to contribute to hypothermia.
2. Additional interventions immediately after birth can optimize thermoregulation.
   a. Barriers to prevent heat loss should be used in extremely premature infants. These infants should be placed in a polyethylene bag immediately after birth; the wet body is placed in the bag from the neck down. Plastic wraps and bags which are inexpensive and widely available are also effective in infants born at <29 weeks.
   b. Gel mattresses have been found to be as effective as the plastic bags and wraps. Both may be used in combination at the time of delivery. The infant should be placed on a thermal mattress (with cloth cover) and wrapped in plastic bag/wrap without drying. Care must be taken to avoid hyperthermia.

Table 15.1. Neutral Thermal Environmental Temperatures

Age and Weight	Temperature*	
	At Start (°C)	Range (°C)
0–6 hours		
<1,200 g	35.0	34.0–35.4
1,200–1,500 g	34.1	33.9–34.4
1,501–2,500 g	33.4	32.8–33.8
>2,500 g (and >36 weeks' gestation)	32.9	32.0–33.8
6–12 hours		
<1,200 g	35.0	34.0–35.4
1,200–1,500 g	34.0	33.5–34.4
1,501–2,500 g	33.1	32.2–33.8
>2,500 g (and >36 weeks' gestation)	32.8	31.4–33.8
12–24 hours		
<1,200 g	34.0	34.0–35.4
1,200–1,500 g	33.8	33.3–34.3
1,501–2,500 g	32.8	31.8–33.8
>2,500 g (and >36 weeks' gestation)	32.4	31.0–33.7
24–36 hours		
<1,200 g	34.0	34.0–35.0
1,200–1,500 g	33.6	33.1–34.2
1,501–2,500 g	32.6	31.6–33.6
>2,500 g (and >36 weeks' gestation)	32.1	30.7–33.5
36–48 hours		
<1,200 g	34.0	34.0–35.0
1,200–1,500 g	33.5	33.0–34.1
1,501–2,500 g	32.5	31.4–33.5
>2,500 g (and >36 weeks' gestation)	31.9	30.5–33.3

(continued)

Table 15.1. ***(Continued)***

Age and Weight	Temperature*	
	At Start (°C)	Range (°C)
48–72 hours		
<1,200 g	34.0	34.0–35.0
1,200–1,500 g	33.5	33.0–34.0
1,501–2,500 g	32.3	31.2–33.4
>2,500 g (and >36 weeks' gestation)	31.7	30.1–33.2
72–96 hours		
<1,200 g	34.0	34.0–35.0
1,200–1,500 g	33.5	33.0–34.0
1,501–2,500 g	32.2	31.1–33.2
>2,500 g (and >36 weeks' gestation)	31.3	29.8–32.8
4–12 days		
<1,500 g	33.5	33.0–34.0
1,501–2,500 g	32.1	31.0–33.2
>2,500 g (and >36 weeks' gestation)		
4–5 days	31.0	29.5–32.6
5–6 days	30.9	29.4–32.3
6–8 days	30.6	29.0–32.2
8–10 days	30.3	29.0–31.8
10–12 days	30.1	29.0–31.4
12–14 days		
<1,500 g	33.5	32.0–34.0
1,501–2,500 g	32.1	31.0–33.2
>2,500 g (and >36 weeks' gestation)	29.8	29.0–30.8
2–3 weeks		
<1,500 g	33.1	32.2–34.0
1,501–2,500 g	31.7	30.5–33.0

(continued)

Table 15.1. Neutral Thermal Environmental Temperatures *(Continued)*

Age and Weight	Temperature*	
	At Start (°C)	Range (°C)
3–4 weeks		
<1,500 g	32.6	31.6–33.6
1,501–2,500 g	31.4	30.0–32.7
4–5 weeks		
<1,500 g	32.0	31.2–33.0
1,501–2,500 g	30.9	29.5–32.2
5–6 weeks		
<1,500 g	31.4	30.6–32.3
1,501–2,500 g	30.4	29.0–31.8

*Generally speaking, the smaller infants in each weight group will require a temperature in the higher portion of the temperature range. Within each time range, the younger infants require the higher temperatures.

Source: Reprinted from Fanaroff AA, Klaus MH. The physical environment. In: Fanaroff AA, Fanaroff JM, eds. *Klaus and Fanaroff's Care of the High Risk Neonate*. 6th ed. Philadelphia, PA: Elsevier Saunders; 2013:132–150. Copyright © 2013 Elsevier. With permission.

c. A radiant warmer should be used during resuscitation and stabilization, and the servo-controlled temperature probes should be placed promptly on the infant. A heated incubator should be used for transport.
d. External heat sources including skin-to-skin care (>28 weeks) and TransWarmer mattresses have demonstrated a reduction in the risk of hypothermia.

3. In the neonatal intensive care unit (NICU), infants require a thermoneutral environment to minimize energy expenditure and optimize growth; skin mode or servo control can be set so that the incubator's internal thermostat responds to changes in the infant's skin temperature to ensure a normal temperature despite any environmental fluctuation. If a skin probe cannot be used due to the potential damage to skin in small premature infants, the incubator should be kept at an appropriate temperature on air mode (see Table 15.1).
4. Humidification of incubators has been shown to reduce evaporative heat loss and decrease insensible water loss, typically used for patients <1,200 g or 30 to 32 weeks' gestation for the first 10 to 14 days after birth. Risks and concerns for possible bacterial contamination have been addressed in current incubator designs which include heating devices that elevate the water temperature to a level that destroys most organisms.

Notably, the water transforms into a gaseous vapor and not a mist, thus eliminating the airborne water droplet as a medium for infection.

5. Servo-controlled open warmer beds may be used for very sick infants when access is important. The use of a tent made of plastic wrap or barrier creams such as Aquaphor (or sunflower seed oil in resource-limited settings) prevent both convection heat loss and insensible water loss (see Chapter 23). Due to potential infectious risk, these creams and oils should be used sparingly and not for longer than 72 hours after birth.
6. Incubators are designed to decrease all four forms of heat loss, namely, evaporation, conduction, radiation, and convection. Double-walled incubators further decrease heat loss primarily due to radiation and, to a lesser degree, conduction.
7. Current technology includes hybrid devices such as the Versalet Incuwarmer (Hill-Rom Air-Shields, Batesville, Indiana) and the Giraffe OmniBed (Ohmeda Medical, Madison, Wisconsin). They offer the features of both a traditional radiant warmer bed and an incubator in a single device. This allows for the seamless conversion between modes, which minimizes thermal stress and allows for ready access to the infant for routine and emergency procedures. Panda Warmers (GE Healthcare Products, Chicago, Illinois) in the delivery room setting offer the features of a traditional warmer with the added capacity to provide blended oxygen to the neonate.
8. Premature infants in relatively stable condition can be dressed in clothes and caps and covered with a blanket. This intervention offers a broader range of safe environmental temperatures. Heart rate and respiration should be continuously monitored because the clothing may limit observation.

VI. HAZARDS OF TEMPERATURE CONTROL METHODS

A. Hyperthermia. A servo-controlled warmer can generate excess heat, which can cause severe hyperthermia if the probe becomes detached from the infant's skin. Temperature alarms are subject to mechanical failure.

B. Undetected infections. Servo control of temperature may mask the hypothermia, hyperthermia, or temperature instability associated with infection. A record of both environmental and core temperatures, along with observation for other signs of sepsis, will help detect infections.

C. Volume depletion. Radiant warmers can cause increased insensible water loss. Body weight, urine output, and fluid balance should be closely monitored in infants cared for on radiant warmers.

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16 Follow-up Care of Very Preterm and Very Low Birth Weight Infants

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KEY POINTS

Children born as very preterm and with very low birth weight (VLBW)

- Are at high risk for neurodevelopmental deficits and respiratory, cardiovascular, and growth abnormalities.
- Have increased risk for learning disabilities and have attentional problems requiring special educational services.
- Have an increased risk of abnormal visual and auditory function and require additional early screening and follow-up evaluations in the first years of life.
- Require long-term, specialized follow-up care to monitor for medical and neurodevelopmental problems to allow for early identification and intervention to optimize their long-term outcomes.
- Require care planning and coordination that aims to integrate the primary care pediatrician, subspecialty providers, and community-based services and addresses the needs of both the child and the family given their risk for medical and developmental complexity.

I. INTRODUCTION. Of the over 4 million children born each year in the United States, 2% (88,000) are born very preterm, defined as <32 weeks' gestational age (GA). Advances in obstetric and neonatal care have resulted in increased survival of these infants. The ramifications of this improvement are vast because these infants are at increased risk for long-term complication including neurodevelopmental sequelae, such as cognitive delay, cerebral palsy (CP), fine and gross motor coordination problems, learning disabilities, visual and hearing problems, and medical problems, such as respiratory, cardiovascular, and growth issues. The more preterm an infant, the greater the risk of such difficulties. It is thus critical that these children have appropriate long-term follow-up care which includes close monitoring of the most common problems of the preterm infant.

II. MEDICAL CARE ISSUES

A. Respiratory health (see Chapter 34). Very preterm infants are at high risk for respiratory ailments, especially during the first year of life. Lung development continues during the postnatal period, and exposure to volutrauma and barotrauma along with oxygen (O_2) toxicity may impede this process. This can damage lung tissue and decrease pulmonary blood flow. The resultant lung disease can extend into adulthood.

Approximately 23% of very low birth weight (VLBW) infants and 40% of extremely low birth weight (ELBW; birth weight <1,000 g) infants develop bronchopulmonary dysplasia (BPD) (defined as O_2 dependence beyond 28 days with the severity assessed at 36 weeks' postmenstrual age [PMA]). Very preterm infants with BPD are most likely to suffer respiratory ailments in the short and long term and should be monitored for related morbidities, including acute respiratory exacerbations, upper and lower respiratory infections, pulmonary hypertension, cor pulmonale, growth failure, and developmental delay. Infants with severe BPD may require treatment with long-term ventilator support via tracheostomy. More commonly, infants with significant BPD may be discharged home on some combination of supplemental O_2, bronchodilator, steroid, and/or diuretic therapy. In the longer term, children with BPD may develop asthma-like symptoms in childhood which are not uniformly responsive to bronchodilators. In later life, survivors of BPD also lack catch-up growth in lung function and have an accelerate decline in lung function. It is important to note that children born preterm who do not meet criteria for BPD diagnosis are also at increased risk for these respiratory morbidities.

Chronic respiratory problems lead to increased utilization of health services after neonatal intensive care unit (NICU) discharge. Many preterm infants present to primary care practitioners and specialists with chronic wheezing and recurrent respiratory tract infections. Children of the lowest gestations and birth weights suffer the greatest burden of respiratory illness. VLBW (birth weight <1,500 g) infants are 4 times more likely to be rehospitalized during the first year than are higher birth weight infants; up to 60% are rehospitalized at least once by the time they reach school age. The increased risk of hospitalization persists into early school age; 7% of VLBW children are hospitalized in a given year, compared with 2% of higher birth weight children. In a recent study of extremely premature infants, 57% of infants born between 23 and 25 weeks' gestation, and 49% of those born between 26 and 28 weeks' gestation required rehospitalization in the first 18 months of life. Admissions during the first year of life are most commonly for complications of respiratory infections among very preterm and VLBW infants.

1. **Home O_2.** Some infants discharged home from the NICU on supplementary O_2 may be weaned off within the first few months following discharge, whereas others may remain on O_2 for 2 years or more. Infants with BPD who are discharged home on O_2 are rehospitalized at twice the rate during the first 2 years of life compared to those who are not.
2. **Respiratory syncytial virus (RSV).** RSV is the most important cause of respiratory infection in premature infants, particularly in those with chronic lung disease. To minimize illness caused by RSV, VLBW infants

should receive prophylactic treatment with palivizumab (Synagis) monoclonal antibody. The American Academy of Pediatrics (AAP) recommends treatment during RSV season for at least the first year of life for all infants born <29 0/7 weeks and those born 29 0/7 to 31 6/7 weeks' gestation with BPD. To prevent illness caused by respiratory viruses, families should be counseled regarding good hand hygiene by all those in close contact with infants, avoidance of exposure to others with respiratory infections (especially young children during the winter season), and avoidance of passive cigarette smoke exposure. The influenza vaccine is also recommended for VLBW infants once they are older than 6 months chronologic age; until then, care providers in close contact with the infant should strongly consider receiving the influenza vaccine. Close contacts should also ensure that their pertussis immunity is up to date.

3. **Air travel.** In general, air travel is not recommended for infants with BPD because of the increased risk of exposure to infection and because of the lowered cabin pressure resulting in lower O_2 content in the cabin air. If an infant's partial pressure of oxygen (PaO_2) is ≤80 mm Hg, supplemental O_2 will be needed while flying.

B. Immunizations. VLBW infants should receive their routine pediatric immunizations according to the same schedule as term infants, with the exception of rotavirus and hepatitis B vaccine. The AAP recommends initial vaccination of preterm infants at or following discharge from the hospital if clinically stable and chronologic age between 6 weeks and 14 weeks 6 days. Medically stable, thriving infants should receive the hepatitis B vaccine as early as 30 days of age regardless of GA or birth weight. If the baby is ready for discharge to home before 30 days of age, it can be given at the time of discharge to home. Although studies evaluating the long-term immune response to routine immunizations have shown antibody titers to be lower in preterm infants, most achieve titers in the therapeutic range.

C. Growth. VLBW infants have a high incidence of feeding and growth problems for multiple reasons. Infants with severe BPD have increased caloric needs for appropriate weight gain. Many of these infants also have abnormal or delayed oral motor development and have oral aversion because of negative oral stimulation during their early life. Growth should be followed carefully on standardized growth curves (World Health Organization [WHO] International Growth Curves 2006) using the child's age corrected for prematurity for the first 2 years of life and then using the Centers for Disease Control and Prevention (CDC) standardized curves. Supplemental caloric density is commonly required to optimize growth. Specialized preterm infant formulas with increased protein, calcium, and phosphate (either added to human milk or used alone) should be considered for the first 6 to 12 months of life for infants who have borderline growth. ELBW infants may demonstrate growth that is close to or below the 5th percentile. However, if their growth runs parallel to the normal curve, they are usually demonstrating a healthy growth pattern. Infants whose growth curve plateaus or whose growth trajectory falls off warrant further evaluation to assess caloric intake. If growth failure persists, consultation with a gastroenterologist or endocrinologist to rule out gastrointestinal pathology such as severe

gastroesophageal reflux disease or endocrinologic problems such as growth hormone deficiency should be considered. Monitoring for excessive weight gain is also recommended with adjustment of caloric density if weight has normalized to the 50th percentile or demonstrates a rapid acceleration over a short period of time. There is some evidence that links rapid weight gain of low birth weight (LBW) infants to excess accretion of adipose and subsequent risks of adult obesity and associated morbidities.

Gastrostomy tube placement may be necessary in a small subset of patients with severe feeding problems. Long-term feeding problems are frequent in this population of children, and they usually require specialized feeding and oral motor therapy to ultimately wean from gastrostomy tube feedings.

1. **Anemia.** VLBW infants are at risk for iron deficiency anemia and should receive supplemental iron for the first 12 to 15 months of life.
2. **Rickets.** VLBW infants who have had nutritional deficits in calcium, phosphorous, or vitamin D intake are at increased risk for rickets. Infants who are at highest risk are those treated with long-term parenteral nutrition and furosemide and those with decreased vitamin D absorption due to fat malabsorption. Infants with rickets diagnosed in the NICU may need continued supplementation of calcium, phosphorous, and vitamin D during the first year of life. Supplemental vitamin D (400 IU/day) should also be provided to all infants discharged home on human milk or who taking less than 1 L of formula per day, which is enough to provide 400 IU/day.

D. Sensory issues that need special follow-up include vision and hearing.

1. **Ophthalmologic follow-up** (see Chapter 67). Infants with severe retinopathy of prematurity (ROP) are at increased risk for significant vision loss or blindness in the setting of retinal detachment. The risk of severe ROP is highest in the ELBW population, in whom the incidence of blindness is 2% to 9%. Infants who have required treatment with laser therapy or bevacizumab (Avastin) warrant additional close monitoring to ensure that the infant's retina becomes fully vascularized without complications.

   In addition to ROP, other ophthalmologic conditions seen in NICU graduates include the following:

   a. Refractive errors are more frequent in premature than term infants. Myopia is the most common problem and may be severe. Hyperopia also occurs more commonly in premature infants. Vision is corrected with eyeglasses.

   b. Amblyopia (reduced vision caused by lack of use of one eye during the critical age for visual development) is more frequent in premature infants usually related to strabismus, anisometropia, or bilateral high refractive error (bilateral ametropia). Amblyopia can become permanent if it is not treated before 6 to 10 years of age.

   c. Strabismus, or misalignment of the eyes, is more common in premature infants, especially in those with a history of ROP, intracranial hemorrhage, or white matter injury; the most common form is esotropia (crossed eyes), although exotropia ("wall eye") and hypertropia (vertical misalignment of the eyes so that one eye is higher than the other)

also occur. Strabismus may be treated with eye patching, atropine drops, corrective lenses, or surgery depending on the cause.

d. Anisometropia, defined as a substantial difference in refractive error between the two eyes, occurs more often in premature than term infants. Because the eyes cannot accommodate (focus) separately, the eye with the higher refractive error can develop amblyopia. Treatment for anisometropia is vision correction with eye glasses.

e. In infants who have had severe ROP including those treated with laser therapy, there is an increased risk of cataracts, glaucoma, late retinal detachment, abnormal color vision development, and visual field deficits. Infants who have received intravitreal bevacizumab (Avastin) treatment are known to have delayed maturation of their retinal vessels. Potential long-term outcomes of this treatment are still unknown and are currently being studied.

f. All VLBW infants should have follow-up with an ophthalmologist who has experience with ophthalmologic problems related to prematurity. Close monitoring until the retinal vessels have reached maturity should occur in the first months of life. Subsequent assessments should occur by 8 to 12 months of age and then according to the ophthalmologist's recommendation, usually annually or again at 3 years of age at the latest.

2. **Hearing follow-up.** Hearing loss occurs in approximately 2% to 11% of VLBW infants. Prematurity increases the risk of both sensorineural and conductive hearing loss. All VLBW infants should be screened both in the neonatal period and again before 1 year of age (earlier if parental concerns are noted or if the infant has additional risk factors for hearing loss) (see Chapter 68). There is also evidence that VLBW infants are at increased risk for auditory dyssynchrony (also called auditory neuropathy) and central auditory processing problems.

3. **Dental problems.** VLBW infants have been noted to have an increased incidence of enamel hypoplasia and discoloration. Long-term oral intubation in the neonatal period may result in palate and alveolar ridge deformation affecting tooth development. Initiation of routine supplemental fluoride at 6 months PMA is recommended, as is referral to a pediatric dentist in the first 12 months of life.

III. NEURODEVELOPMENTAL OUTCOMES.

Preterm infants are at higher risk for adverse neurodevelopmental outcomes when compared to full-term infants. Risk factors for neurodevelopmental problems are multifactorial and include perinatal risk factors as well as environmental exposures. Greater GA and a higher birth weight is associated with a lower risk of developmental delay. Perinatal risk factors for developmental delay include BPD, necrotizing enterocolitis, late-onset sepsis, ROP, and abnormal neuroimaging. Environmental risk factors for poorer developmental outcomes include spoken language other than English, Black race, lower parental education, and low socioeconomic status (SES). Interestingly, the impact of perinatal risk factors seems to decrease over time, whereas the influence of environmental factors becomes more prominent.

A. Neuromotor problems. Premature infants have a 70 to 80 times greater risk of CP compared to full-term infants. The most common type of CP is

spastic diplegia. Encouragingly, an analysis of motor development in a large cohort of extremely preterm infants revealed improved motor function by 18 to 26 months. Although only 10% to 12% of children born very preterm demonstrate severe neurologic impairment (such as CP) into the school-age years, 25% to 50% are affected by more subtle motor problems. Transient motor abnormalities include abnormal general movements (GMs), dystonia, and postural instability. These conditions usually reach a peak during the first 2 to 5 months after term and then resolve with time. Late-onset disorders include fine and gross motor delays, persistent neuromotor abnormalities (asymmetries), and problems with motor coordination and motor planning. Both transient and long-term motor problems in infants require assessment and treatment by physical and occupational therapists. These services are usually provided in the home through local early intervention programs. Some infants with CP are candidates for treatment with orthotics or other adaptive equipment. Children with hemiparesis may be candidates for constraint therapy. Children with significant spasticity are candidates for treatment with botulinum-A toxin (Botox) injections. In the case of severe spasticity, treatment with baclofen (oral or through an intrathecal catheter with a subcutaneous pump) may be helpful. Older children are candidates for surgical procedures. Infants with sensorineural problems require coordination of appropriate clinical services and developmental programs. For older children, consultation with the schools and participation in an educational plan are important.

B. Cognitive impairment. Risk of cognitive impairment in preterm infants is associated with degree of prematurity, presence of cerebral injury on neuroimaging, low parental education, and SES. Cognitive ability is typically assessed using an established scale such as the Bayley Scales of Infant and Toddler Development or the Mullen Scales of Early Learning. Additional instruments are available, but their psychometric properties are not as robust.

In the first 2 years of life, the incidence of cognitive impairment is 30% to 40% in extremely preterm and very preterm infants. VLBW infants tend to have scores somewhat lower on such scales than term infants, but many still fall within the normal range. The percentage of infants with scores >2 standard deviations below the mean is 5% to 20% for VLBW infants and 14% to 40% for ELBW infants. Most studies reflect the status of children younger than age 2 years. Among older children, the percentage of children who are severely affected appears to be the same, but the percentage with school failure or school problems is as high as 50%, with rates of 20% even among children with average IQ scores. When children were tested at ages 8 to 11 years, learning disabilities particularly related to visual spatial and visual motor abilities, written output, and verbal functioning were more common in ELBW infants (without neurologic problems diagnosed) compared to term infants of similar sociodemographic status. More than 50% of ELBW infants require some type of special education assistance compared to $<15\%$ of healthy term infants. Studies of teen and adult survivors born preterm are limited but reflect ongoing problems including lower rates of educational achievement, lower income, and higher levels of unemployment. However, a report of ELBW infants assessed in the teenage years with measures of self-esteem noted that they do not differ from

term controls. Further longitudinal follow-up of these children into early adulthood assessing quality of life measures in addition to the incidence of neurodevelopmental disability is essential.

Referral to **early intervention programs** at the time of discharge from the NICU allows early identification of children with delays and referral for therapy from educational specialists and speech therapists when appropriate. Children with severe language delays may also benefit from referral to special communication programs that use adaptive technology to enhance language and communication. Caretakers may require significant assistance not only in understanding the importance of specialized interventions but also in navigating the idiosyncrasies of available programs. Managed care pressures, the availability of specific specialists within programs, and the quality and frequency of each direct service to be delivered can vary significantly from program to program. Parents and caretakers may not be aware of these factors, and this in turn could affect the delivery of crucial services at a most important critical developmental period.

C. Social communication difficulties are increasingly a concern in the population of preterm infants. Prematurity is an identified risk factor for autism spectrum disorder (ASD), with a prevalence rate of 7% based on a large prospective study and a meta-analysis. Risk factors for ASD in preterm infants include lower GA and birth weight, intracranial hemorrhage, and acute and chronic lung disease. The relationship between GA and risk for ASD is significant, as there is an increased probability of ASD with each reduction in the week of prematurity between weeks 25 and 31. The probability of a later diagnosis of ASD is 22.6% for infants born at 25 weeks' gestation versus 6% at 31 weeks' gestation. This trend is more robust for females than males. The developmental trajectory of preterm infants who develop ASD shows a pattern of declining mental development from ages 12 to 24 months. The developmental profile of preterm infants most likely to be diagnosed with ASD is characterized by low cognitive scores at 6 months with further decline over time. Diagnosis of ASD typically involves a semistructured assessment of the child's social communication and play skills using the Autism Diagnostic Observation Schedule (ADOS). Reliable diagnoses can be made by experienced clinicians as early as the second year of life. For children who are not diagnosed with ASD, less severe social difficulties may include difficulties establishing friendships, greater social withdrawal, and poorer social skills. Following a diagnosis of ASD, coordination with early intervention is critical to establish behavioral intervention strategies that target social communication skill development and reduction of restricted interests and repetitive and challenging behaviors.

D. Moderate and late preterm (MLPT) births (34 to 37 weeks' gestation) comprise most preterm infants. Therefore, long-term developmental concerns in this population potentially have a large public health influence. MLPT children at 2 years' corrected age performed more poorly in cognitive, language, and motor domains compared with term-born controls. The disparity was greatest in the language domain, where MLPT children had 3 times higher odds of language impairment than their term-born peers, with both receptive and expressive language equally affected. It is also of great concern that MLPT children appear to be at much greater risk for motor impairment as well as delays in social competence.

E. Emotional and behavioral health

1. **Sleep.** Preterm infants have a higher rate of sleep problems compared to those born at term. The cause is frequently multifactorial with medical and behavioral components. Patience and predictability are important caveats to remember when caring for preterm infants. It is important to remind parents that their infant should sleep supine in a crib or bassinet per the AAP guidelines for infant sleep safety and sudden infant death syndrome (SIDS) risk reduction. Co-sleeping with parents and allowing infants to sleep in infant swings or car seats should be advised against. Parents may benefit from books on sleep training or, in more severe cases, referral to a sleep specialist.
2. **Behavior problems.** VLBW children are at increased risk for behavior problems related to poor behavioral self-regulation, which can include hyperactive/aggressive behavior and attention problems; sensory sensitivities; and anxiety, depression, and somatic symptoms. Problems reported in the first 2 years include somatic symptoms as well as lower social orientation and pretend play skills. By the preschool years, very preterm–born children show increased behavior difficulties in most domains including hyperactivity, conduct problems, emotional dysregulation, peer problems, and lower prosocial behavior. At school age, the most prevalent psychiatric disorder is the inattentive subtype of attention deficit hyperactivity disorder, with an estimated prevalence of 7% to 23%, followed by emotional disorders such as anxiety (9%), and ASDs (3.6% to 8%). Recent research findings indicate that parenchymal lesions/ventricular enlargement during the neonatal period predict attentional difficulties without hyperactivity in these children. Environmental risk factors for behavioral problems include stress within the family, maternal depression, financial difficulties, and smoking. Detection of behavioral problems is achieved most commonly through parent interview and using scales developed to elicit parental and teacher concerns. Management depends on the nature of the problem and the degree of functional disruption. Some problems may be managed with special educational programs; others may involve referral to appropriate behaviorally based psychotherapy services.
3. **Parental mental health.** More than 40% of mothers experiencing preterm suffer from depression. More than one-third of mothers may experience an acute stress disorder within 3 to 5 days after their infant's admission into the NICU with 15% later developing posttraumatic stress disorder (PTSD) at 1 month. Maternal anxiety and depression in the postnatal period can interfere with maternal–infant attachment and is associated with poorer developmental outcomes. Paternal mental health is less well studied, but the available evidence points to paternal symptoms of anxiety and depression predicting poorer mother–child interactions as well as developmental outcomes. Screening of NICU parents for postpartum depression or PTSD is recommended; the identification of which provides an opportunity for intervention that will enhance both parental and child health.

IV. HIGH-RISK INFANT FOLLOW-UP PROGRAMS. Initially established as important sources of quality assurance data for NICU care, follow-up has become a health service in and of itself providing medical and developmental support for NICU graduates aiming to optimize health outcomes for infants and families. Activities can include the following:

A. Management of sequelae associated with prematurity. As ever smaller infants survive, the risk of chronic sequelae increases. These include medical morbidities like BPD, feeding problems, and poor growth. They may also include neurologic, behavioral, and neurosensory problems like CP, attention deficits, vision or hearing impairment, and developmental delays.

B. Consultative assessment and referral. Regardless of specific morbidity at the time of discharge, NICU graduates require surveillance for the emergence of a variety of problems that may require referral to and coordination of multiple preventive and rehabilitative services.

C. Monitoring outcomes. Information on health problems and use of services by NICU graduates is integral to both the assessment of the effect of services and the counseling of parents regarding an individual child's future.

D. Program structure

1. The population requiring follow-up care differs with each NICU and the availability and quality of community resources. Most programs use as criteria some combination of GA, birth weight, and specific complications. The criteria must be explicit and well understood by all members of the NICU team, with mechanisms developed for identifying and referring appropriate children.
2. Visits depend on the infant's needs and community resources. Some programs recommend a first visit within a few weeks of discharge to assess the transition to home. If not dictated by acute problems, future visits are scheduled to assess progress in key activities. In the absence of acute care needs, patients are commonly assessed at 6-month intervals.

E. Program content

1. Because the focus of follow-up care is enhancement of individual and family function, personnel must have a breadth of expertise, including (i) clinical skill in the management of sequelae of prematurity; (ii) the ability to perform neurologic and cognitive diagnostic assessment; (iii) familiarity with general pediatric problems presenting in premature infants; (iv) the ability to manage children with complex medical, motor, and cognitive problems; (v) knowledge of the availability of and referral process to community programs; and (vi) facility with providing family-centered, culturally competent, trauma-informed care. Families will require varying degrees of advice and guidance.
2. Methods for assessing an individual's progress depend on the need for direct assessment by health professionals and the quality of primary care and early intervention services. A variety of indirect approaches of assessing developmental progress including parental surveys exist that provide information identifying children who have delays or other developmental concerns and warrant further assessment and/or intervention.

This strategy of initial assessment may be helpful when it is difficult for families to travel the distance back to the medical centers or to reduce program costs. Recommended staff team members and consultants include pediatrician (developmental specialist or neonatologist), neonatology fellows or pediatric residents (for training), pediatric neurologist, pulmonologist, physical therapist, psychologist, occupational therapist, dietitian, speech and language specialist, and social worker.

F. Special considerations

1. **Care integration.** Preterm infants often receive care from multiple subspecialty providers and community-based support services in addition to their pediatrician. Care is integrated among team members and across settings to ensure needs are met and not missed or duplicated. Newer models of integrated care place the child and family at the center of a network of providers and provide tools for measuring the effectiveness, quality, and value of care for children with medical and developmental complexity.
2. **Family/parent function and support.** Having a premature infant is often an extremely stressful experience for the parents. Providing specialized care in assessment, supportive counseling, and resources to families caring for a VLBW infant is essential and includes particular attention to issues of postpartum affective conditions and anxiety following the potentially traumatic experience of having a critically ill infant. Provision of specialized behavioral guidance and supportive counseling in addition to facilitating referrals to community providers for additional care should be made available by the team. Addressing the basic needs of families including health insurance issues, respite, advocating for services in the community, financial resources, and marital stress are also important.

Suggested Readings

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17 Neonatal Transport

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KEY POINTS

- Whenever possible, transport of the mother and fetus prior to delivery is preferable to postnatal transport.
- Newborns transported by air are subject to specific physiologic stresses associated with altitude.
- The risk of interfacility transport can be reduced by the use of specially trained and equipped neonatal transport teams.

I. INTRODUCTION.

Regionalization of perinatal services necessitates that newborns requiring intensive care or specialty treatment be transported between facilities. Most experts agree that whenever possible, it is preferable to provide safe and expeditious prenatal transfer of the mother to a center with the necessary resources prior to delivery of a high-risk newborn. Unfortunately, some infants requiring expert neonatal care are not identifiable prior to birth, and others deliver or require delivery too quickly to permit maternal–fetal transfer. It is important that a system exists for timely referral, clear communication of information and recommendations, and access to specially trained personnel who can provide neonatal resuscitation and stabilization before and during transport.

II. INDICATIONS

A. Interhospital transport should be considered if the medical resources or personnel needed for specialized neonatal care are not available at the birth hospital. Because the birth of a high-risk infant cannot always be predicted, all facilities providing maternity services should ensure that personnel caring for newborns in the delivery room and/or in the immediate postnatal period are proficient in **basic neonatal resuscitation and stabilization**.

B. Transfer to the appropriate neonatal center should be expedited following initial stabilization. Medical personnel from the referring center should contact their affiliated neonatal intensive care unit (NICU) transport service to arrange transfer and to discuss a management plan to optimize the patient's condition before the transport team's arrival. Depending on the capabilities of the referring hospital and the anticipated need for advanced resuscitation, some neonatal transport programs will mobilize a team to be present at the time of delivery of a high-risk newborn.

C. Criteria for neonatal transfer depend on the capability of the referring hospital as defined by the American Academy of Pediatrics (AAP) policy statement on levels of neonatal care and as dictated by local and state public health regulations. The AAP defines neonatal levels of care as shown in Table 17.1.

All hospitals with level 1 or 2 neonatal care services should have agreements with regional referral centers outlining criteria for perinatal

Table 17.1. Levels of Neonatal Care

Level of Care	Services
Level 1 (including well newborn nurseries)	Neonatal resuscitation at delivery Postnatal care for stable term newborns Postnatal care for late preterm newborns who are physiologically stable Stabilization of the preterm or critically ill newborn prior to transfer to a higher level of care
Level 2 (special care nurseries)	Level 1 capabilities plus: Care for newborns born <32 weeks or >1,500 g with physiologic immaturity or transient conditions related to prematurity Ongoing care of infants recovering from critical conditions Time-limited provision of mechanical ventilation or continuous positive airway pressure Stabilization prior to transfer for any infant needing transfer to a higher level of care
Level 3 (neonatal intensive care units)	Level 2 capabilities plus: Provision of life support and comprehensive neonatal intensive care Subspecialty medical and surgical expert consultation Mechanical ventilation (all forms) Diagnostic imaging capabilities
Level 4 (regional neonatal intensive care units)	Level 3 capabilities plus: Specialized surgical capabilities for repair of congenital or acquired conditions Critical care transport services and outreach education

Source: Reproduced with permission from American Academy of Pediatrics Committee on Fetus and Newborn. Levels of neonatal care. *Pediatrics* 2012;130(3):587–597.

consultations and neonatal transfer. Conditions that typically require transfer to a center that provides neonatal intensive care (level 3 or 4) include the following:

1. Prematurity (<32 weeks' gestation) and/or birth weight <1,500 g
2. Respiratory distress requiring escalating support on continuous positive airway pressure (CPAP) or high concentrations of oxygen (FiO_2 >0.6).
3. Hypoxic respiratory failure requiring invasive mechanical ventilation
4. Persistent pulmonary hypertension
5. Congenital heart disease or cardiac arrhythmias
6. Congenital anomalies and/or inborn errors of metabolism
7. Hypoxic-ischemic encephalopathy
8. Seizures
9. Neonatal sepsis requiring vasoactive support
10. Hepatic or renal failure
11. Acquired complications of prematurity such as necrotizing enterocolitis or intraventricular hemorrhage
12. Other conditions that may be indications for neonatology consultation and/or transfer
    - **a.** Severe hyperbilirubinemia that may require exchange transfusion
    - **b.** Infant of diabetic mother with hypoglycemia or other complications
    - **c.** Severe intrauterine growth restriction (IUGR)
    - **d.** Birth weight between 1,500 and 2,000 g and gestational age between 32 and 36 weeks
    - **e.** Diagnostic procedures or therapies unavailable at referring hospital such as echocardiogram (ECHO), specialized surgical care, or extracorporeal membrane oxygenation (ECMO).

III. ORGANIZATION OF TRANSPORT SERVICES

A. The hospital-based or regional NICU transport team should have an appointed **medical director**. The transport team should follow practice guidelines detailed in easily accessible written protocols and procedures that are reviewed on a periodic basis. A **medical control physician**, who may be the attending neonatologist or fellow (supported by an attending), should supervise each individual patient transport. The medical control physician should be readily available by telephone for consultation to assist in the management of the infant during transport. Programs with telemedicine capabilities may employ this technology to support referring providers prior to the transport team's arrival and to inform triage and disposition decisions.

B. Transport teams. Qualified transport teams should be composed of individuals with pediatric/neonatal critical care experience and training in the needs of infants and children during transport and who participate in the care of such patients with sufficient frequency to maintain their expertise. Such teams typically consist of a combination of two or three trained personnel and can include one or more of the following: neonatal nurse practitioners, critical care nurses, respiratory therapists,

paramedics, and physicians. Senior pediatric residents and subspecialty fellows can participate in transports for those services that include physician team members. The transport team's skills should be assessed periodically, and procedural and simulation training should be part of routine ongoing education.

C. Types of transport teams

1. Unit-based transport teams consist of personnel such as nurses, respiratory therapists, and neonatal nurse practitioners who are involved in routine patient care in the NICU and are deployed when a request for transport is received. If transport volume is low, this type of staffing may be most cost-effective; however, each team member has little opportunity to gain experience or maintain skills specific to transport.
2. Dedicated, hospital-based specialty transport teams are staffed separately from NICU personnel specifically for the purpose of transport of patients to and from the hospital. These clinicians do not have patient assignments, although they may assist NICU or other hospital staff when they are not on transport. A large volume of transports is necessary to justify a dedicated transport team, which must consist of sufficient personnel for around-the-clock coverage. This arrangement allows dedicated team members to maintain specialized skills for transport and facilitates rapid mobilization to transport requests. Hospital-based specialty transport teams often transport both neonatal and pediatric patients.
3. General critical care transport teams may be hospital based or non–hospital based and typically transport a range of patient types including adults. Their experience with neonates may be variable, but they provide essential services to areas without access to specialty neonatal teams.

D. Modes of transport include ground ambulance, rotor-wing aircraft (helicopter), and fixed-wing (airplane) aircraft. The type of vehicle(s) operated will depend on each program's individual needs, specifically the distance of transports anticipated, acuity of patients, and geographic terrain to be covered. Some hospitals own, maintain, and insure their own vehicles, whereas others contract with commercial vendors for vehicles that can accommodate a transport incubator and appropriate equipment. Although the type(s) of vehicle chosen for transport will vary depending on the individual program's needs, the vehicles chosen must be outfitted to conform to standards that ensure safety and efficiency of transport. Vehicles should comply with all local, state, and federal guidelines for air transport and/or ground ambulances. The vehicles should be large enough to allow the transport team to adequately assess and treat patients as needed *en route* to the receiving hospital and should be equipped with appropriate electrical power supply, medical gases (with reserve capacity, in case of a breakdown), and communication systems. All equipment and stretchers should be properly secured, and transport team personnel should use appropriate passenger safety restraints.

Each mode of transport—ground, rotor wing, and fixed wing—has advantages and disadvantages.

1. **Ground transport** is used most commonly among neonatal transport programs. Advantages include a larger workspace than air ambulances, ability to accommodate multiple team members and passengers (including

parents), and the option to stop the vehicle to assess the patient or perform procedures.

2. **Rotor-wing transport** may provide more rapid mobilization and has the advantage of decreased travel time between the referring and receiving hospitals especially if there is an on-site helipad. Helicopter transports are generally used for distances of up to ~150 miles, although a rotor-wing service is more expensive to operate, has limitations with regard to weather and weight, and has inherently more safety considerations.
3. **Fixed-wing transport** is advisable for transport of patients over greater distances (over ~150 miles each way), is moderately expensive to operate, and requires an airport to land and an ambulance at either end of the flight to transport the patient between the airport and the hospital. Fixed-wing aircraft have fewer restrictions for weather than do helicopters.

E. Equipment. The team should carry with them all equipment, medications, and other supplies that might be needed to stabilize an infant at a referring hospital. Teams should use checklists prior to departure to ensure that vital supplies and equipment are not forgotten. Packs especially designed for neonatal transport are commercially available. These packs or other containers should be stocked by members of the transport team, which ensures that they will know where to find required items promptly. The weight of the stocked packs should be documented for air transport (Tables 17.2 to 17.4).

F. Oxygen. Although ground and air ambulances are typically equipped with an adequate supply of onboard oxygen and compressed air for operating mechanical ventilators, the transport team should be familiar with the amount of oxygen available in the isolette's portable tanks in the event of a system malfunction. The duration of time a portable tank will provide oxygen depends on the size of the cylinder, the starting pressurization, and the gas flow rate, as shown in Table 17.5, and the accompanying formula. This information is also relevant for intrahospital transports using portable oxygen tanks. In general, oxygen tanks should be changed when they reach 500 psi remaining.

G. Legal issues. The process of neonatal transport may raise legal issues, which vary among states. The proactive use of transfer agreements can address the roles and responsibilities of referring and receiving institutions and their staffs. Transport teams should periodically review all routine procedures and documentation forms with their hospital legal counsel to ensure compliance with changing laws that govern the transport of infants and accompanying family members (if present). The team should have the ability to contact via telephone appropriate hospital legal counsel as needed. Federal regulations known as the Emergency Medical Treatment and Active Labor Act (EMTALA), published by the Centers for Medicare & Medicaid Services (CMS), outline the responsibilities of referring physicians and receiving institutions during emergency interhospital transport (http://www.cms.gov/Regulations-and-Guidance/Legislation/EMTALA).

H. Quality assurance and performance improvement activities should be performed routinely using established benchmarks whenever possible. The Ground Air Medical qUality Transport (GAMUT) Quality Improvement Collaborative (http://www.gamutqi.org) uses the GAMUT Database as a

Table 17.2. Neonatal Transport Team Equipment

Transport incubator equipped with neonatal-capable ventilator and gas supply (oxygen and compressed air tanks), blender, and flow meter
Monitors for heart rate, invasive and noninvasive blood pressures, oxygen saturation, end-tidal CO_2 and temperature, with associated electrodes/probes/transducers/cuffs
Defibrillator with neonatal-appropriate energy settings and paddles/pads
Suction device and suction catheters
Feeding tubes, sump tubes (e.g., Replogle)
Oxygen tubing, masks, nasal cannulas, CPAP devices, bubble CPAP devices if used
Nitric oxide tank and delivery equipment
Infusion pumps
Gel-filled mattress
Glucometer or another point-of-care testing device
Airway equipment
Flow-inflating bag with manometer and oxygen tubing
Face masks (premature and term infant)
Oropharyngeal airways
Laryngoscopes with no. 00, 0, and 1 blades, with extra batteries/bulbs (if needed)
Endotracheal tubes sizes 2.5–4.0 mm
Magill forceps
Supraglottic airways
CO_2 detectors or waveform capnography
Instrument tray for chest tubes and umbilical vessel catheters
Chest tubes and connectors, Heimlich valves, closed suction/water seal system
Vascular access supplies, including intraosseous needles
Medication delivery supplies, including needles and syringes
Stethoscope
Gloves, masks, disposable gowns, eye protection

(continued)

Table 17.2. Neonatal Transport Team Equipment *(Continued)*
Source of electrical power, heat, and light
Adaptors to plug into both hospital and vehicle power
Clipboard with transport data forms, permission forms, progress notes, and booklet for parents
Medication guide for dosing and infusion preparation
CO_2, carbon dioxide; CPAP, continuous positive airway pressure.

free resource for transport teams to track, report, and analyze their performance on transport-specific quality metrics and to compare themselves with other programs. The Commission on Accreditation of Medical Transport Systems (http://www.camts.org) performs voluntary surveys of transport programs and grants accreditation based on rigorous standards of safety and quality.

I. Malpractice insurance coverage is required for all team members. The tertiary hospital should decide whether transport is considered as an off-site or extended on-site activity because this can affect the necessary coverage.

J. Ground and air ambulance regulations as well as requirements for medical control physicians involved with prehospital care providers vary from state to state and may conflict with transport team goals or procedures. For example, some states require that an ambulance stop at the scene of an unattended accident to render aid until a second ambulance arrives.

K. Safety. The mobile environment carries inherent risks for transport team members and patients. Transport programs should have clear guidelines for parents who wish to accompany the team, including policies if there is concern for impairment or potential violence. During the transport, all equipment must be secured to avoid passenger injury. Likewise, providers and parents, if present, should use appropriate vehicle restraint devices during travel or flight. Commercial restraint devices for newborns transported in isolettes are available, but their crashworthiness has not been adequately assessed.

IV. REFERRING HOSPITAL RESPONSIBILITIES

A. Identify the appropriate tertiary care facility for transfer. Neonatal referral centers have varying capabilities. Management of specific conditions such as congenital heart disease or therapies such as ECMO may not be available at all tertiary care NICUs. Prompt notification of the receiving hospital will allow timely deployment of the transport team and verify that the required services are available. Any risk of communicable diseases posed by the patient must be disclosed to the tertiary center at the time of the request for transfer.

Table 17.3. Medications Used during Neonatal Transport
Adenosine
Albumin 5%
Ampicillin
Atropine
Calcium chloride
Calcium gluconate
Cefotaxime
Dexamethasone
Dextrose 10% in water ($D_{10}W$)
Dextrose 5% in water (D_5W)
Dobutamine
Dopamine
Epinephrine (0.1 mg/mL)
Erythromycin eye ointment
Fentanyl
Fosphenytoin
Furosemide
Gentamicin
Heparin
Lidocaine
Lorazepam
Midazolam
Morphine
Naloxone
Normal saline (0.9% NaCl)
Phenobarbital
Potassium chloride
Prostaglandin E_1 (requires refrigeration)
(continued)

Table 17.3. Medications Used during Neonatal Transport *(Continued)*
Rocuronium
Sodium bicarbonate 4.2% (0.5 mEq/mL)
Sterile water for injection
Surfactant (bovine surfactant products require refrigeration)
Vecuronium
Vitamin K_1

B. Documentation. Staff at the referring hospital should complete the administrative forms required for transfer, which include parental consent. A transfer summary should document the care given to the infant at the referring hospital, including a complete medication list. Transport team documentation begins upon the team's arrival and should note all treatment rendered to the patient by either the referring hospital staff or the transport team.

V. TRANSPORT TEAM RESPONSIBILITIES

A. When receiving the initial request for transfer, the medical control physician should obtain a sufficiently detailed summary from the referring clinician to decide the appropriate team composition and equipment required, in consultation with the transport team.

B. The medical control physician should discuss the patient's condition, anticipated problems, and potential therapies with the transport team members before their departure. This provides an opportunity for the team members to ask questions and to determine if there is any additional equipment or medications that might be needed.

Table 17.4. Barometric Pressure and Partial Pressure of Oxygen with Increasing Altitude

	Sea Level	2,000	4,000	6,000	8,000	10,000
Barometric pressure (torr)	760	706	656	609	565	523
Partial pressure of FiO_2 0.21 (torr)	160	148	138	128	119	110

$$F_iO_2 \text{ required} = \frac{F_iO_2 \times BP_1}{BP_2}$$

F_iO_2, fraction of inspired oxygen patient is currently receiving; BP_1, barometric pressure prior to flight; BP_2, barometric pressure at altitude.

Table 17.5. Portable Oxygen Tank Characteristics

Cylinder Type	Conversion Factor	Amount of Oxygen When Full (L)
D	0.16	350
E	0.28	625
M	1.56	3,000
H or K	3.14	6,500

Formula for determining available duration of gas delivery:

$$\text{Cylinder starting pressure}^{*} \times \frac{\text{Conversion factor}}{\text{Flow rate (L/minute)}} = \text{Duration of flow (minutes)}$$

*Usual full cylinder maximum = 2,200 psi (pounds per square inch).

C. Upon arrival at the referring NICU, transport team members should introduce themselves clearly and politely to the referring hospital staff and family members. Appropriate photo identification should be worn. The referring and/or primary physicians should be identified and their names documented.

D. Transfer of patient information (handoff) should be clear. Use of checklists or standardized templates for communication decreases the likelihood of omissions during handoff.

E. The team should work collegially with the referring hospital staff and be objective in their assessment and stabilization. The transfer of care from referring hospital staff to the transport team is a stepwise process that requires clear communication about roles and responsibilities. Any differences of opinion related to the care of the infant should be discussed with the medical control physician.

F. Parents should be given an opportunity to see the infant before the team leaves the referring hospital. While meeting with the family, the team should obtain consent for transfer and other anticipated procedures (including blood transfusion, if indicated) and obtain accurate contact information for the parents.

G. Whenever possible following completion of the transport, the team should call the referring hospital staff with pertinent follow-up of the patient's condition and how he or she tolerated the transport to the tertiary facility.

H. Transport teams should consider an active outreach education program for referring hospital staff that could include conferences, in-service presentations, and case reviews.

VI. MEDICAL MANAGEMENT BEFORE TRANSPORT

A. The medical control physician should support the medical management and stabilization of the neonate while the transport team is mobilizing and *en route*. The extent of pretransport diagnostic testing and treatment depends

on the nature of the patient's condition as well as the resources available at the referring hospital. In general, pretransport interventions should focus on respiratory, cardiac, neurologic, and metabolic stabilization.

B. Pretransport management should include attention to the following:

1. Establish and maintain a neutral thermal environment or allow for passive or active cooling if the infant meets criteria for therapeutic hypothermia.
2. Ensure airway patency and security and support oxygenation and ventilation.
3. Support hemodynamics and perfusion with fluids and/or vasoactive infusions.
4. Ensure adequate blood glucose concentration.
5. Obtain vascular access (peripheral intravenous [PIV], umbilical venous catheter [UVC], umbilical artery catheter [UAC]) as indicated.
6. Obtain appropriate cultures and give first doses of antibiotics, if indicated.
7. Obtain copies of obstetric and neonatal charts for the transport team, including digital copies of radiographic studies.
8. Prepare the parents for transport of their infant and, if possible, allow them time to visit with their newborn.

VII. MEDICAL MANAGEMENT DURING RETURN TRANSPORT

A. The mobile environment. The period of time after leaving the referring hospital and arriving at the receiving hospital is the most vulnerable for the patient due to challenges with monitoring, assessment, and interventions in the mobile environment. Most modern monitors are built to withstand interference from road vibration and 60 cycle electrical signals. Direct observation of the patient may be challenging due to the use of the isolette, movement of the vehicle, and restraint use by the transport team members, so it is essential that monitoring devices are functioning and easily visible.

B. Adverse events. Dislodgment of lines and tubes can occur with movement of the ambulance or patient. Properly securing tubes and lines prior to transport is the most effective prevention strategy, and team members should carefully coordinate transfers into and out of the isolette so that someone is responsible for supporting the endotracheal tube if present. Travel in both the ground and air environments involves physiologic stressors that are different than in the hospital setting, and judicious use of sedation may be indicated to maintain the patient's comfort and safety and, in particular, avoid inadvertent extubation. In the event of an unexpected clinical deterioration, auscultation may be unreliable due to background noise, and capnography may be more reliable to assess endotracheal tube position. If the patient continues to deteriorate, it may be appropriate during ground transport to ask the driver to pull over so that the team can accurately assess breath sounds and perform necessary interventions. Ambulance sirens and flashing lights should be used only in rare circumstances because they increase the risk of causing accidents and have not been shown to save substantial time.

C. Communication. The transport team should notify the medical control physician of any significant changes in the patient's condition during transport. On rare occasions, it may be appropriate to return to the referring hospital or divert to a closer hospital if the patient is not responding to interventions. Cellular phones are most commonly used to communicate during transport, but a backup system (i.e., radio) should be available in the event there is no cellular phone service due to terrain or distance. The use of a video connection in a ground transport vehicle is feasible but may be challenging due to issues with connectivity. If indicated, the medical control physician should notify subspecialty services that may need to be involved urgently in the care of the patient on arrival, such as cardiology or surgery.

VIII. ARRIVAL AT THE NEONATAL INTENSIVE CARE UNIT

A. The team should give the NICU caregivers a succinct and complete summary of the infant's clinical condition and copies of the referring hospital's medical record and radiographic studies. Use of a standardized handoff script will ensure relevant information is not inadvertently omitted.

B. A team member should telephone the parents to let them know that their infant has arrived safely.

C. Relevant documentation regarding the transport should be completed, and, when appropriate, the medical control physician should sign orders for treatment during transport.

D. All transport medications should be immediately restocked and all equipment checked and prepared for subsequent transports.

E. If an untoward incident occurred during transport, appropriate documentation should be completed, and the transport team's leadership should be notified to allow appropriate investigation and debriefing.

IX. SPECIFIC CONDITIONS AND MANAGEMENT

A. Premature infants with respiratory distress syndrome (RDS) who have not responded to early application of CPAP may benefit from exogenous surfactant administration. When a preterm infant requires intubation and mechanical ventilation, the transport team should consider administration of surfactant while at the referring hospital rather than delaying treatment until arrival at the tertiary care center. Ideally, a chest x-ray should be obtained after intubation and prior to surfactant delivery to avoid administration of surfactant into one lung. The transport team should anticipate rapid changes in lung compliance and be prepared to wean ventilatory support during the first 30 minutes after surfactant delivery due to the risk of pneumothorax. The practice of "INSURE" (*IN*tubation, *SUR*factant, *E*xtubation) is not recommended for use by critical care transport teams.

B. Hypoxic respiratory failure. Management should focus on ensuring adequate lung recruitment using ventilatory strategies and, in preterm and select term infants, surfactant administration, while avoiding injurious

ventilator settings and/or hyperventilation. Although high-frequency oscillatory ventilation (HFOV), high-frequency flow interruption (HFFI), and high-frequency jet ventilation (HFJV) are feasible during interhospital transport, safe usage requires the ability to perform frequent blood gas analysis by point-of-care testing to adjust settings and avoid the risk of pneumothorax. The transport of newborns cannulated for ECMO at a referring facility can be safely performed by teams with extensive training and experience, usually in collaboration with the tertiary center's perfusionists or ECMO specialists.

C. Pulmonary hypertension. If the infant has signs of severe pulmonary hypertension (e.g., tachycardia, respiratory failure with hypoxemia, and preductal and postductal oxygen saturation differential), transport teams should be prepared to institute inhaled nitric oxide at the referring hospital and continue administration during transport. If inhaled nitric oxide has been started at the referring hospital, it is important to avoid interruption during transport due to the risk of rebound pulmonary hypertension.

D. Cardiac disease. Ideally, a pediatric cardiologist or cardiac intensive care specialist at the tertiary care facility should be available to make recommendations for care prior to and during transport of the infant. For infants with suspected ductal-dependent congenital heart disease, prostaglandin E_1 (PGE_1) may be initiated prior to transport. Apnea, fever, and hypotension are common side effects of PGE_1 and appear to be dose dependent. In the past, endotracheal intubation was routinely recommended for neonates receiving PGE_1. More recently, many transport teams have adopted the approach of using low-dose PGE_1 for infants without significant respiratory distress, acidosis, or impaired perfusion. In such cases, it may not be necessary to secure the airway prior to transport, which may be beneficial to the balance of pulmonary and systemic blood flow in certain infants such as those with single ventricle physiology.

E. Surgical conditions. Surgical conditions such as gastroschisis or omphalocele require careful attention to positioning of the newborn to avoid tension or twisting of the extra-abdominal contents as well as the use of warmed, moisturized coverings to prevent loss of heat and fluids. Newborns with suspected esophageal atresia are at risk for aspiration from secretions in the upper esophageal pouch and may benefit from prone positioning with the head of the isolette mattress elevated in addition to an oral or naso-esophageal drain. Special consideration should be given to infants being transported by air (see section X.B) who may benefit from gastric decompression if there is suspicion of intestinal obstruction or condition such as congenital diaphragmatic hernia.

F. Neonatal encephalopathy. Therapeutic hypothermia is recommended to improve neurologic outcome in term or near-term infants with hypoxic-ischemic encephalopathy who meet specific criteria. Current guidelines call for the initiation of cooling by 6 hours of life. Passive cooling initiated at the referring hospital can be continued during transport; alternatively, several devices are now available to provide servo-controlled active cooling in the mobile environment. Continuous esophageal or rectal temperature monitoring is essential to avoid excessive hypothermia.

X. PHYSIOLOGIC CONSIDERATIONS OF AIR TRANSPORTS. Rotor-wing aircraft are not pressurized, so the interior pressure will vary with altitude. Fixed-wing aircraft are pressurized but typically maintain a cabin pressure equivalent to an altitude of 5,000 to 8,000 ft at which barometric pressure is decreased.

A. Alveolar hypoxia (Dalton law). As altitude increases, the barometric pressure and partial pressure of oxygen in the air decrease (see Table 17.4), leading to a reduction in alveolar oxygen tension. Even in aircraft with pressurized cabins, because the cabin pressure is usually maintained at a level equal to 5,000 to 8,000 ft above sea level, it may be necessary to increase the FiO_2 delivered to the infant to compensate. The FiO_2 required at altitude to approximate the same oxygen tension that the patient is receiving at sea level can be calculated by the formula in Table 17.4. If neonates with severe lung disease are transported by air, it may be necessary to request the pilot to pressurize the cabin closer to sea level to avoid severe hypoxemia. Ultimately, pulse oximetry and blood gas estimations should be used to guide adjustments in delivered FiO_2 to maintain adequate oxygen delivery.

B. Gas expansion (Boyle law). As altitude increases and barometric pressure decreases, the volume of gases will increase. As a result, gases trapped in closed spaces will expand. This can result in a small pneumothorax or the normal gaseous distention of the gastrointestinal tract causing clinical deterioration in an infant that was stable at ground level. To prevent decompensation in flight, pneumothoraces should be drained and, if the patient is intubated or has gastric distension, the stomach should be vented with a nasogastric tube before air transport.

XI. SIMULATION IN TRANSPORT MEDICINE. Transport of critically ill infants involves high-stress situations where it is crucial for the team members to work well together to ensure patient and team member safety using clear communication and principles of crisis resource management (CRM). Simulation-based training allows high-performance teams to practice critical clinical situations in a safe environment and is most effective if accompanied by facilitated debriefing.

Suggested Readings

American Academy of Pediatrics. *Guidelines for Air and Ground Transport of Neonatal and Pediatric Patients*. 4th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2016.

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Insoft RM. Transport of the ventilated infant. In: Goldsmith JP, Keszler M, Karotkin E, et al, eds. *Assisted Ventilation of the Neonate*. 6th ed. Philadelphia, PA: Elsevier; 2017:425–433.

Schwartz HP, Bigham MT, Schoettker PJ, et al. Quality metrics in neonatal and pediatric critical care transport: a national Delphi project. *Pediatr Crit Care Med* 2015;16(8):711–717.

18 Neonatal Intensive Care Unit Discharge Planning

Vincent C. Smith and Theresa M. Andrews

KEY POINTS

- Begin discharge planning shortly after admission and continue until families are prepared to bring their infant home.
- Incorporate the tenets of family-centered care (FCC) as much as is feasible during the discharge planning process.
- Include a structured family education program that is tailored to a family's specific needs and circumstance with frequent evaluations of progress and the capacity for adjustment as necessary.

I. INTRODUCTION. A successful transition from the neonatal intensive care unit (NICU) to home is critical in order to ensure a safe and confident transition home for newborns and their families. The optimal safe and successful discharge requires mutual participation between the family and the medical faculty and should begin at admission and follow the continuum of the infant's hospital stay. This chapter discusses the infant's discharge readiness as well as the discharge preparation for the family.

NICU **discharge readiness** is the attainment of technical skills and knowledge, emotional comfort, and confidence with infant care by the primary caregivers at the time of discharge. NICU **discharge preparation** is the process of facilitating discharge readiness to successfully make the transition from the NICU to home. Discharge readiness is the desired outcome, and discharge preparation is the process.

II. INFANT'S DISCHARGE READINESS. The American Academy of Pediatrics (AAP) recommends the transition to home occur when the infant achieves physiologic maturity and has completed all predischarge testing and treatment.

A. Healthy growing preterm infants are considered ready for discharge when they meet the following criteria:

1. Able to maintain temperature in an open environment
2. Can be fed in a safe and sustained way: orally by bottle or breast without respiratory compromise or by an alternative method which may include the following:
   - **a.** Gastric tube
   - **b.** Gastric/jejunal tube

c. Nasogastric tube
d. Nasojejunal tube

3. Demonstrates steady weight gain evidenced by an average weight gain of 20 to 30 g/day
4. Free of significant apnea, bradycardia, or oxygen desaturation events for a minimum of 3 to 5 days (see Chapter 31)
5. Able to sleep with head of bed flat without compromising health and safety; incorporating safe sleep recommendations according to AAP
6. Completed routine screening tests and immunizations according to AAP, local, and regional guidelines (Table 18.1)
   a. **For all infants**
      i. Newborn screening (see Chapter 8)
      ii. Hearing screening (see Chapter 68)
      iii. Immunizations administered according to AAP guidelines based on chronologic, not postmenstrual, age (http://www.cdc.gov/vaccines and see Chapter 7)
      iv. Critical congenital heart defect (CCHD) screening
      v. Car seat/bed challenge: Prior to discharge home, all infants much be assured a safe method of transport.[1]
         a) Conduct a car seat test for all infants <37 weeks' gestation or with conditions that may compromise respiratory status (e.g., chronic lung disease, airway anomalies, and tracheostomy).
         b) Conduct a car seat fit assessment for infants >37 weeks but <2.5 kg.
   b. **For preterm infants**
      i. Head ultrasound evaluation or follow-up if indicated
      ii. Ophthalmologic evaluation or follow-up if indicated (see Chapter 67)

Table 18.1. Guidelines for Routine Screening, Testing, Treatment, and Follow-up at Neonatal Intensive Care Unit (NICU)

Newborn Screening
Criteria
■ All infants admitted to the NICU
Initial
■ At 24 hours of life and no later than 48 hours or at transfer or D/C (whichever comes first)
■ Obtain screen prior to any blood transfusion before 24 hours of life.

(continued)

Table 18.1. Guidelines for Routine Screening, Testing, Treatment, and Follow-up at Neonatal Intensive Care Unit (NICU) *(Continued)*

Follow-up
■ Day 14 or D/C date (whichever comes first)
■ Day 30 or D/C date (whichever comes first)
■ Continue monthly.
■ On D/C date if more than 7 days since prior screen
Transfusion Considerations
■ If infant is transfused within 48 hours before a screen is collected, a repeat must be sent 48 hours following the transfusion.
Head Ultrasound (see Chapter 54)
Criteria
■ All infants with gestational age (GA) <32 weeks
Initial
■ Days 7–10 (In the case of critically ill infants, when results of an earlier ultrasonography may alter clinical management, an ultrasonography should be performed at the discretion of the clinician.)
Follow-up (Minimum if No Abnormalities Noted)
■ If no hemorrhage or germinal hemorrhage only: week 4 and at 40 weeks' PMA (or D/C if <40 weeks)
■ If intraventricular (grade 2+) or intraparenchymal hemorrhage: Follow up at least weekly until stable (more frequently if unstable posthemorrhagic hydrocephalus). (Daily head circumference measurement should also be performed in the case of ventricular dilatation.)
Note: An ultrasound should be done at any GA at any time if thought to be clinically indicated.
Audiology Screening (see Chapter 68)
Criteria
■ All infants being discharged home from NICU or who are at 34 weeks' PMA or greater at the time of transfer to a level 2 nursery
Timing
■ Examine at 34 weeks' gestation or greater when infant is medically stable (e.g., not on mechanical ventilation or CPAP).

(continued)

Table 18.1. ***(Continued)***

- Screening should be done prior to D/C to home. If infant is transferred to another facility before screening is done, need for screening should be clearly documented in the D/C summary.
- Infants who refer on their final screen should have CMV screening done.

Car Seat and Car Bed Fit Assessment and Screening

Criteria

- All infants to be discharged home from NICU and born at <37 weeks or with other conditions that may compromise respiratory status (e.g., chronic lung disease, airway anomalies, and tracheostomy) will have a car seat or car bed test.
- All infants born >37 weeks GA weighing <2,500 g will have a car seat or car bed fit assessment.

Timing

- Fit assessment or screening prior to D/C home

Ophthalmologic Examination (see Chapter 67)

Criteria

- All infants with BW ≤1,500 g or GA <31 0/7 weeks
- Infants with a BW between 1,500 and 2,000 g or GA 31 0/7–34 0/7 weeks with high illness severity (e.g., those who have had severe respiratory distress syndrome, hypotension requiring pressor support, or surgery in the first several weeks of life) per the discretion of the attending neonatologist

Timing of Initial Exam

GA	Postmenstrual Age	Week after Birth
22	29	7
23	30	7
24	31	7
25	31	6
26	31	5
27	31	4
28	32	4
29	33	4
30	34	4
31+	—	4

(continued)

Table 18.1. Guidelines for Routine Screening, Testing, Treatment, and Follow-up at Neonatal Intensive Care Unit (NICU) *(Continued)*

- If the infant is transferred to another nursery prior to 4 weeks of age, recommend exam at the receiving hospital.
- If the infant is discharged home prior to 4 weeks of age, examine prior to D/C.

Follow-up (Based on Most Recent Exam Findings)

- Follow-up examinations should be recommended by the examining ophthalmologist on the basis of retinal findings classified according to the international classification. The following schedule is suggested:

Stage	Zone	Follow-up
Immature (no ROP)	I	≤1 week
Immature	Posterior II	1–2 weeks
Immature	Midanterior II	2 weeks
Immature (no hx ROP)	III	3 weeks
I	I	≤1 week
I	II	2 weeks
I	III	2–3 weeks
II	I	≤1 week
II	II	1–2 weeks
II	III	2–3 weeks
III	II	≤1 week
Regressing	I	1–2 weeks
Regressing	II	2 weeks
Regressing	III	2–3 weeks

- Follow up after resolution of ROP depends on the severity of the active phase of ROP but should occur by age 1 year. The following findings warrant consideration of treatment:

Stage	Zone
I, II, or III with plus disease	I
III no plus disease	I
II or III with plus disease	II

(continued)

Table 18.1. ***(Continued)***

Hepatitis B Vaccination (see Chapter 48) **for Hepatitis B–Negative Mothers** (See hepatitis B immunoprophylaxis guidelines from *Red Book* if maternal status is HBSAg positive or unknown.)
Criteria
■ All infants being discharged home from NICU
Initial
■ If weight ≥2,000 g and stable: Vaccinate at birth or shortly thereafter.
■ If weight ≥2,000 and unstable: Defer vaccination until their clinical condition has stabilized.
■ If weight <2,000 g: Vaccinate at 30 days or D/C (whichever comes first).
Synagis RSV Prophylaxis
Criteria
■ Synagis RSV prophylaxis should be considered from November to March for infants who meet any of the following criteria:
□ GA at birth <29 0/7 weeks
□ GA at birth 29 0/7–31 6/7 weeks with chronic lung disease defined as need for supplemental oxygen for at least 28 days after birth
□ Certain types of hemodynamically significant congenital heart disease
□ Pulmonary abnormality or neuromuscular disease that impairs ability to clear secretions from upper airways
□ Profound immunocompromised condition
Timing
■ Give first dose 48–72 hours before D/C.
Early Intervention Program (EIP)
Criteria
■ Infant meeting four or more of the following criteria:
□ BW <1,200 g
□ GA <32 weeks
□ NICU admission >5 days
(continued)

Table 18.1. Guidelines for Routine Screening, Testing, Treatment, and Follow-up at Neonatal Intensive Care Unit (NICU) *(Continued)*

□ Apgar <5 at 5 minutes
□ Intrauterine growth restriction (IUGR) or small for gestational age (SGA) (Refer to growth curves.)
□ Chronic feeding difficulties
□ Suspected central nervous system abnormality
□ Maternal age <17 years or three or more births at maternal age <20 years
□ High school education <10 years
□ Parental chronic illness or disability affecting caregiving
□ Lack of family supports
□ Inadequate food, shelter, and clothing
□ Open or confirmed protective service investigation ("51-A")
□ Substance abuse in the home
□ Violence in the home
Timing
■ Referral completed before D/C

D/C, discharge; PMA, postmenstrual age; CPAP, continuous positive airway pressure; CMV, cytomegalovirus; BW, birth weight; ROP, retinopathy of prematurity; hx, history; HBSAg, hepatitis B surface antigen; RSV, respiratory syncytial virus.

B. When planning discharge, it is important to consider the infant's relative fragility and the complexity of care needs. Infants with specialized needs require a complex, flexible, ongoing discharge care plan. Because medications, special formulas, and/or dietary supplements may be challenging for the parents to obtain, the need for these items should be identified early, so they can be obtained as soon as possible to optimize discharge teaching opportunities. If an infant will require in-home respiratory support or alternative methods of feeding, make a referral to a durable medical equipment (DME) company. A respiratory therapist (RT) or similarly qualified provider should assess the home to evaluate outlets in the infant's area, measure door openings, inquire about electrical panel location and capacity, and ensure a safe environment.

III. PARENT'S DISCHARGE PREPARATION. The AAP recommends an active program for parental involvement and preparation for care of the infant at home, arrangements for health care of the infant after discharge in a medical home by a physician or other health care professional who is experienced in the

care of high-risk infants, and an organized program of tracking and surveillance to monitor growth and development.

A. Family-centered care (FCC)

FCC is the concept that parents are an integral part of the care team who work in partnership with the medical/surgical providers on decision making and providing care for the infant. FCC may ameliorate the stressors that families experience due to the separation of family and infant, inability to experience a traditional parenting role, and the inclusion of multiple caregivers in daily care.

1. The four central tenets of FCC are dignity and respect, information sharing, family participation in care, and collaboration with the family.
2. FCC can shorten the length of stay, decrease the risk for readmission, enhance breastfeeding outcomes, boost families' confidence with infant care, and increase staff satisfaction.
3. FCC should be incorporated in all aspects of discharge preparation for the families.
4. Family presence/participation in medical rounds is an easy opportunity to help promote FCC and prepare families for the transition home.
5. Begin identification of caregivers early:
   a. The early establishment of parents as partners and participants in their infant's care helps a family cope with the stress and separation associated with NICU care and promotes an easier transition home.
   b. Designate at least two individuals who will be familiar with the infant's care in the event that one is unavailable.

B. Discharge teaching

1. **Discharge planning team includes the following:**
   a. Family
   b. Staff including some combination of the following: clinical nurses, physicians, midlevel providers (e.g., neonatal advance practice nurses and physician assistants), case managers, social worker, and other providers (e.g., primary care pediatric provider or subspecialist) as appropriate
2. **Diversity and inclusion in the NICU.** The rich diversity of families in the NICU cover the spectrum of race/ethnicity, gender, age, religion, immigration status, identity, and experience. As part of the discharge process, be inclusive. There are multiple approaches and points of view. Be committed to understanding a family's perspective and, as much as possible, take that perspective into account as part of the discharge planning.
   a. The makeup of NICU families is changing with more individuals becoming parents.
   b. Avoid making assumptions about parents based on physical appearance and/or manner.
   c. There are ever-increasing opportunities to improve how we care for all types of families in our NICUs. Each family provides an opportunity to refine the care we provide.
3. **Support of families with limited English proficiency**
   a. Families with limited English proficiency are at increased risk for not understanding discharge teaching and to have poor transitions home.

b. Support for families with limited English proficiency should include the following:

i. Use of appropriately trained interpreters for all discharge teaching
ii. Verification of comprehension of discharge teaching and needed medical follow-up with interpreters
iii. Provision of supplemental materials in the families' preferred language when possible

4. **Circumstances that could affect discharge planning** and increase risk of admission

a. Discharge planning should take into account descriptive and demographic characteristics of families that could make the discharge planning process more challenging, including the following:

i. History of parental substance use, domestic violence, marital instability
ii. Mental health issues especially anxiety or depression
iii. Nontraditional family structure
iv. Unique cultural and philosophical expectations
v. Inadequate prenatal care
vi. Teenage parents
vii. Lower socioeconomic status
viii. Illiteracy and/or functional health illiteracy
ix. Transient or migratory lifestyle

5. **Additional challenges** associated with the discharge process including clinical care and resources vary within and across hospitals and regions; clinical care and family education are complicated by inconsistencies, omissions, and duplications; there is often substandard communication between families and health care professionals as well as among health care professionals. All of these factors make it not possible to have a specific discharge planning program that will work in every clinical situation. A component of any discharge planning program is that it should be standardized but flexible enough to meet the individual needs of the family and can be accomplished with the available local resources.

C. Discharge teaching structure

1. Discharge teaching should begin early and be distributed throughout the NICU hospitalization to prevent the family from being overwhelmed with a large volume of content near the end of the hospitalization.
2. The education program should be structured to include all the skills and knowledge they are expected to master, tailored to their specific circumstance. It should offer repetition and frequent opportunities to evaluate progress and the capacity for adjustment as necessary.
3. Checklists can be helpful to make sure educational content is consistent and provides the family with an idea of what they will be expected to master (Table 18.2). A nursing discharge planning worksheet will allow all staff providing family education to be aware of which topics already have and which ones need to be covered (Table 18.3).

Table 18.2. Sample Family Discharge Checklist
Equipment for Home
Stroller
Baby carrier
Bouncy seat
Infant swing
Pacifiers
Fingernail files
Supplies for Home
Bath supplies
Dye- and fragrance-free laundry detergent
Developmentally appropriate toys (soothing music, mobile, board books)
Journal for important information (milestones, feedings, questions for doctor, etc.)
Food for yourself/family for at least the first few days home
Clothes for your baby
List of important phone numbers accessible (pediatrician, poison control, etc.)
Other Helpful Tips
Review CPR video if you need a refresher from CPR class.
If you would like to stay in touch with families you meet in the NICU, you can exchange contact information.
Ask pediatrician when it's safe to travel with your baby.
Introduce pets to your baby gradually.

CPR, cardiopulmonary resuscitation; NICU, neonatal intensive care unit.

Nurse Discharge Planning Worksheet

Baby's name in hospital: _____ **Medical record #:** _____
Baby's name after discharge: _____

During discharge meeting	Date	Completed by (RN Initials)	Not Required	Family Declined	Comments
Discharge meeting held				☐	
Family given discharge packet					
Family obtained a car seat					
Family offered CPR class				☐	
Family received "shaken baby" brochure					
Pediatrician chosen					
No later than 1 week prior to anticipated discharge					
Early intervention (EI) arranged			☐	☐	
Visiting nurse (VNA) arranged Agency: _____ Phone: _____ Fax: _____ Anticipated visit date: __ / __ / __			☐	☐	
Infant data sent to infant follow-up program (IFUP)			☐	☐	
Ophthalmology follow-up Dr. _____ Date/time: _____ Phone: _____			☐	☐	
Other follow-up appointments Specialty: _____ Dr. _____ Date/time: _____ Phone: _____ Specialty: _____ Dr. _____ Date/time: _____ Phone: _____ Specialty: _____ Dr. _____ Date/time _____ Phone: _____			☐ ☐ ☐		Other: ____
Palivizumab (Respiratory syncytial virus [RSV] season only) Patient meets requirements? Yes ☐ No ☐					
Palivizumab parent information sheet given			☐	☐	
Palivizumab parent consent obtained			☐	☐	
Palivizumab injection given			☐	☐	
Hepatitis B vaccine Hepatitis B vaccine information statement given					

Table 18.3. Sample Nurse Discharge Planning Worksheet

Hepatitis B vaccine consent obtained			☐	☐	
Hepatitis B vaccine given			☐	☐	
No later than 1 week prior to anticipated discharge	**Date**	**Completed by (RN Initials)**	**Not Required**	**Family Declined**	**Comments**
Discharge Teaching Feeding/nutrition reviewed				☐	
Bowel and bladder patterns reviewed				☐	
Bulb syringe use reviewed				☐	
Bathing, skin care, cord care reviewed				☐	
Temperature taking reviewed				☐	
Circumcision care			☐	☐	
Protection from infection reviewed				☐	
Feeding Infant transitioned to discharge feeding: (BM/formula: _____ kcal/oz: ____)			☐		
Family received written feeding plan			☐		
Family received milk/formula recipe			☐		
Appropriate WIC forms given to family			☐	☐	
Medication/Medical Equipment Family received discharge prescriptions			☐		
Medication administration teaching completed Med: _____ Dose/frequency: _____			☐		
Med: _____ Dose/frequency: _____					
Med: _____ Dose/frequency: _____					
Requires home equipment? Yes ☐ No ☐					
If equipment required; case management contacted					
Equipment (e.g., O_2 monitor)	**Company Contact Information**				**Date Teaching Completed**
No later than 1–2 days prior to anticipated discharge	**Date**	**Completed by (RN Initials)**	**Not Required**	**Family Declined**	**Comments**
Pediatrician appointment scheduled Dr. _____ Date/time: _____ Phone: _____					
Family given immunization book				☐	

Table 18.3. *(Continued)*

Family learned how to administer home medications			☐	☐	
Hearing screening complete Passed ☐ Referred L ☐ R ☐					
Car seat form complete			☐		
Discharge newborn screen sent					
Family attended CPR class				☐	
Family offered CPR refresher video				☐	
When to call your baby's doctor reviewed			☐	☐	
Car seat instruction reviewed			☐	☐	
Attending completed discharge summary					If not, reason: _____
Family received a copy of discharge summary					If not, reason: _____
Completed Nurse Discharge Readiness Questionnaire					
RNs, please provide quality improvement feedback/comments on this form and discharge process:					

Table 18.3. *(Continued)*

D. Skills demonstration

1. Provide parents with adequate opportunities to practice skills initially under direct supervision and then with supervisory support as needed.
2. Repetition and return demonstrations (i.e., teach-back technique) can be used to increase parental retention of the education content.
3. Provide specific, practical information with examples that are meaningful to the family's everyday experiences.
4. Supplement discharge teaching with other materials to reinforce the teaching and increasing retention of the material. Use of simulation labs when available.
   a. Prepare written information in a manner that is simple, clear, and devoid of medical jargon, with complex words and concepts defined in precise terms.
   b. Some families may have limited functional health literacy; therefore, pictographs, visual aids, multimedia, and recorded information are helpful to illustrate key concepts.

E. Discharge teaching content. Parents need instruction in all the following:

1. **Technical infant care skills**
   a. Breastfeeding/bottle feeding and mixing of breast milk/formula
   b. Bathing and dressing an infant
   c. Caring for the infant's skin, umbilical cord, and genitalia
   d. Placing the infant in a safe sleeping position and environment
   e. Administering and storing medications properly
   f. Using medical equipment as appropriate
   g. Cardiopulmonary resuscitation (CPR)

2. **Normal and abnormal preterm infant behavior**
   a. Typical preterm infant behaviors include normal breastfeeding and bottle-feeding patterns, bowel and bladder function, and infant sleep–wake cycles.
   b. Some typical, normal preterm infant behaviors may seem abnormal to those not accustomed to preterm infants. Specifically, preterm infants are frequently less active, alert, and responsive as well as more irritable and having more gaze aversion than term infants.
   c. Changes in behavior that may be signs of illness and that require close monitoring: apparent lack of appetite, decreased oral intake, sleepier or less active, more irritable or fussy than usual
   d. Physical signs that may reflect illness and require close monitoring: altered respiratory flushed, very pale, or mottled (spotted or blotched) skin; or lower muscle tone than usual.
   e. Abnormal signs and symptoms that should prompt a discussion with the medical home: vomiting and/or diarrhea, dry diapers for more than 12 hours, no stool for more than 4 days, black or bright red stool, a rectal temperature >100°F, or an axillary temperature >99.6°F or <97°F.

3. **Home environment preparation.** Equipment and supplies to acquire in anticipation of discharge:
   a. Feeding-related supplies: breast pump, nipples/bottles, formula, feeding pumps if indicated
   b. Crib or bassinet (safety approved)
   c. Diapers
   d. Infant clothes
   e. Thermometer (axillary or forehead for common use and rectal to be used when directed by a medical provider)
   f. Working smoke and carbon monoxide detectors and fire extinguisher
   g. Education regarding minimizing exposure of infant to secondhand smoke

4. **Anticipatory guidance**
   a. Provide a realistic idea of what their home life will be like during the immediate and longer-term period following discharge including the following:
      i. Expected number and type of physician visits for routine infant health maintenance, illness, and follow-up with subspecialty providers
      ii. How to soothe their crying infant and education regarding shaking baby syndrome and the harm caused by shaking, slamming, hitting, or throwing the infant
      iii. Families may also be given anticipatory guidance related to potential parental mental health issues such as posttraumatic stress disorder, anxiety, and depression that can arise in the period following discharge.

5. **Special circumstances**
   a. Infants going home on oxygen should notify local emergency care providers including community hospital emergency departments and local emergency medical technicians (EMTs) or first responders of the child's condition, medical needs, and possible problems. This will help optimize appropriate emergency response. Helping the family to prepare

a succinct written summary of the infant's medical conditions and current medications can be extremely useful. An electronic copy is preferable so that the information can be updated easily. Local utility companies such as telephone, electricity, fuel, and public works for snow removal should be notified in writing of the child's presence in the home so they will assign priority resumption of services if there is an interruption.

b. Family members should anticipate how they will manage an emergency in the home setting, including response to a life-threatening emergency associated with equipment malfunction, instruction on emergency procedures (e.g., CPR), availability of community resources, and advanced preparation of a list of relevant individuals or organizations to call with questions and concerns.

c. Home care services are becoming more widely available; however, their ability to provide specialized pediatric or neonatal services is variable. Consult the NICU case manager to assess the infants home care needs, review insurance, and make community referrals.

F. Home nursing care

1. Nurses from the Visiting Nurse Association (**VNA**) provide home visits to reinforce teaching, perform health and psychosocial assessments, and provide short-term treatments and nursing care. They communicate with the pediatrician if concerns or needs are identified.
2. Private duty nursing (**PDN**) or block nursing (**BN**) may be provided to infants who are discharged home with complex medical needs, such as a tracheostomy. Case management should be consulted as soon as it is known that an infant with complex medical needs will be discharged to home. The case manager will make referrals to have an infant's care reviewed by their insurance company to determine the allotment of hours. This level of in-home care will require secondary insurance. In some circumstances, the hours are approved but it is difficult to secure nurses with appropriate training and experience to fill those hours.

G. Family assessment. Family assessment is a key component of a successful discharge process. Families can build on their strengths if given the opportunity to participate in their baby's care early and be an active participant in the discharge process. Early partnership with the family promotes confidence and decreases stress by enhancing the parents' feeling of control. The ability to provide adequate parent education is vital for the successful transition to home. With early planning, ongoing teaching, and attention to the family's needs and resources, the transition to home can be smooth, even in the most complex cases. The family assessment should address the following questions:

1. Who will be the primary care giver(s) for the infant? How willingly is this responsibility assumed?
2. What is the family structure? Do they have a support system? Do supports need to be developed or strengthened?
3. Are there language or learning barriers? If so, address them as soon as they are identified.
4. How do they learn best? The nursing team should maximize the use of educational tools, written materials, visual props, and demonstrations.

5. How do previous or present experiences with the infant's care affect the family's ability to oversee care after discharge?
6. What are the actual and perceived complexities of the skills required to care for the infant?
7. What are their coping habits and styles?
8. Do the parents have any medical or psychological concerns that may have an impact on caretaking abilities?
9. What are the cultural beliefs, and how might this affect the care of the infant?
10. What are the financial concerns? Will the family's income change? If so, what resources are available to compensate?
11. Are there issues related to the family's living conditions that will be challenging? Families can become overwhelmed by the volume of medical equipment that will be delivered to the home in the days before discharge. Have the parents describe the home nursery and other spaces for the infant/caregivers and supplies. Ask them to take pictures to evaluate layout options. Discuss supply storage recommendations such as plastic bins on wheels, baskets, etc.

H. Transfer and/or coordination of care

1. The medical home

a. The AAP recommends that high-risk infants receive their primary care in a medical home with a primary care provider who has expertise in caring for patients who have required NICU care.

b. The medical home is usually staffed by a pediatrician, family practitioner, and/or nurse practitioner. Ongoing communication between NICU staff and the primary care provider begins long before discharge. This provides continuity and facilitates appropriate medical care after discharge. A family should make a medical home appointment for 1 to 3 days after discharge, preferably not on the same day as a visiting nurse appointment. (Of note, insurance does not pay for same-day visits.)

c. The communication between the NICU team and the medical home provider should, at a minimum, include a written physician's discharge summary.

d. A phone call or in-person meeting between the NICU provider and the medical provider is appropriate for complex medical or social situations.

2. Discharge summary

a. A standardized format for the discharge summary improves clarity and helps to ensure that all the pertinent information is included and organized in a useful fashion. Define complex words and concepts with precise terms.

b. Discharge summary suggested content (Tables 18.4 and 18.5)

- **i.** Pertinent maternal history
- **ii.** Infant's birth history
- **iii.** Neonatal history
- **iv.** NICU medical/surgical course synopsis

Table 18.4. Sample Neonatal Intensive Care Unit (NICU) Discharge/Interim Summary Dictation Guideline/Discharge Summary Content

1. Name of attending
2. Service ("Neonatology")
3. Patient's name as it appears in the hospital records
4. Patient's postdischarge name (spell name)
5. Patient's medical record number
6. Date of birth
7. Sex of patient
8. Date of admission
9. Date of discharge
10. History
a. Reason for admission, birth weight, and gestational age
b. Maternal history including prenatal labs, pregnancy, labor, and birth history
11. Physical examination at discharge including weight, head circumference, and length with percentiles at birth and discharge
12. Summary of hospital course by systems (*concise*). Include pertinent lab results:
a. *Respiratory*: initial impression. Surfactant given? Maximum level of support. Days on ventilation, CPAP, supplemental oxygen. If apnea, report how patient was treated, when treatment ended, and condition resolved.
b. *Cardiovascular*: diagnoses/therapies in summary form; Echo/ECG results
c. *Fluids, electrolytes, nutrition*: Brief feeding history. Include most recent weight, length, and head circumference.
d. *GI*: maximum bilirubin and therapy used
e. *Hematology*: patient's blood type, brief transfusion summary, most recent Hct
f. *Infectious disease*: white blood counts, cultures, colonization if appropriate, antibiotic courses
g. *Neurology*: Describe findings on head imaging.
h. *Psychosocial*: relevant observations of family function and psychosocial needs

(continued)

Table 18.4. ***(Continued)***

i. *Sensory*
i. *Audiology*: "Hearing screening results" (*If didn't pass, indicate date/place of follow-up test. If not done, recommend test prior to discharge.*)
ii. *Ophthalmology*
a) Indicate if infant did not meet criteria for eye exam.
b) Indicate if infant has not yet been examined but does require exam.
c) If ROP was ever detected, include maximum stage of ROP and date of that exam.
d) For all, include date and results of last exam.
e) If not mature, state plans for follow-up including date and time of scheduled appointment.
f) If mature, state time frame for routine follow-up.
13. Condition at discharge (e.g., "stable") including prognosis if guarded.
14. Discharge disposition (e.g., "home," "level 2," "level 3," "chronic care")
15. Name of primary pediatrician. Phone #: Fax #:
16. Care/recommendations
a. Feeds at discharge including volume, caloric density, and frequency (include the recipe)
b. Medications including each medication's dose (concentration if volume), route, frequency
c. Medical equipment and supply needs
d. Car seat challenge *if indicated*
e. State newborn screening status including dates and known results
f. Immunizations received including dates
g. Follow-up appointments scheduled/recommended
17. Discharge diagnoses list

CPAP, continuous positive airway pressure; Echo, echocardiogram; ECG, electrocardiogram; GI, gastrointestinal; Hct, hematocrit; ROP, retinopathy of prematurity.

Table 18.5. Additional Discharge Instruction Sheet

Community Resources
Poison Control Center
■ (800) 222-1222
■ https://triage.webpoisoncontrol.org/#/exclusions
Parental Stress Line
■ (800) 632-8188
■ https://www.parentshelpingparents.org/parental-stress-line
Battered Women's Hotline (24-hour)
■ (800) 799-SAFE
■ https://www.thehotline.org/
National Organization on Fetal Alcohol Syndrome (NOFAS) National and State Resource Directory
■ http://www.nofas.org/resource-directory
Recovering Mothers Anonymous (RMA)
■ http://www.recoveringmothers.org
Substance Abuse and Mental Health Service Administration's National Helpline
■ 1-800-662-HELP (4357)
■ https://www.samhsa.gov/find-help/national-helpline
Multiples of America
■ https://www.multiplesofamerica.org/
Breastfeeding
La Leche League International
■ (877) 452-5324
■ https://www.llli.org/

(continued)

Table 18.5. ***(Continued)***

Guidelines for When Parents Should Call Their Infant's Doctor
Any sudden changes in infant's usual patterns of behavior
■ Increased sleepiness
■ Increased irritability
■ Poor feeding
Any of the following
■ Breathing difficulty
■ Blueness around lips, mouth, or eyes
■ Fever (by rectal temperature) >100.0°F or (under the arm) >99.6°F or low temperature (rectal) <97.0°F
■ Vomiting or diarrhea
■ Dry diaper for >12 hours
■ No bowel movement for >4 days
■ Black or bright red color in stool

v. Discharge diagnoses
vi. Condition at discharge
vii. Prognosis if guarded
viii. Home feeding plan and discharge weight
ix. Discharge medications, dosages, and intervals
x. Medical equipment needs (e.g., oxygen, gastrostomy tube)
xi. Follow-up appointments that were either arranged prior to discharge or recommended but not yet arranged
xii. Newborn hearing screen results
xiii. Newborn state screenings dates and (if known) results
xiv. Car seat challenge results if relevant
xv. Immunizations administered
xvi. Pending test or lab results
xvii. Referrals made to community service programs (e.g., community health nursing agencies, early intervention programs [EIPs])

3. **Early intervention** (Mandated by the Federal Individuals with Disabilities Education Act, EIPs are community based and offer multidisciplinary services for children from birth to age 3 years. For details, see Table 18.1.)
   a. Children deemed at biologic, environmental, or emotional risk are eligible. Programs are partially federally funded and are offered at a reduced rate based on household income.

b. They provide multidisciplinary services including physical, occupational, speech, and feeding therapy; early childhood education; social services; and parental support groups.
c. Services may be home based or center based.

4. **Alternatives to home discharge.** Alternatives to home discharge may be temporary or permanent. Integrating the child into the home may be difficult because of medical needs or family situation. Decisions regarding alternative placement may be painful for the family and therefore require extra support. Alternatives vary widely from community to community and state to state.
a. Inpatient pediatric ward or level 2 nurseries may be options for the infant who is stable but needs a less intense level of hospital care before going home. Pediatric wards may have a parent sleep space, and community hospitals may be closer to home. Both options can offer more opportunities for families to be together to participate in and learn about their baby's care.
b. Pediatric rehabilitation hospitals can be appropriate for the high-risk infant who requires ongoing but less acute hospital care and further education for the transition to home.
c. Pediatric nursing homes provide extended care at a skilled level.
d. Medical foster care places the special needs infant in a home setting with specially trained caregivers. The goal is to place the infant back with the family.
e. Hospice care may be institutional based or home based. It focuses on maximizing the quality of life when cure is not expected.

Suggested Readings

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Reference

1. Bull MJ, Engle WA; and the American Academy of Pediatrics Committee on Injury, Violence, and Poison Prevention, Committee on Fetus and Newborn. Safe transportation of preterm and low birth weight infants at hospital discharge. *Pediatrics* 2009;123(5):1424–1429.

19 Decision Making and Ethical Dilemmas

Frank X. Placencia and Christy L. Cummings

KEY POINTS

- Parents are generally accorded the right to make decisions on behalf of their child, in their best interests, as surrogate decision makers (parental authority and responsibility).
- Shared decision making should involve the medical team and family (to the degree they desire) and should incorporate the most current medical evidence along with parental values and perspectives.
- Skills in advanced communication and relational competence are needed so that clinicians can better facilitate shared decision making, help parents clarify or construct values, and mitigate their own potential biases.
- Parental authority may be challenged when parental medical decisions clearly oppose their child's best interests or fall below the harm threshold.
- Withholding and withdrawing life-sustaining interventions are regarded as morally equivalent and ethically acceptable in certain situations in the neonatal intensive care unit, although in practice, withdrawing may sometimes feel more difficult for families and staff.
- Ethics committee consultation may be an invaluable resource and should be sought in ethically challenging cases.

I. BACKGROUND. The practice of neonatology necessitates decision making in all aspects of care. Most neonatologists feel comfortable making routine clinical decisions regarding management of pulmonary or cardiac function, infection, nutrition, and neurodevelopment care. On the other hand, clinical situations with ethical implications are often more difficult for professionals and families. These include decisions regarding fetal therapies as well as instituting, withholding, or withdrawing life-sustaining therapy in patients with irreversible or terminal conditions such as extreme immaturity, severe hypoxic-ischemic encephalopathy, certain severe genetic or congenital anomalies, or other conditions that are refractory to the best available treatments. Decision making in neonatology necessarily is informed by and reflects the cultural, social, and religious diversity of clinicians, patients, and families.[1,2] More recently, attention

has turned to the *process* of shared decision making in the neonatal intensive unit (NICU), focusing on an ethic of value clarification.[3,4]

A. The **ethical principles** that must be considered in the decision-making process in the NICU care include beneficence, nonmaleficence, respect for autonomy, justice, and other ethical frameworks associated with the physician–patient relationship, such as narrative ethics, feminist ethics, or care ethics.[5,6] Other principles and frameworks that must be considered include the following:

1. Treatment decisions must be based on the infant's best interests and harm minimization,[7] free from considerations of race, ethnicity, ability to pay, bias, or other influences. The American Academy of Pediatrics (AAP), the judicial system, and various bioethicists have all embraced some form of this standard, although their interpretations have differed.
2. The infant's parents generally serve as the legal and moral fiduciaries (or advocates) for their child. The relationship of parents to children is that of responsibility, not rights. Because infants are incapable of making decisions for themselves, the parents become their surrogate decision makers. Therefore, the parents are owed respect for autonomy in making decisions for their infants as long as their decisions do not conflict with the best interests of their child.[1,2]
3. The clinical team serves as a fiduciary who acts in the best interest of the patient using the most current evidence-based medical information. In this role as infant advocate, the physician oversees the responses (decisions) of his or her patient's parents. It is the responsibility of the clinical team to involve the court system when he or she perceives that the infant's interests are inappropriately threatened by the parents' decision.

B. There is considerable debate on how to define the "best interests" of the infant and from whose perspective. The most controversial issue is whether the primary focus should be the preservation of life (the vitalist approach) or the maintenance of a particular quality of life (the nonvitalist approach) and who makes this decision. This debate enters into difficult decisions more frequently as it becomes technically possible to sustain smaller and sicker infants. Staff and parents often struggle with identifying the medical and moral choices and with making decisions based on those choices. These choices, including the understanding of what defines a fulfilling or meaningful quality of life, vary substantially among families and professionals.

C. Informed consent versus parental permission. The 1995 AAP Committee on Bioethics policy statement "Informed Consent, Parental Permission, and Assent in Pediatric Practice" (revised in 2016) embraced the concept of **parental permission**. Parental permission, like informed consent, requires that parents be informed of the various treatment options, as well as their risks and benefits, and allows them to make decisions in cooperation with the physician. However, it differs from informed consent in that it is derived from the obligation shared by the parents and physicians to make decisions in the best interest of the infant, thereby enabling the physician to proceed with a treatment plan without parental permission (or even against parental wishes) if doing so is clearly in the best interests of the infant.[1,2]

II. DEVELOPING A PROCESS FOR ETHICAL DECISION MAKING.

An ethically sound, well-defined, and rigorous process for making decisions in ethically challenging cases is key to avoiding unwanted outcomes or intervention by a state agency or court. A NICU should define the decision-making process and identify the individuals (primary medical team, nursing staff, subspecialists, social services, ethicists, hospital legal counsel) that may need to participate in that process. Developing this process in advance allows for healthy discussions among NICU personnel that incorporate knowledge, ethical considerations, and values independent of a specific patient. Ideally, this preparation will ease the stress when an actual decision needs to be made.[8]

A. **Develop an educational program to prepare NICU caregivers** to address difficult decisions regarding patient care. Focus on process (who, when, where) as well as on substance (how). Identifying areas of frequent consensus and disagreement within a NICU and outlining a general approach to those situations can provide helpful guidance. Skills in advanced communication and relational competence are needed so that clinicians can better facilitate shared decision making, help parents clarify or construct values, and mitigate their own potential biases.[3] These educational programs should be available for NICU staff and discussed during the orientation of new personnel. The hospital ethics committee can serve as an educational resource for personnel regarding how to approach ethical decision making.[9]

B. **Identify common ethical situations** (e.g., extreme prematurity, multiple congenital anomalies, severe asphyxia) that might produce conflict and have a series of multidisciplinary discussions about these models as part of an educational program. These conversations should include a review of updated evidence and the common underlying ethical principles likely to be in conflict and illuminate common areas of agreement or disagreement. These discussions help develop a consensus on group values, promote a tolerance for individual differences, and establish trust and respect among professionals. The overall goal is to better prepare caregivers when actual situations arise while recognizing that each situation will be unique.

C. **Define and support the role of the parents** who should be seen as the primary decision makers for their infant unless they have indicated otherwise. The parents' desired degree of involvement in decision making should be explored with them in open and honest discussions.[4] The ethical and legal presumption is that they will make decisions that are in the best interests of their child (best interests standard) and within the context of accepted legal and social boundaries.[1,2] If the health care providers believe that the parental choice is not in the child's best interest and/or falls below the harm threshold, then they have an obligation as the infant advocate to override the parental decision.[1,2,7] Although every effort must be made to align the views of the parents and medical team, in cases of continued disagreement regarding the treatment course most likely to serve the best interests of the infant, the hospital ethics committee, hospital legal counsel, and social services should be consulted and the court system may need to be involved. In this situation, the physician should continue to serve as the infant's advocate while also maintaining open communication with the parents.

D. Develop consensus among the primary clinical team and consultants prior to meeting with the parents. Team meetings prior to family meetings provide the opportunity for caregivers to clarify the dilemmas and options that will be offered to the family and, hopefully, to reach a consensus regarding recommendations.[8] It also allows the team to establish who will communicate with the family to help maintain consistency during the discussion of complicated medical and ethical issues. In large practices, a diverse array of opinions is common. Establishing a forum in which the primary team may solicit the opinions of other staff members on the medical and ethical questions specific to the case serves multiple purposes: (i) identification of alternative treatment options, (ii) identification of staff members (physicians, nurses, etc.) comfortable with pursuing a course of action that current members may not be, and (iii) creation of consensus within the group on a specific course of action that can be presented to the hospital ethics committee if need be. One approach that may be helpful in these situations is the I-P-O framework,[8] which incorporates existing theoretical concepts to enhance decision making and communication between clinicians, as well as with families. A proposed intervention can be located along this spectrum and identified as either ethically **impermissible, permissible, or obligatory (I-P-O)**. Treatments determined to be ethically impermissible should not be made available by physicians. Those deemed ethically permissible should be explained to parents, often with a specific recommendation, and informed parents should then choose from among permissible options. Potential treatments deemed ethically obligatory should be provided to the patient, even in the face of parental objection. This framework provides a structure for ethical conversation and decision making related to a specific patient as well as in the formation of institutional and national guidelines.[8]

E. Identify available resources. Determine the roles of social service, chaplain, advanced care/palliative care service, hospital attorney, patient relations, and the hospital ethics committee. Individuals with a general knowledge of existing hospital policies on common situations such as "do not attempt resuscitation" orders or withdrawal of life support should be included in the multidisciplinary discussion. One or two key resource people with additional expertise who are easily accessible should also be identified. These professionals should be familiar with hospital policies, the ethics codes of the hospital as well as those of national organizations such as the AAP or the American Medical Association, and applicable federal and state laws. These key resource people are often members of the hospital ethics committee who can be available without necessarily pursuing a formal ethics consult.[9]

F. Base decisions on the most accurate, up-to-date medical information. Good ethics begins with good facts. Take the time to accumulate the relevant data. Consultation services are likely to provide valuable input. Be consistent in asking the same appropriate questions in each clinical setting. The answers to these questions may vary from case to case, but the questions regarding the ethical principles must always be asked. Be wary of setting certainty as a goal because it is almost never achievable in the NICU. Instead, a **reasonable degree of medical certainty** is often more achievable. As the weight of a decision's consequences increases, so does the rigor of

the requirement for a reasonable degree of certainty and the importance of parental involvement in the decision-making process.

G. People of good conscience can disagree. Individual caregivers must feel free to remove themselves from patient care if their ethical sense conflicts with the decision of the primary team and parents. This conflict should be handled with the medical or nursing director of the NICU. Parents and caregivers must be able to appeal decisions to an individual such as the NICU medical director or to the hospital's ethics committee. No system will provide absolute certainty that the "right" decision will always be made. However, a system that is inclusive, systematic, and built on an approach that establishes a procedure for handling these difficult issues is most likely to produce acceptable decisions.

III. MATERNAL–FETAL ETHICS.

The field of maternal–fetal medicine is rapidly evolving. Recent advances in stem cell therapies, gene editing, prenatal imaging, and fetal interventions have expanded opportunities for the treatment and even prevention of some congenital diseases.[10] This evolution creates ethical questions that must be addressed. Among the first questions are "When is the fetus a patient?" and "How do clinicians balance obligations to the fetus and to the pregnant person?"

The fetus may be considered a patient when the following two conditions are met: when the fetus is presented to the health care professional and when there exist medical interventions that are reliably expected to provide more benefit than harm to the fetus. This means the previable fetus is a patient when the pregnant person freely chooses to bestow this status on it. The viable fetus becomes a patient whenever the pregnant person presents for medical care.[11]

Health care professionals have beneficence-based obligations to pregnant persons to provide more benefit than harm.[5,6] They also have autonomy-based obligations to them as well. These must be balanced against the beneficence-based obligations to the fetus who is also a patient. The pregnant person also has beneficence-based obligations to take reasonable risks to her health for the good of the fetus. Although a pregnant person remains an autonomous agent, a moral (but not legal) obligation to her fetus is widely recognized. However, this obligation does not belong to the health care professional; rather, it rests with the pregnant person. Attempts to enforce this obligation against the pregnant person's will go against the beneficence-based obligations to them; the resulting balance makes it difficult if not impossible to justify such efforts. Therefore, through shared decision making, clinicians must balance their autonomy- and beneficence-based obligations to the pregnant person with the beneficence-based obligations to the fetus in order to determine together which clinical alternative is most ethically justified.[5,6,10,11]

IV. EXTREMELY PREMATURE INFANTS.

Nearly all NICUs have struggled with decisions about infants born at the threshold of viability and the question of "how small is too small." The practice of resuscitating extremely preterm infants presents difficult medical and ethical challenges.[4,12–15] Current technology allows some of these infants to survive but with a great risk of substantial neurodevelopmental impairment. Parents may ask that neonatologists pursue intensive

therapies despite poor prognoses. Neonatologists are concerned that instituting those therapies may not be the most appropriate course of action in some cases. The AAP statement on perinatal care at the threshold of viability stresses several key areas: (i) Parents must receive adequate and current information about potential infant survival and short- and long-term outcomes, (ii) physicians are obligated to be aware of the most current national and local survival data, and (iii) parental choice should be respected as much as possible with joint decision making by both the parents and the physicians as the standard.[14] As more experience is gained with these very difficult situations, further debate and discussion are likely to lead to greater consensus in this area. Guidelines for resuscitation by gestational age or birth weight are intentionally vague because these are only a few of the factors involved in predicting outcome. In making these decisions and recommendations, clinicians should take into account the specifics of each pregnancy, individual values and beliefs elicited from parents or constructed with the help of clinicians,[3,4] as well as the local outcomes data (see National Institute of Child Health and Human Development perinatal outcome calculator: https://www.nichd.nih.gov/research/supported/EPBO/use).

V. THE DECISION TO REDIRECT LIFE-SUSTAINING TREATMENT TO COMFORT MEASURES.

One of the most difficult issues is deciding when to withhold or withdraw life-sustaining therapies. Philosophies and approaches vary among caregivers and NICUs. The AAP statement on noninitiation or withdrawal of intensive care for high-risk newborns[12] stresses several key areas: (i) Decisions about noninitiation or withdrawal of intensive care should be made by the health care team in collaboration with the parents, who must be well informed about the condition and prognosis of their infant; (ii) parents should be active participants in the decision-making process; (iii) compassionate comfort care should be provided to all infants, including those for whom intensive care is not provided; and (iv) it is appropriate to provide intensive care when it is thought to be of benefit to the infant and not when it is thought to be harmful, of no benefit, or physiologically futile.[12]

One model to consider emphasizes an objective, interdisciplinary approach to determine the best course of action.

A. The goal of the process is to **clarify or help construct parental values**[3] and identify the action that is in the **baby's best interest**. The interests of others, including family and caregivers, are of less priority than are the baby's but should also be considered.

B. Decision-making preferences. The degree to which parents wish to be involved with decision making should be determined, as some parents prefer to make decisions on their own, others prefer to have clinicians make decisions for them, whereas others prefer a balanced or "shared" approach.[4]

C. Shared decision making should be guided by data. Caregivers should explore every reasonable avenue to maximize collection of data relevant to the ethical question at hand. Information about alternative therapies and prognosis should be sought. The objective data are evaluated in the context of the primary team's meetings. Subspecialty consultations should be obtained when indicated and included in the primary team's deliberations. Often, these consultations may add extra input to assist in the questions that the

primary team is trying to address. It is important that these consultants' input be reviewed with the primary team before discussing such findings with the parents.

D. Shared decision making should be guided by parental values and goals. As the decision to withhold or withdraw life-sustaining medical treatment becomes the focus, the team discusses the best data available, their implications, and their degree of certainty. The goal should be to build a **consensus** regarding the best plan of care for the baby and/or recommendations for the parents. Sometimes, there will be strong scientific support for a particular option. In other instances, the best course of action must be estimated. During this time, it is especially important to actively seek feedback from the parents regarding their thoughts, feelings, and understanding of the clinical situation. It should be emphasized that different caregivers reach the consensus at different rates and times. Supporting each participant through this process is important until all understand and accept the consensus and can then readily agree on a decision.

E. The parents' role as surrogate decision makers should be respected. This starts with communication that is completely transparent. The primary care team should meet regularly with the parents to discuss the baby's progress, current status, and plan of care and to summarize the team's medical and ethical discussions. Parental views are always considered; they are most likely to influence decisions when it remains unclear which option (e.g., continuing vs. discontinuing life-sustaining treatment) is in the child's best interest. Parents are not expected to evaluate clinical data in isolation. Even in instances of medical uncertainty, the primary team objectively assesses what is known, as well as what remains uncertain about the infant's condition and/or prognosis, in conjunction with parental values and wishes. The team should also provide the parents with their best assessment and recommendation. In the face of true medical uncertainty, parental wishes should be supported in deference to those of the primary medical team (parental zone of discretion).[4]

F. There is agreement among ethical and legal scholars that no ethical distinction exists between **withholding and withdrawing life-sustaining treatments**. Therefore, a therapeutic trial of life-sustaining treatment is acceptable, and it is ethically permissible for parents and staff to decide to withdraw those treatments if they no longer, or never did, improve the infant's condition and therefore serve their best interests.[12] In practice, this may be more difficult emotionally and psychologically for families and even staff. However, not using the approach of starting and then stopping therapy that is nonbeneficial may result in one of two adverse outcomes: (i) Nonbeneficial, possibly even harmful, treatment may be continued longer than necessary and (ii) some infants who might benefit from treatment may be excluded if it is feared that treatment would needlessly prolong the lives of a greater number of infants whose condition would not respond. The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research argues that withdrawal of life-sustaining treatment after having shown no efficacy may be more justifiable than presuming futility, and thus withholding treatment.[16] This approach supports the concept of a "trial of intensive care" wherein the staff and family agree

to start life-sustaining treatment and to discontinue it if it becomes clear that continued treatment is no longer in the infant's best interest. The 1984 Amendment to the Child Abuse Prevention and Treatment Act (CAPTA) defines **treatment as NOT medically indicated if the infant is irreversibly comatose; if it would merely prolong dying, not be effective in ameliorating or correcting all of the life-threatening conditions; if it would be futile in terms of survival; or if it would be virtually futile in terms of survival and be inhumane**.[17] These conditions both protect the rights of children to treatment despite underlying conditions or potential disabilities and support the importance of quality of life determinations in the provision of care. Substantial conflict can arise if the caregivers and parents disagree about the goals of care. A NICU must be prepared for these circumstances.

G. The hospital ethics committee is helpful when the primary team is unable to reach consensus or disagrees with the parents' wishes when they are clearly harmful and/or opposed to the child's best interests. Consultation with the ethics committee helps encourage communication among all involved parties and improve collaborative decision making. They can often ease tensions between parents and caregivers, allowing for a resolution to the dilemma.[9]

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20 Management of Neonatal End-of-Life Care and Bereavement Follow-up

Xenia T. Bateman and David A. Munson

KEY POINTS

- Deaths in the neonatal period are more common than in any other time in childhood; most follow a decision to withdraw life-sustaining treatment.
- Clear and collaborative communication supports families in effective decision making.
- High-quality end-of-life and bereavement care is the natural extension of a family-centered approach in the neonatal intensive care unit (NICU).
- Combining available guidelines with family preferences ensures sensitive and appropriate end-of-life and bereavement care.

I. INTRODUCTION. Despite advances in neonatal care, more children die in the perinatal and neonatal period than in any other time in childhood. The majority of neonatal deaths in the United States are due to congenital malformations and disorders related to short gestation and low birth weight.

For many families, a lethal or life-limiting condition may be diagnosed early in the pregnancy; thus, the opportunity to begin the decision-making process occurs prior to admission to the neonatal intensive care unit (NICU). A perinatal palliative comfort care plan is an alternative to termination of the pregnancy and provides a structured approach for the parents and the care team when developing a plan to create the best possible outcome for the baby and family.

Shifting from life-sustaining treatment to end-of-life care in the NICU environment can be challenging for caregivers. The care team must balance the burdens and benefits of interventions for the infant while engaging the hopes and fears of the parents and extended family. Parents are profoundly affected by the compassion and treatment they receive from health care providers during end-of-life care. Parents often remember what was said more than the events themselves. Although the death of a baby is a devastating event, the knowledge and skill of the multidisciplinary team can greatly influence the ability of the parents to cope effectively with their loss.

II. FAMILY-CENTERED END-OF-LIFE CARE PRINCIPLES AND DOMAINS.

The provision of quality end-of-life care is a process that allows for clear and consistent communication delivered by a compassionate multidisciplinary team within a framework of shared decision making. Providing physical and emotional support and follow-up care enables the parents to begin the healing process as they return home.

End-of-life domains comprise family-centered care in the NICU. These domains provide guidance and process measures to assess and provide quality of care at the end of life.

A. Patient- and family-centered decision making

B. Communication among the multidisciplinary team members and between the team and the parents and extended family

C. Spiritual support of families

D. Emotional and practical support of families

E. Symptom management and comfort care

F. Continuity of care

G. Emotional and organizational support for health care workers

III. COORDINATION OF CARE

A. Communication and collaboration. Family support in the NICU relies heavily on communication between the family and the health care team and the relationship among the members of the care team. A collaborative care model that allows physicians, nurses, and other team members to work cooperatively and share decisions, while respecting each professional's unique contribution, promotes an environment where the best care can be delivered.

1. Care provided at the end of life is an extension of the relationship already in place between the care providers and the infant and family. Staff can facilitate this relationship in the following ways:

a. Communicate with families through frequent meetings with the primary team.

b. Include the obstetrical care team and other consultants when appropriate.

c. Encourage sibling visitation and extended family support.

d. Encourage and respect the incorporation of cultural and spiritual customs.

e. Provide an environment that allows parents to develop a relationship with their infant; visiting, holding, and participating in care as often as is desired and medically appropriate.

2. All medical information should be presented in a clear, concise manner with the desired goal of conveying honesty, transparency, and compassion.

a. Clear recommendations about the goals of care (life support vs. comfort care) from the health care team are appropriate and may relieve parents of some of the burden of decision making in the end-of-life context.

b. Prior to meeting with the family to discuss redirection of care from treatment to comfort, it is important for the multidisciplinary team to

agree on reasonable remaining medical and surgical options and identify the needs of the patient and family.

c. Address conflicts within the team early in the process, utilizing available professional supports, such as ethical or spiritual consultants.

d. One spokesperson (usually the attending physician or a member of the NICU team the family has a strong bond with) is recommended to maintain continuity of communication.

B. Patient- and family-centered decision making

1. First, try to elicit what the parents understand and what their values, hopes, fears, and wishes are.
2. Most parents want to be involved in the decision to transition care from treatment to comfort; yet, not all are able to participate or want to feel responsible for the final decision. They rely on the care team to interpret the information and deliver the choices in a compassionate, sensitive manner that incorporates their individual needs and desired level of involvement.
3. The parents need to feel supported and heard regardless of the decision that is made.
4. The quality of the relationship and the communication style of the team members can influence the ability of the parents to understand the information presented and to reach consensus with the heath care team.
5. Shared decision making involves the support and participation of the entire team.
6. Meet with the family in a private, quiet area and allow ample time for the family to understand the information presented and the recommendations of the team.

   a. Provide a medical translator if needed.

   b. Refer to the baby by name.

   c. Ask the parents how they feel and how they perceive the situation.

   d. Once the decision has been made to redirect care away from supporting life to comfort measures, develop a specific plan with the family that involves a description of how life-sustaining technology will be withdrawn and determine their desired level of participation.

   e. It is important to describe what the family will see—changes in color, changes in respiratory patterns.

   f. Signs of distress should similarly be reviewed along with a description of how they will be managed.

   g. Allow ample time for parents to ask questions of team members.

C. Withdrawing life-sustaining treatment

1. Once a decision has been made to withdraw life-sustaining treatment and provide comfort care, the family should be provided an environment that is quiet, private, and will accommodate everyone the family wishes to include. This can include siblings, grandparents, and extended family and friends to the extent care is safe and the parents' wishes are maintained.
2. Staffing should be arranged so that one nurse and one physician will be readily available to the patient and family at all times.

3. Allow parents ample time to create memories and experience parenthood. Allow them to hold, photograph, bathe, and dress their infant before, during, or after withdrawing mechanical ventilation or other life support.
4. Discuss the process with parents, including endotracheal tube removal and pain and symptom control. Gently describe how the infant will look and measures that the staff will take to provide the infant with a comfortable, pain-free death. Let them know that death will not always occur immediately.
5. Arrange for spiritual support and incorporate spiritual and cultural customs into the plan of care if desired by the parents.
6. The goal of comfort care is to provide a pain-free comfortable death. Anticipate medications that may be required, leaving intravenous access in place. Discontinue muscle relaxants well before extubation as they interfere with the ability to assess discomfort. Give sedation and ensure deep sedation has been achieved prior to removal of the breathing tube. If turning down the ventilator settings or starting to remove the endotracheal tube tape elicits agitation, pause the procedure and give additional sedation prior to proceeding.
7. When the infant is extubated, discontinue all unnecessary intravenous catheters and equipment while ensuring sufficient access to address ongoing needs.
8. Allow parents to hold their infant for as long as they desire after discontinuing life support. The nurse and attending physician should be nearby to assist the family and assess symptoms and comfort of the infant.
9. When the family has a surviving multiple, it is important that the care team acknowledge the difficulty that this will present both at the time of death and during the grieving process.
10. Organ donation should be offered prior to removal of technology to give time to make the appropriate referral.
11. Autopsy should be discussed before or after death at the discretion of the attending physician or per hospital protocol.
12. Create a memory box including crib cards, photographs, clothing, a lock of hair, footprints, handprints, and any other mementos accumulated during the infant's life. Keep them in a designated place if the family does not desire to see or keep them at the time of death. Although parents often change their minds later and are grateful that these items have been retained, it is also important to remember that some families decline them due to cultural or spiritual practices.
13. Be sure that photographs of the infant have been taken. Parents of multiples will often want a photograph of their children together or a family picture. It is helpful for the NICU to have a digital camera and printer available. Now I Lay Me Down To Sleep (NILMDTS) is an organization that uses volunteer professional photographers and is available in many communities.

D. Emotional and organizational support for staff

1. A debriefing meeting for all members of the health care team after a baby's death provides an opportunity for those involved with the death to share their thoughts and emotions, if desired. Chaplains and social workers are often good resources for staff support and are usually considered a part of the care team.
2. Reviewing the events surrounding the death helps to identify what went well and opportunities for improvement.
3. Institutional support may include paid funeral leave, counseling, and remembrance ceremonies.
4. Recognizing and addressing staff response to grief in the workplace is a necessary part of providing end-of-life care.
5. Many institutions have developed formal programs to support staff working with dying patients. Programs often include support groups, counseling, writing workshops, and other interventions. Creating rituals around the time of death and providing time to reflect before returning to care for patients can be helpful.

IV. BEREAVEMENT FOLLOW-UP

A. General principles. Bereavement follow-up provides continuing support to families as they return home to continue the grieving process. Some families may not wish any contact with the team after they return home, and others may desire more frequent meetings or calls. Prior to leaving the hospital, it is important for a member of the team to review the follow-up support that will be provided. A bereavement packet with literature and a summary of hospital-specific programs is useful to provide the family with grief resources and contact information. Most programs include follow-up calls and cards within the first week and again between 4 and 6 weeks after the death of the infant. A follow-up meeting with the team allows the family the opportunity to review the events that surrounded the death, including the autopsy results if appropriate. In addition to providing support to the family, the meeting allows the team to assess the need for further support and provide referrals that might include support groups or counseling.

B. Hospital care

1. A designated team member or bereavement coordinator should review the program and bereavement materials with the parents or a family member. Often, a family support person is best able to absorb this information and communicate to the parents at the appropriate time.
2. Briefly describe the normal grieving process and what to expect in the following days and weeks.
3. Lactation support should be offered if appropriate and a plan made for lactation suppression and follow-up.
4. Provide assistance in making burial, cremation, or funeral arrangements.
5. The family's obstetrician, pediatrician, and other community supports should be notified of the infant's death.

6. A representative from the primary team, social worker, or other appropriately trained designee should assume responsibility for coordinating bereavement follow-up. This person will be responsible for arranging and documenting the follow-up process.
7. Provide assistance to the family as they leave the hospital without their child. If possible, arrange for prepaid valet parking or an escort to the door.

C. Follow-up after discharge

1. Contact the family within the first week to provide an opportunity for questions and offer support. The designated follow-up coordinator usually takes responsibility for placing the call and documentation. Other members of the care team may wish to maintain contact if they developed a close relationship with the family. It is important to discuss specific follow-up details with the family prior to discharge home.
2. Parents appreciate receiving a sympathy card, signed by members of the primary team sent to their home within the first few weeks, and communication at selected intervals.
3. Schedule a follow-up meeting with the family approximately 4 to 6 weeks after the infant's death. Timing will depend on availability of autopsy results and parental preference. In some cases, the family will not want to return to the hospital or continue contact. The coordinator will be sure this is documented and arrange for the family to be followed through a primary care provider or other community agency. Follow-up calls can still be made if the family consents.
4. Meetings should include a review of events surrounding the infant's death, results of the autopsy or other studies, and implications for future pregnancies.
5. Assessment should be made to determine the coping ability of the family as they continue with the grieving process and referrals made to appropriate professionals or agencies including bereavement support groups if needed.
6. Send a card and initiate a phone call around the first anniversary of the infant's death. This can be a difficult time for the family. Many families develop their own rituals to celebrate the life of their child during this time. Contact from members of their care team is greatly appreciated.
7. Plan for future meetings if the family desires.

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21 Nutrition

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KEY POINTS

- Human milk, especially mother's own milk, is the best nutrition for term and preterm infants.
- Careful provision of enteral and parenteral nutrition (PN) is required to adequately support infant growth.
- Growth assessment is essential to ensure optimal nutrition.
- Early nutrition influences childhood growth and neurodevelopment.

I. INTRODUCTION. Following birth, term infants rapidly adapt from a relatively constant intrauterine supply of nutrients to intermittent feedings of milk. Preterm infants, however, are at increased risk for nutritional compromise. Preterm infants are born with limited nutrient accretion and reserves due to their abbreviated time *in utero*, immature metabolic pathways, and increased nutrient demands. In addition, medical and surgical conditions commonly associated with prematurity have the potential to alter nutrient requirements and complicate adequate nutrient delivery. As survival of high-risk newborns continues to improve, current data suggest that early nutrition can improve both short- and long-term outcomes.

II. GROWTH

A. Fetal body composition changes throughout gestation, with accretion of most nutrients occurring primarily in the late second and throughout the third trimester. Term infants will normally have sufficient glycogen and fat stores to meet energy requirements during the relative starvation of the first days after birth. In contrast, preterm infants will rapidly deplete their limited nutrient reserves of glycogen and nitrogen, becoming both hypoglycemic and catabolic unless appropriate nutritional therapy is provided. In practice, it is generally assumed that the severity of nutrient insufficiency is inversely related to gestational age at birth and birth weight.

B. Postnatal growth varies from intrauterine growth in that it begins with a period of **weight loss**, primarily through the loss of extracellular fluid. The typical postnatal weight loss in the term infant is 5% to 10% of birth weight.

1. Infants born by cesarean section demonstrate greater weight loss compared to infants born vaginally. Breastfed infants also demonstrate greater weight loss compared to infants who are formula fed.

2. The Newt newborn weight tool (newbornweight.org) is a free tool that allows providers to see how a 2- to 5-kg newborn's weight in the first 30 days compares to a large sample of newborns, and accounts for feeding method and delivery type.
3. In preterm infants, weight loss from the physiologic contraction of extracellular fluid is equivalent to a 0.8 decrease in *z* score. This postnatal weight loss pattern, however, can be attenuated in most preterm infants with optimized, early nutrition. Although currently, there is no widely accepted measure of neonatal growth that captures both the weight loss and subsequent gain characteristic of this period, in general, the goals in practice are to limit the degree and duration of initial weight loss in preterm infants and to support the growth velocity after birth weight is regained.

C. After achieving birth weight, **intrauterine growth and nutrient accretion rate data** are used as reference standards for assessing growth and nutrient requirements for the growing preterm infant. Although goals for weight gain are 15 to 20 g/kg/day for infants <2 kg and 25 to 35 g/day for larger infants, the most important concept is keeping the individual baby growing along their trajectory on the appropriate growth curve. A personalized approach for each infant will follow the average and exponential growth velocity calculation over 5 to 7 days and follow *z* scores (standard deviation score). One available free resource to aid bedside clinicians in this calculation is the Growth Calculator for Preterm Infants available at Peditools.org. Approximately 1 cm/week in length and 1 cm/week in head circumference are used as a goal for growth in these parameters. Length gain is an important growth indicator but dependent on accurate measurement. Although these goals may not be initially attainable in some ill preterm infants, replicating growth of the fetus at the same gestational age remains an appropriate goal as recommended by the American Academy of Pediatrics (AAP). Efforts to minimize cumulative postnatal nutrient deficits begin in the first postnatal days and require a combined approach with parenteral nutrition (PN) and enteral nutrition.

1. **Exponential method.** Weight growth velocity (g/kg/day) = 1,000 × ln[weight on day last / weight on day first(g)] / day last − day first (days)
2. **Average method.** Weight growth velocity (g/kg/day) = (weight on day last [g] − weight on day first [g]) / (mean of weights on day first and day last [kg] / day last − day first [days])

D. Serial measurements of weight, length, and head circumference plotted on **growth curves** provide valuable information in the nutritional assessment of the preterm infant. Sex-specific intrauterine growth curves for each parameter are available. The Revised Fenton growth charts combine intrauterine growth with the World Health Organization (WHO) chart to construct a growth chart from 22 to 50 weeks' postmenstrual age (PMA). Preterm growth is taken from six countries, and the growth curve is smoothed from the preterm to the term WHO curve at 50 weeks. The smoothing reflects the rapid growth demonstrated by preterm infants (Figs. 21.1A and 21.1B). The Olsen growth curves are drawn from a large, racially diverse U.S. sample (Figs. 21.2A–D). The Aris growth curves

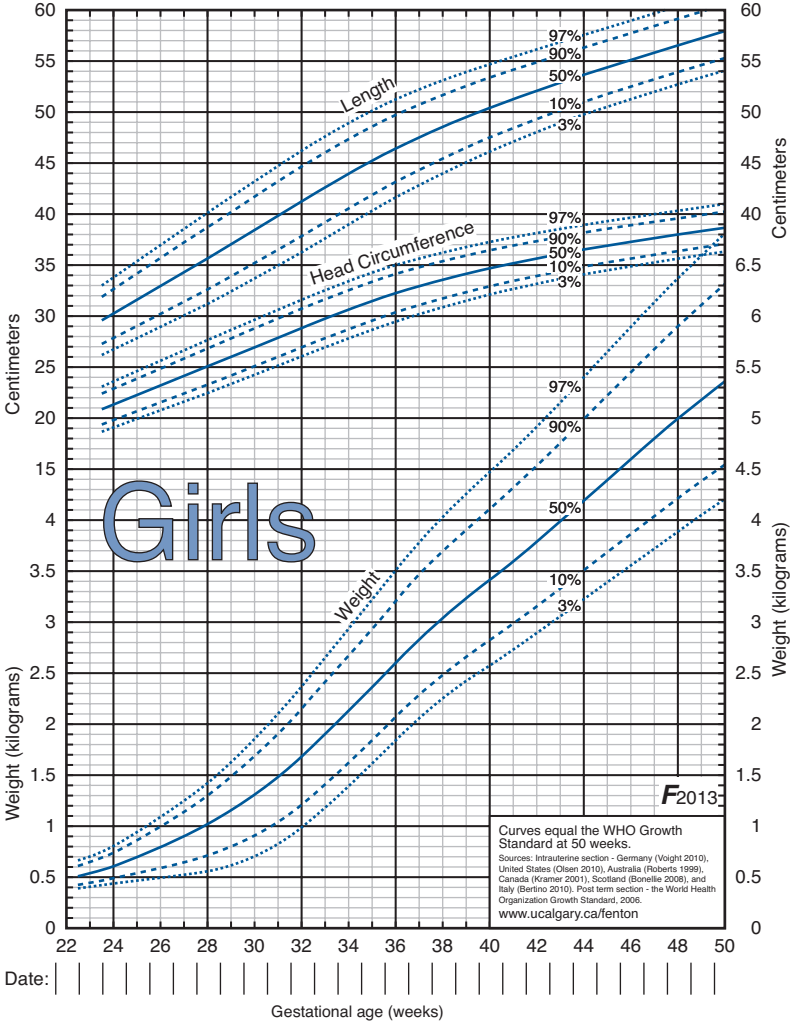


Figure 21.1. **A:** Fenton growth chart for girls. (From Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr* 2013;13:59.)

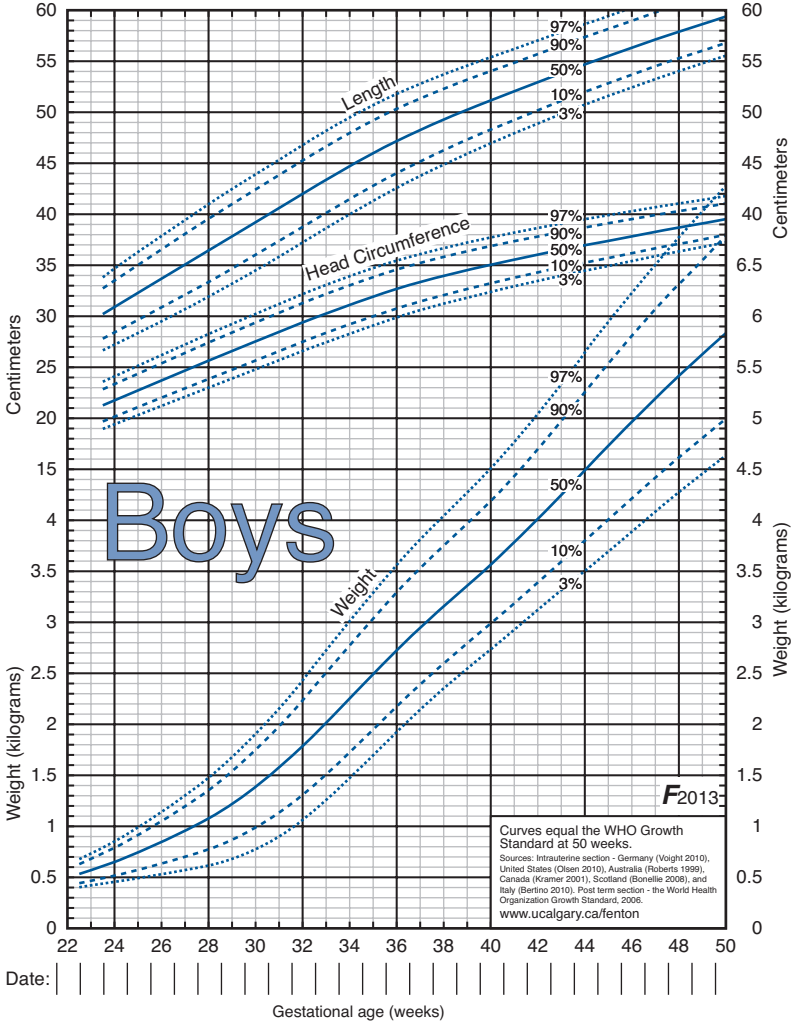
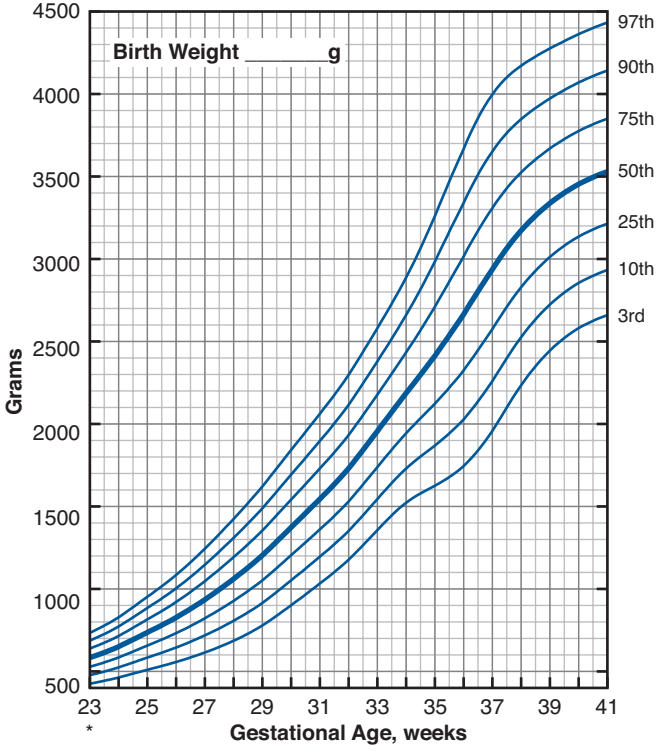


Figure 21.1. **B:** Fenton growth chart for boys. (From Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr* 2013;13:59.)

Intrauterine Growth Curves Name _____

Record # _____

FEMALES



BIRTH SIZE ASSESSMENT

Date of birth: / / (wks GA)	Select one
Large-for-gestational age (LGA) >90th percentile	☐
Appropriate-for-gestational age (AGA) 10-90th percentile	☐
Small-for-gestational age (SGA) <10th percentile	☐

* 3rd and 97th percentiles on all curves for 23 weeks should be interpreted cautiously given the small sample size.

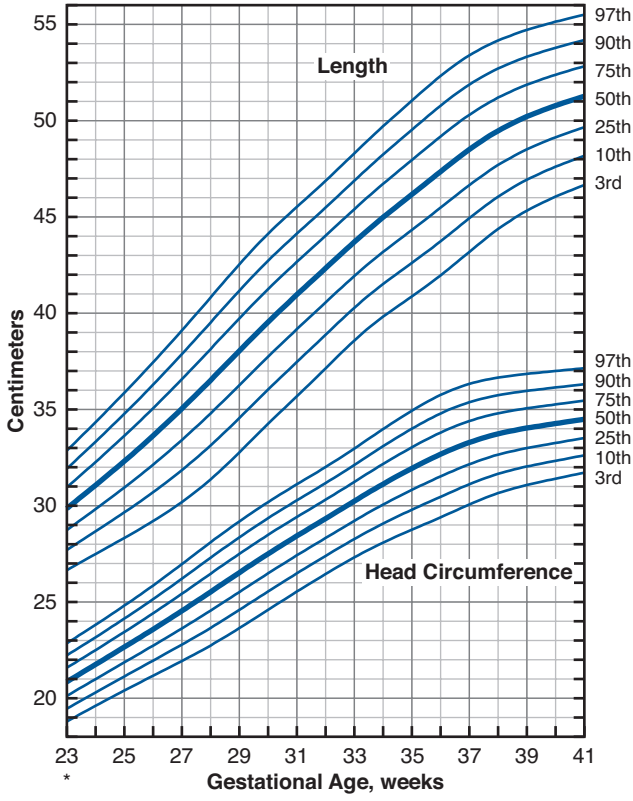
Figure 21.2. A: Olsen weight chart for girls. (Reprinted with permission from Olsen IE, Groveman SA, Lawson ML, et al. New intrauterine growth curves based on United States data. *Pediatrics* 2010;125[2]:e214–e224. https://pediatrics.aappublications.org/content/125/2/e214.long. Accessed October 21, 2021. Copyright 2010 by the American Academy of Pediatrics. Data from Pediatrix Medical Group; and Groveman SA. New preterm infant growth curves influence of gender and race on birth size [master's thesis]. Philadelphia, PA: Drexel University; 2008.)

Page 2

Name _____

Record # _____

FEMALES



Date																		
GA (wks)																		
WT (g)																		
L (cm)																		
HC (cm)																		

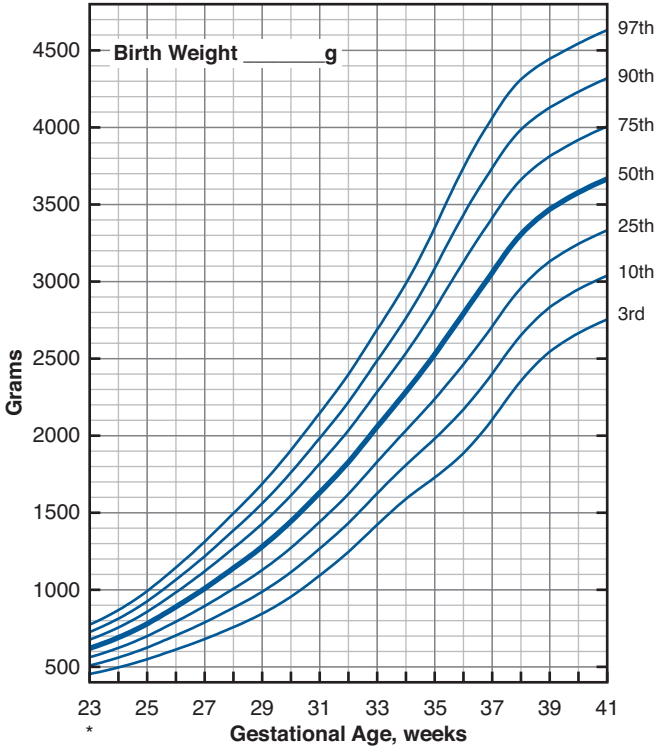
* 3rd and 97th percentiles on all curves for 23 weeks should be interpreted cautiously given the small sample size.

Figure 21.2. **B:** Olsen length and head circumference chart for girls. (Reprinted with permission from Olsen IE, Groveman SA, Lawson ML, et al. New intrauterine growth curves based on United States data. *Pediatrics* 2010;125[2]:e214–e224. https://pediatrics.aappublications.org/content/125/2/e214.long. Accessed October 21, 2021. Copyright 2010 by the American Academy of Pediatrics. Data from Pediatrix Medical Group; and Groveman SA. New preterm infant growth curves influence of gender and race on birth size [master's thesis]. Philadelphia, PA: Drexel University; 2008.)

Intrauterine Growth Curves Name _____

Record # _____

MALES



BIRTH SIZE ASSESSMENT:

Date of birth: / / (wks GA)	Select one
Large-for-gestational age (LGA) >90th percentile	☐
Appropriate-for-gestational age (AGA) 10-90th percentile	☐
Small-for-gestational age (SGA) <10th percentile	☐

* 3rd and 97th percentiles on all curves for 23 weeks should be interpreted cautiously given the small sample size.

Figure 21.2. C: Olsen weight chart for boys. (Reprinted with permission from Olsen IE, Groveman SA, Lawson ML, et al. New intrauterine growth curves based on United States data. *Pediatrics* 2010;125[2]:e214–e224. https://pediatrics.aappublications.org/content/125/2/e214.long. Accessed October 21, 2021. Copyright 2010 by the American Academy of Pediatrics. Data from Pediatrix Medical Group; and Groveman SA. New preterm infant growth curves influence of gender and race on birth size [master's thesis]. Philadelphia, PA: Drexel University; 2008.)

Page 2

Name _____

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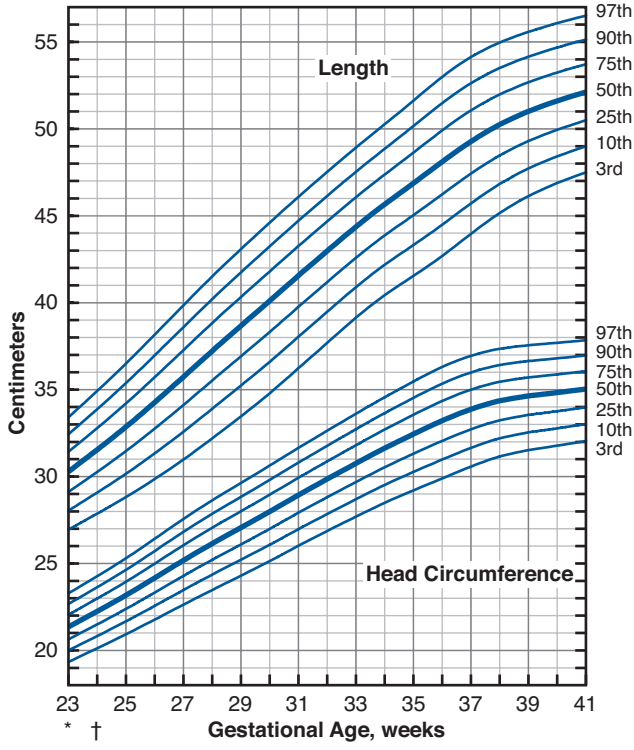
MALES



Date																		
GA (wks)																		
WT (g)																		
L (cm)																		
HC (cm)																		

* 3rd and 97th percentiles on all curves for 23 weeks should be interpreted cautiously given the small sample size.

† Male head circumference curve at 24 weeks all percentiles should be interpreted cautiously as the distribution of data is skewed left.

Figure 21.2. D: Olsen length and head circumference chart for boys. (Reprinted with permission from Olsen IE, Groveman SA, Lawson ML, et al. New intrauterine growth curves based on United States data. *Pediatrics* 2010;125[2]:e214–e224. https://pediatrics.aappublications.org/content/125/2/e214.long. Accessed October 21, 2021. Copyright 2010 by the American Academy of Pediatrics. Data from Pediatrix Medical Group; and Groveman SA. New preterm infant growth curves influence of gender and race on birth size [master's thesis]. Philadelphia, PA: Drexel University; 2008.)

are drawn from a large, more contemporary U.S. sample. Infants can be plotted from 23 to 42 weeks' PMA on sex-specific weight, length, and head circumference curves. Postnatal growth curves and body mass index (BMI) curves are also available. Postnatal growth curves follow the same infants over time (i.e., longitudinal growth curves) and are available from a number of single-neonatal intensive care unit (NICU) studies, from the National Institute of Child Health and Human Development (NICHD) multicenter study (2000), and from the INTERGROWTH-21st international consortium. These curves, however, show *actual*, not ideal growth. Intrauterine growth remains the gold standard for comparison.

1. Available growth curves include a small number of infants born at 22 to 24 weeks. This is expected because the incidence of birth at this gestational age is low. Growth curves may still be helpful to guide care for these infants with understanding that this is a limitation.
2. When an infant is term corrected age, the Centers for Disease Control and Prevention (CDC) recommends the WHO Child Growth Standards 2006 be used for monitoring of growth. Infants should be plotted by corrected age and followed for catch-up growth. The charts can be downloaded from http://www.cdc.gov/growthcharts/who_charts.htm.
3. One study found that a weight *z* score < -1.0 at 36 weeks corrected age and a decline < -1.0 in weight *z* score from birth to 36 weeks corrected age (using the INTERGROWTH-21st curves) was associated with a risk of cognitive delay at 2 years of age. Another study has found that using a definition of weight $<$10th percentile at 36 weeks corrected age using the Fenton growth curve is not predictive of adverse neurodevelopment. These studies highlight the importance of definitions and selection of growth curves in neonatal nutrition research.

III. NUTRIENT RECOMMENDATIONS FOR PRETERM INFANTS

A. Sources for nutrient recommendations for preterm infants include the American Academy of Pediatrics Committee on Nutrition (AAP-CON), the European Society for Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition (ESPGHAN-CON), and in the textbook *Nutritional Care of Preterm Infants: Scientific Basis and Practical Guidelines*, 2nd edition.

B. Fluid (see Chapters 13 and 23). The initial step in nutritional support is to determine an infant's fluid requirement, which is dependent on gestational age, postnatal age, and environmental conditions. Generally, baseline fluid needs are inversely related to gestational age at birth and birth weight. During the first postnatal week, very low birth weight (VLBW) infants are known to experience increased water loss because of the immaturity of their skin, which has a higher water content and increased permeability, and the immaturity of their renal function with a decreased ability to concentrate urine. Environmental factors, such as radiant warmers, phototherapy, and incubators, also impact insensible losses and may affect fluid requirements. Extremely preterm infants 22 to 25 weeks need careful attention to insensible fluid losses and may need frequent adjustment.

C. Energy. Estimates suggest that preterm infants in a thermoneutral environment require approximately 40 to 60 kcal/kg/day for maintenance of body weight, assuming adequate protein is provided. Additional calories are needed for growth, with the smallest neonates tending to demonstrate the greatest need, because their rate of growth is highest (Table 21.1). The three sources, AAP-CON, ESPGHAN-CON, and Koletzko et al. recommend a range of 105 to 135 kcal/kg/day. Practice generally strives for energy intakes of 110 to 130 kcal/kg/day (Table 21.2). Infants with severe and/or prolonged illness frequently require a range of 130 to 150 kcal/kg/day.

D. PN for preterm infants

1. **Indication and goals.** PN provides calories and amino acids to prevent negative energy and nitrogen balance. Goals thereafter include the promotion of appropriate growth while awaiting the attainment of enteral autonomy. PN is started the first postnatal day for infants who are VLBW, <1,500 g birth weight. PN should be considered in preterm infants with a higher birth weight if significant enteral intake is not anticipated by 3 to 5 days of life.

2. **Peripheral versus central administration**

   a. Parenteral solutions may be infused through a peripheral or central vein. Peripheral solutions may not be able to adequately support growth in extremely low birth weight (ELBW; birth weight <1,000 g) infants due to osmolarity. Central PN allows for the use of hypertonic solutions but incurs greater risks, particularly catheter-related sepsis.

Table 21.1. Estimation of Energy Requirement of the Low Birth Weight Infant

	Average Estimation (kcal/kg/day)
Energy expended	40–60
Resting metabolic rate	40–50*
Activity	0–5*
Thermoregulation	0–5*
Synthesis	15†
Energy stored	20–30†
Energy excreted	15
Energy intake	90–120

*Energy for maintenance.

†Energy cost of growth.

Source: Republished with permission of American Academy of Pediatrics, from Kleinman RE, Greer FR, eds. *Pediatric Nutrition*. 8th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2019; permission conveyed through Copyright Clearance Center, Inc.

Table 21.2. Examples of Caloric Provision

Total Fluid Goal (mL/kg/day)	Dextrose %	Amino Acid (g/kg/day)	Lipid (g/kg/day)	Enteral Feeding	Total Calories Provided (kcal/kg)	Comment
105	10	3	1	NPO	56	Although not at the goal energy intake, this is a reasonable intake DOL 1–2.
120	12.5	4	2	NPO	86	Although not at the goal energy intake, this is a reasonable intake DOL 2–3.
160	12.5	4	3	NPO	113	Even without feeding, TPN can supply sufficient energy.
160	15	3	2	Breast milk 35 mL/kg/day	115	
160	7.5	2	3	Fortified 24 kcal/oz breast milk, 75 mL/kg/day	114	
140	—	—	—	Fortified 24 kcal/oz breast milk, 140 mL/kg/day	112	

NPO, nothing by mouth; DOL, day of life; TPN, total parenteral nutrition.

b. Central PN is warranted under the following conditions:
- **i.** Nutritional needs exceed the capabilities of peripheral PN.
- **ii.** An extended period (e.g., >7 days) of inability to take enteral feedings, such as in infants with necrotizing enterocolitis (NEC)
- **iii.** Imminent lack of peripheral venous access

3. Parenteral carbohydrate. Dextrose (D-glucose) is the carbohydrate source in intravenous (IV) solutions.

a. The caloric value of dextrose is 3.4 kcal/g.

b. Because dextrose contributes to the osmolarity of a solution, it is generally recommended that the concentration administered through peripheral veins be limited to ≤12.5% dextrose. Higher concentrations of dextrose may be used for central venous infusions.

c. Dextrose infusions are typically referred to in terms of the milligrams of glucose per kilogram per minute (mg/kg/minute) delivered, which expresses the total glucose load and accounts for infusion rate, dextrose concentration, and the patient's weight (Fig. 21.3).

d. The initial glucose requirement for term infants is defined as the amount that is necessary to avoid hypoglycemia. In general, this may be achieved with initial infusion rates of approximately 4 to 6 mg/kg/minute.

e. Initial rates may be advanced daily as tolerated. This may be accomplished by increasing dextrose concentration, by increasing infusion rate, or by a combination of both. Insulin infusion should not be routinely started to increase the glucose infusion rate and should be reserved for treatment of hyperglycemia.

f. The quantity of dextrose that an infant can tolerate will vary with gestational and postnatal age. Signs of glucose intolerance include hyperglycemia and secondary glucosuria with osmotic diuresis.

Dextrose %	5	6	7	7.5	8	9	10	11	12	12.5	14	15	20
mL/kg/day													
10	0.3	0.4	0.5	0.5	0.6	0.6	0.7	0.8	0.8	0.9	1.0	1.0	1.4
20	0.7	0.8	1.0	1.0	1.1	1.3	1.4	1.5	1.7	1.7	1.9	2.1	2.8
30	1.0	1.3	1.5	1.6	1.7	1.9	2.1	2.3	2.5	2.6	2.9	3.1	4.2
40	1.4	1.7	1.9	2.1	2.2	2.5	2.8	3.1	3.3	3.5	3.9	4.2	5.6
50	1.7	2.1	2.4	2.6	2.8	3.1	3.5	3.8	4.2	4.3	4.9	5.2	6.9
60	2.1	2.5	2.9	3.1	3.3	3.8	4.2	4.6	5.0	5.2	5.8	6.3	8.3
70	2.4	2.9	3.4	3.6	3.9	4.4	4.9	5.3	5.8	6.1	6.8	7.3	9.7
80	2.8	3.3	3.9	4.2	4.4	5.0	5.6	6.1	6.7	6.9	7.8	8.3	11.1
90	3.1	3.8	4.4	4.7	5.0	5.6	6.3	6.9	7.5	7.8	8.8	9.4	12.5
100	3.5	4.2	4.9	5.2	5.6	6.3	6.9	7.6	8.3	8.7	9.7	10.4	13.9
110	3.8	4.6	5.3	5.7	6.1	6.9	7.6	8.4	9.2	9.5	10.7	11.5	15.3
120	4.2	5.0	5.8	6.3	6.7	7.5	8.3	9.2	10.0	10.4	11.7	12.5	16.7
130	4.5	5.4	6.3	6.8	7.2	8.1	9.0	9.9	10.8	11.3	12.6	13.5	18.1
140	4.9	5.8	6.8	7.3	7.8	8.8	9.7	10.7	11.7	12.2	13.6	14.6	19.4
150	5.2	6.3	7.3	7.8	8.3	9.4	10.4	11.5	12.5	13.0	14.6	15.6	20.8
160	5.6	6.7	7.8	8.3	8.9	10.0	11.1	12.2	13.3	13.9	15.6	16.7	22.2

Figure 21.3. Chart to quickly calculate glucose infusion rate in neonates. (Reprinted by permission from Nature: Chowning R, Adamkin DH. Table to quickly calculate glucose infusion rates in neonates. *J Perinatol* 2015;35:463.)

4. **Parenteral protein.** Crystalline amino acid solutions provide the nitrogen source in PN.
   a. The caloric value of amino acids is 4 kcal/g.
   b. Pediatric amino acid formulations theoretically are better adapted to the needs of newborns than standard adult formulations because they have been modified for improved tolerance and contain conditionally essential amino acids. However, the optimal amino acid composition for neonatal PN has not yet been defined. The addition of cysteine is recommended because this amino acid may be conditionally essential in premature infants.
   c. It has been demonstrated that VLBW infants who do not receive amino acids in the first postnatal days catabolize body protein at a rate of at least 1 g/kg/day. Studies investigating the use of early amino acids have consistently shown a reversal of this catabolism without adverse metabolic consequences. Current recommendations support the infusion of amino acids at a dose of 3 g/kg/day beginning in the first 24 hours after birth.

5. **Lipid**
   a. Lipid emulsions provide 10 kcal/g or 2 kcal/mL. The use of 20% emulsions is preferred over 10% because the higher ratio of phospholipids to triglyceride in the 10% emulsion interferes with plasma triglyceride clearance. Twenty percent emulsions also provide a more concentrated source of calories. For these reasons, only 20% lipid emulsions are used.
   b. Current data suggest that preterm infants are at risk for essential fatty acid deficiency within 72 hours after birth, if an exogenous fat source is not delivered. This deficiency state can be avoided by the administration of 0.5 to 1 g/kg/day of a 100% soybean oil lipid emulsion or >2.0 g/kg/day of a fish oil–containing lipid emulsion. A mixed lipid emulsion enriched with fish oil should not be dose restricted because doses are associated with essential fatty acid delivery.
   c. Recommendations given the most recent data report that VLBW infants should be provided with 2 g/kg/day of lipids within the first 24 hours after birth. This rate should be advanced by the next day to a goal of 3 g/kg/day.
   d. Lipid emulsions include pure soybean oil (Intralipid), multicomponent lipid emulsions (SMOFlipid: soybean oil, medium-chain triglycerides, olive oil, fish oil), and pure fish oil (Omegaven).
   e. In the United States, Intralipid and Omegaven are U.S. Food and Drug Administration (FDA) approved for use in pediatric patients. Omegaven is specifically FDA approved for patients with established PN-associated cholestasis.
   f. SMOFlipid is FDA approved for adults only. It is used off-label in infants.
   g. Intralipid lacks arachidonic acid (ARA) and docosahexaenoic acid (DHA) and contains phytosterols, which is thought to be a major contributor to parenteral nutrition-associated cholestasis (PNAC). SMOFlipid has a lower phytosterol content but has not been shown in clinical trials to prevent the development of PNAC in high-risk patients.
   h. Despite a greater amount of ARA and DHA in SMOFlipid compared to Intralipid, the early DHA deficit seen in preterm infants is

not mitigated with SMOFlipid, and there is a greater induced deficit in ARA with fish oil–containing lipid emulsions.

i. Current meta-analyses do not demonstrate benefit of using SMOFlipid over Intralipid for routine maintenance lipid provision in preterm infants.

j. Hypertriglyceridemia can be seen with parental lipid emulsions. There is no clear consensus on what constitutes hypertriglyceridemia and, as a result, it is reasonable to exclude triglyceride levels from routine lab studies. Lipid emulsions should be infused over a 24-hour period to minimize risk. Dose reduction should be considered in preterm infants if the threshold exceeds 250 mg/dL (2.8 mmol/L).

6. **Parenteral vitamins.** The current pediatric vitamin formulations (M.V.I. Pediatric, Hospira, Lake Forest, IL; INFUVITE Pediatric, Baxter, Deerfield, IL) do not maintain blood levels of all vitamins within an acceptable range for preterm infants. However, there are no products currently available that are specifically designed for preterm infants. Table 21.3 provides guidelines for the use of the available formulations for term and preterm infants. For infants <2,500 g, the AAP suggests a dose of 40% of the M.V.I. Pediatric (INFUVITE Pediatric) 5 mL vial/kg/day. For infants ≥2,500 g, the AAP suggests the 5 mL M.V.I. Pediatric (INFUVITE Pediatric) per day. Vitamin A and B vitamins may be affected by photodegradation. This is of particular concern with long-term PN use, and for this reason, consideration should be given to shielding the PN-containing plastic bags and tubing from light.

7. **Electrolytes and parenteral minerals**

a. Sodium and potassium concentrations are adjusted daily based on individual requirements (see Chapter 23). Maintenance requirements are estimated at approximately 2 to 4 mEq/kg.

b. Increasing the proportion of anions provided as acetate aids in the treatment of metabolic acidosis in VLBW infants.

c. The amount of calcium and phosphorus that can be administered through IV is limited by the precipitation of calcium phosphate. Unfortunately, the variables that determine calcium and phosphate compatibility in PN are complex and what constitutes maximal safe concentrations is controversial. The aluminum content of these preparations should also be considered. Early calcium to phosphorus molar ratio of 0.8 to 1:1 is recommended, with transition to 1.3 to 1.5:1 molar ratio if infant requires PN at 1 week of life with lab monitoring (Table 21.4). However, despite efforts to optimize mineral intake, preterm infants receiving prolonged PN remain at increased risk for metabolic bone disease (see Special Considerations and Chapter 59).

8. **Trace elements.** Currently, 1.0 mL/kg of Peditrace (Fresenius Kabi) or 0.2 mL/dL of NeoTrace and 1.5 μg/dL of selenium are added, beginning in the first days of PN. However, when PN is supplementing enteral nutrition or limited to <2 weeks, only zinc may be needed.

9. **Other additives**

a. Carnitine facilitates the transport of long-chain fatty acids into the mitochondria for oxidation. However, this nutrient is not routinely

Table 21.3. Suggested Intakes of Parenteral Vitamins in Infants

Vitamins	Estimated Needs		Two Milliliters of a 5-mL Single-Dose Vial M.V.I. Pediatric (Hospira), INFUVITE Pediatric (Baxter)
	Term Infants (≥2.5 kg) (dose/day)	Preterm Infants (≤2.5 kg)*	
Lipid soluble			
A (μg)†	700	280	280
D (IU)†	400	160	160
E (mg)†	7	2.8	2.8
K (μg)	200	80	80
Water soluble			
Thiamine (mg)	1.2	0.48	0.48
Riboflavin (mg)	1.4	0.56	0.56
Niacin (mg)	17	6.8	6.8
Pantothenate (mg)	5	2	2
Pyridoxine (mg)	1	0.4	0.4
Biotin (μg)	20	8	8
Vitamin B_{12} (μg)	1	0.4	0.4
Ascorbic acid (mg)	80	32	32
Folic acid (μg)	140	56	56

*Dose/kg of body weight per day for preterm infants, not to exceed daily dose for term (>2.5 kg) infants.

†700 μg retinol equivalent = 2,300 IU; 7 mg alpha-tocopherol = 7 IU; 10 μg vitamin D = 400 IU.

added to PN solutions because there has been no evidence of clinical advantage in short-term PN regimens. Preterm infants who receive prolonged, unsupplemented PN are at risk for carnitine deficiency due to their limited reserves and inadequate rates of carnitine synthesis. Infants who are able to tolerate enteral nutrition receive a source of carnitine via human milk and/or carnitine-containing infant formula.

Table 21.4. Schedule for Nutrition Laboratory Monitoring

	Parenteral Nutrition (PN)	Enteral Nutrition
Electrolytes	Daily, until stable; then as clinically indicated	As clinically indicated (Consider with use of diuretics, history of electrolyte abnormality, poor growth.)
Triglycerides	Consider during initiation and/or advancement for extremely low gestational age or growth restricted infants receiving parenteral lipid nutrition.	Not indicated
Calcium, phosphorus, alkaline phosphatase	After 14 days of PN and as clinically indicated	Consider in low birth weight infants 2 and 4 weeks after achieving full enteral feedings and thereafter as clinically indicated.
Alanine amino-transferase (ALT), direct bilirubin	After 14 days of PN and as clinically indicated	Not indicated

However, for infants requiring prolonged (e.g., >2 to 4 weeks) PN, a parenteral source of carnitine may be provided 10 mg/kg/day until enteral nutrition can be established.

b. Cysteine is not a component of current crystalline amino acid solutions because it is unstable over time and will form a precipitate. Cysteine is ordinarily synthesized from methionine and provides a substrate for taurine. Cysteine is considered a conditionally essential amino acid due to low enzyme activity level. Supplementation with L-cysteine hydrochloride lowers the pH of the PN solution and may necessitate the use of additional acetate to prevent acidosis. However, the lower pH also enhances the solubility of calcium and phosphorus and allows for improved mineral intake. Cysteine is routinely supplemented in PN at a rate of approximately 30 to 40 mg/g protein.

c. Glutamine is an important fuel for intestinal epithelial cells and lymphocytes; however, due to its instability, it is presently not a component of crystalline amino acids solutions. Studies to date have not proven its addition to PN as helpful for the neonate.

E. Enteral nutrition for preterm infants

1. **Early enteral feeding.** The structural and functional integrity of the gastrointestinal tract is dependent on the provision of enteral nutrition. Withholding enteral feeding after birth places the infant at risk for all the complications associated with luminal starvation, including mucosal

Table 21.5. Tube Feeding Guidelines

Birth Weight (g)	Initial Rate (mL/kg/day)	Volume Increase (mL/kg every 12 hours)
<1,250	10–20	10–15
1,251–1,500	20–30	10–15
1,501–1,800	30	15
1,801–2,500	30–40	15–20

The initial volume should be administered for at least 24 hours prior to advancement. The guidelines should be individualized based on the infant's clinical status/history of present illness. Once feeding volume has reached approximately 80 mL/kg/day, infants weighing <1,250 g should be considered for feeding intervals of every 2 hours or every 3 hours, as opposed to every 4 hours. Once feeding volume has reached approximately 60 mL/kg/day, consider advancing calories. Consider advancing feeding volume more rapidly than the guidelines once tolerance of >100 mL/kg/day is established, but do not exceed increments of 15 mL/kg every 12 hours in most infants weighing <1,500 g. The recommended volume goal for feedings is 140 to 160 mL/kg/day. These guidelines do not apply to infants capable of ad libitum feedings.

thinning, flattening of the villi, and bacterial translocation. **Minimal enteral nutrition** (also referred to as "gut priming" or "trophic feedings") may be described as the nonnutritive use of very small volumes of human milk or formula, for the intended purpose of preservation of gut maturation rather than nutrient delivery (Table 21.5). Definitive conclusions cannot be drawn as to what constitutes the optimal volume for minimal enteral nutrition.

a. Benefits associated with minimal enteral nutrition include the following:

i. Improved levels of gut hormones
ii. Less feeding intolerance
iii. Earlier progression to full enteral feedings
iv. Improved weight gain
v. Improved calcium and phosphorus retention
vi. Fewer days on PN

b. Guidelines for early minimal enteral nutrition

i. Begin as soon after birth as possible, ideally within the first 48 hours of life. A standardized feeding protocol will help to accomplish this goal.
ii. Use full-strength colostrum/preterm maternal milk or pasteurized donor human milk (PDHM). In instances where the supply of maternal milk is insufficient for 100% gut priming volume, and PDHM has been declined or is unavailable, full-strength 20 kcal/oz preterm formula may be used. Gut priming may be administered as a fixed dose (i.e., 0.5 mL every 3 hours for infants, 800 g at birth).

Alternatively, a low volume per kilogram may be delivered (i.e., 10 to 20 mL/kg/day divided into eight aliquots for VLBW infants).

iii. Gut priming is not used in infants with severe hemodynamic instability, suspected or confirmed NEC, evidence of ileus, or clinical signs of intestinal pathology. Infants who are undergoing medical treatment for patent ductus arteriosus may receive gut priming, pending the discretion of the care team.

iv. Controlled trials of gut priming with umbilical arterial catheters (UACs) in place have not shown an increased incidence of NEC. Therefore, the presence of a UAC is not considered to be a contraindication to minimal enteral nutrition. However, the clinical condition accompanying the prolonged use of a UAC may serve as a contraindication.

2. **Feeding advancement**

a. A standardized feeding protocol should be used.

b. As enteral volumes are increased, the rate of PN and IV fluid is calculated and adjusted to achieve total macronutrient and fluid goals. Nutrient intake from PN and enteral feedings is calculated to provide sufficient protein and energy and avoid overload.

c. There is no evidence that a faster feeding advancement increases the risk of NEC.

d. A modern large multicenter randomized control trial found that advancing enteral feedings faster (30 mL/kg/day vs. 18 mL/kg/day) in VLBW preterm infants did not result in a difference in survival or NEC. Advancing feeding volumes within this range is acceptable and safe. The faster feeds are advanced, the shorter total parenteral nutrition (TPN) is needed. This has the potential advantage of reducing central line–associated infections and preventing PN-associated cholestasis.

e. Feeding intolerance. Signs of feeding intolerance include emesis, abdominal distension, and increased numbers of apnea episodes. Reduction of feeding volume, rate, or even cessation of feeding is sometimes indicated. If these clinical signs prevent attainment of full-volume enteral feedings despite several attempts to advance feedings, radiographic contrast studies may be indicated to rule out underlying pathology. Gastric residuals alone in absence of other physical signs and symptoms of feeding intolerance are not helpful.

3. **Human milk.** Human milk is the gold standard nutrition, and fortified human milk is the preferred feeding for preterm infants. Mother's own milk is superior to pasteurized donor milk with nutritional and immunologic benefits. The use of human milk offers many nutritional and nonnutritional advantages for the premature infant. Feeding tolerance is improved, and the incidence of sepsis and NEC is decreased. Earlier discharge is facilitated by better feeding tolerance and less illness.

a. Preterm human milk contains higher amounts of protein, sodium, chloride, and magnesium than term milk. However, the levels of these nutrients remain below preterm recommendations, the differences only persist for approximately the first 21 days of lactation, and composition is known to vary.

b. For these reasons, human milk for preterm infants is routinely supplemented with human milk fortifier (HMF). The use of HMF is recommended for VLBW infants <1,500 g and may also be considered for infants with birth weights up to 2,000 g and <34 weeks' gestation. Bovine milk–based HMF as well as liquid donor human milk–based HMF are available. Current evidence does not conclusively support the superiority of one of these fortifiers. The FDA and Center for Disease Control and Prevention (CDC) recommend that powdered preparations not be used in premature infants given the risk of bacterial contamination. Nutrient content of human milk fortifiers are available on the manufacturers' websites (Enfamil: https://www.hcp.meadjohnson.com/s/products, Similac: https://abbottnutrition.com/infant-and-new-mother, Prolacta: https://www.prolacta.com/en/products/)

c. HMF is added at 2 to 4 kcal/oz. Fortification should be started according to a standardized feeding protocol as early as enteral feeding 60 mL/kg/day and before reaching full feeding goal.

d. There is considerable variability in human milk macronutrient content. Individualized fortification with bovine milk–based HMF beyond manufacturer's recommendation may be needed to achieve goal growth rate. Targeted fortification is an emerging practice under research investigation now that a Human Milk Analyzer is FDA approved. Protein supplementation, with an extensively hydrolyzed protein modular, may be considered for VLBW infants in order to increase the protein content to approximately 4.5 g/kg/day, as needed.

e. For infants receiving a **liquid donor human milk–based HMF**, the fortifiers are designed to make 24 to 30 kcal/oz milk. The energy and protein content of the milk will be increased with the higher caloric fortifier, and the mineral content will stay constant. In addition, a donor human milk cream supplement is available to increase energy intake when protein needs have been met by the donor human milk–based HMF.

f. When 100% maternal milk is unavailable, PDHM may be offered to infants who are considered to be at highest risk for feeding intolerance and NEC. Most typically, this includes VLBW newborns and/or those born at <32 weeks' gestation. Donor milk may also be used to supplement a new mother's supply for older or larger infants. Depending on the hospital's guidelines, assent or consent is obtained from the parent or guardian prior to administering PDHM. Maternal milk is preferentially fed, as available, with PDHM being used, as needed, to reach goal volumes. PDHM is typically offered until 100% maternal milk is achieved or an established endpoint have been reached. These endpoints may be full-volume feedings for a certain period of time (i.e., for 30 days) or until a goal weight or PMA has been reached (i.e., 34 weeks' PMA and infant weight of >1,500 to 1,800 g). Once the established endpoint is achieved, the infant is slowly transitioned off PDHM by gradually adding in formula feedings. This process usually occurs over several days.

g. Protocols for the collection and storage of human milk are outlined in Chapter 22.

4. **Feeding method.** These should be individualized based on gestational age, clinical condition, and feeding tolerance.

a. Nasogastric/orogastric feedings. Nasogastric tube feedings are used more frequently because orogastric tubes tend to be more difficult to secure.

These are used in infants who have not developed a mature suck-swallow-breathe pattern.

b. Bolus versus continuous. Feedings are usually initiated as bolus, divided every 3 to 4 hours. If difficulties with feeding tolerance occur, the amount of time over which a feeding is given may be lengthened by delivery via a syringe pump for 30 to 120 minutes. When human milk is fed through continuous infusion, incomplete delivery of nutrients may occur, in particular, the nonhomogenized fat and nutrients in the HMF may cling to the tubing. Small, frequent bolus feedings may result in improved nutrient delivery and absorption compared with continuous feedings.

c. Transpyloric feedings. There is some evidence that feeding via the transpyloric route is associated with higher morbidity and mortality, including increased frequency of hypoxemic events in infants with severe bronchopulmonary dysplasia (BPD). This mode also risks fat malabsorption because it bypasses gastric lipase secretions. There are limited indications, such as evidence of severe regurgitation and aspiration. These tubes should be placed under guided fluoroscopy, and feeds are delivered continuously because the small intestine cannot expand like the stomach.

d. Transition to breast/bottle-feedings is a gradual process.

i. Nonnutritive attempts at the breast should be encouraged before 33 to 34 weeks, if tolerated. Early, nonnutritive sucking facilitates milk production and increases the likelihood the infant is still breastfeeding at the time of hospital discharge.

ii. Infants who are approximately 33 to 34 weeks' gestation, who have coordinated suck-swallow-breathe patterns and respiratory rates <60 breaths per minute, are appropriate candidates for introducing breast/bottle-feedings.

iii. Nutritive oral feeding attempts at the breast should precede oral feeding attempts with the bottle.

5. Enteral vitamins and minerals

a. Iron. The AAP recommends that growing preterm infants receive a source of iron, provided at 2 to 4 mg/kg/day, after 2 weeks of age. The AAP further suggests that preterm infants on iron-fortified preterm formula do not need additional iron. However, the current recommendations recommend 2 to 3 mg/kg/day for VLBW infants. It has been suggested that >2 mg/kg/day may be needed, when adjusted for noncompensated phlebotomy losses and the number of days during which the infant does not receive iron due to feeding intolerance or illness. Iron supplementation is recommended until the infant is 12 months of age. Iron-fortified formulas and iron-fortified HMF provide approximately 2.2 mg/kg/day when delivered at a rate of 150 mL/kg/day. Low iron formulas are not recommended for use.

b. Vitamin D supplementation of 400 to 1,000 IU/day is recommended for all premature infants once enteral supplements are tolerated.

c. Vitamin E is an important antioxidant that acts to prevent fatty acid peroxidation in the cell membrane. The recommendation for preterm infants is 2.2 to 12 IU vitamin E/kg/day.

6. **Immunonutrients for preterm infants**

a. Glutamine and **arginine** are important sources of fuel and substrates for distal protective compounds (e.g., glutathione and nitric oxide, respectively). However, evidence-based replacement strategies for these elements are lacking. Thus, as with parenteral glutamine supplementation, there are presently no recommendations for enteral glutamine and/or arginine supplementation in preterm infants.

b. Long-chain polyunsaturated fatty acids. DHA and ARA have important roles in neurotransmitter and vision development. Premature infants are deficient in DHA and ARA because of missing accumulation during the third trimester, inability to convert from precursor fatty acids, and deficient postnatal intake. Despite a plausible rationale, enteral supplementation has demonstrated increase in serum levels but has not demonstrated improved long-term neurodevelopmental outcomes. Some experts have concerns about the potential for inadvertent harm given the knowledge gap on the appropriate fatty acid dose and balance between DHA and ARA. Routine enteral supplementation is not recommended.

c. Probiotics. Given the lack of pharmaceutical-grade products in the United States and paucity of studies of probiotics in infants <1,000 g, current evidence does not support the routine administration of probiotics to preterm infants with a birth weight of <1,000 g. The AAP recommends that centers electing to routinely administer probiotics to this high-risk population obtain consent from families and carefully monitor safety outcomes. See also Chapter 27.

IV. SPECIAL CONSIDERATIONS

A. NEC

1. Nutritional support of the patient with NEC focuses around providing complete PN during the acute phase of the disease, followed by gradual introduction of enteral nutrition after the patient has stabilized and the gut has been allowed to heal.
2. **PN.** For at least 5 to 14 days after the initial diagnosis of NEC, the patient is kept nothing by mouth (NPO) and receives total PN. The goals for PN were delineated previously in section II.
3. **Initiation of feedings.** If the patient is clinically stable after bowel rest, feedings are generally introduced at approximately 10 to 20 mL/kg/day, preferably with maternal milk or PDHM. Stability criteria include adequate hemodynamics and ventilation, a reassuring abdominal examination, minimal electrolyte abnormalities, discontinuation of antibiotics, and a reassuring abdominal radiograph. A standard preterm formula may also be used. Specialized formula (e.g., semi-elemental or elemental) may be used in the setting of intestinal failure, but these are not designed to meet the increased nutrient needs of a preterm infant (particularly protein and mineral needs).
4. **Feeding advancement.** If low-volume feedings (10 to 20 mL/kg/day) are tolerated for 24 to 48 hours, advancement can be continued per routine.

Supplemental PN is continued until enteral feedings are providing approximately 100 to 120 mL/kg/day volume.

5. **Feeding intolerance.** Inability to attain full-volume enteral feedings despite several attempts to advance feedings, radiographic contrast studies may be indicated to rule out intestinal strictures.

B. Infants with surgical conditions

1. **Enterostomies.** If one or more enterostomies are created as a result of surgical therapy for NEC or other gastrointestinal condition (e.g., volvulus, atresia), it may be difficult to achieve full nutritional intake by enteral feedings. Depending on the length and function of the upper intestinal tract, increasing feeding volume or nutritional density may result in problems with malabsorption, dumping syndrome, and poor growth.
   a. Refeeding. Output from the proximal intestinal enterostomy can be refed into the distal portion(s) of the intestine through the mucous fistula(s). This may improve the absorption of both fluid and nutrients.
   b. Infants with ostomy outputs lose excessive zinc and copper. Additional supplementation may be indicated.
   c. PN support. If growth targets cannot be achieved using enteral feedings, continued use of supplemental PN may be indicated depending on the patient's overall status and liver function. Enteral feedings should be continued at the highest rate and nutritional density tolerated, and supplemental PN should be given to achieve the nutritional goals and growth outcomes as previously outlined.

C. BPD. Preterm infants who have BPD have increased caloric requirements due to their increased metabolic expenditure and, at the same time, have a lower tolerance for excess fluid intake (see Chapter 34).

1. **Fluid restriction.** Total fluid intake is typically restricted to 140 mL/kg/day or less depending on severity of lung disease. In cases of severe BPD, further restriction to 120 mL/kg/day may be required. Careful monitoring is required when fluid restrictions are implemented to ensure adequate caloric and micronutrient intake. Growth parameters must also be monitored so that continued growth is not compromised.
2. **Caloric density.** Infants with BPD may require up to 30 kcal/oz feedings in order to achieve the desired growth targets. Infants with severe BPD should be carefully monitored for proportional growth.
3. **Transpyloric feedings** are often considered in infants with severe BPD (see section III.E.4.c).
4. **Vitamin A.** Vitamin A is important for normal growth and differentiation of epithelial tissue, particularly the development and maintenance of pulmonary epithelial tissue. ELBW infants are known to have low vitamin A stores at birth, minimal enteral intake for the first several weeks after birth, reduced enteral absorption of vitamin A, and unreliable parenteral delivery. Some studies have suggested that vitamin A supplementation can reduce the risk of BPD for infants weighing $<$1,000 g at birth with 5,000 IU vitamin A intramuscularly three times per week for the first 4 postnatal weeks, beginning in the first 72 hours.

However, data are conflicting as to whether vitamin A reduces the risk for BPD. At most, it appears that vitamin A would only result in a modest reduction of BPD. Centers have varying incidence of BPD, and so each center may wish to balance the modest decrease of BPD with availability of the medication and cost.

D. Metabolic bone disease. The use of earlier enteral feedings and central PN, with higher calcium and phosphorus concentrations, has reduced the incidence of metabolic bone disease. However, this continues to be seen with the prolonged use of PN in place of enteral nutrition or the feeding of enteral formulations designed for the term infant (see Chapter 59).

E. Gastroesophageal reflux (GER). Episodes of GER, as monitored by esophageal pH probes, are common in both preterm and full-term infants. The majority of infants, however, do not exhibit clinical compromise from GER.

1. **During introduction of enteral feedings.** Emesis can be associated during the introduction and advancement of enteral feedings in preterm infants. These episodes are most commonly related to intestinal dysmotility secondary to prematurity and will respond to modifications of the feeding regimen.

   a. Temporary reductions in the feeding volume, lengthening the duration of the feeding (sometimes to the point of using continuous feeding), removal of nutritional additives, and temporary cessation of enteral feedings are all possible strategies depending on the clinical course of the infant. Continuous human milk feedings can lead to milk fat adherence to the feeding tube and decreased infant growth. When the infant has demonstrated feeding tolerance, the feedings can be switched back to bolus feedings. Transitioning to bolus feedings by decreasing the pump time in a gradual fashion may be helpful.

   b. Rarely, specialized formulas are used when all other feeding modifications have been tried without improvement. In general, these formulas should only be used for short periods of time with close nutritional monitoring.

   c. Infants who have repeated episodes of symptomatic emesis that prevent achievement of full-volume enteral feedings may require evaluation for anatomic problems such as malrotation or Hirschsprung disease. In general, radiographic studies are not undertaken unless feeding problems have persisted for 2 or more weeks or unless bilious emesis occurs (see Chapter 62).

2. **After attaining full enteral feedings.** Preterm infants on full-volume enteral feedings may have occasional episodes of emesis. If these episodes do not compromise the respiratory status or growth of the infant, no intervention is required other than continued close monitoring of the infant. If symptomatic emesis is associated with respiratory compromise, repeated apnea, or growth restriction, therapeutic maneuvers are indicated.

   a. Positioning. Holding the infant upright (e.g., on caregiver's shoulder) for 20 to 30 minutes after feedings may improve symptoms. Semi-supine positioning in an infant seat can increase reflux.

   b. Feeding intervals. Shortening the interval between feedings to give a smaller volume during each feeding may sometimes improve signs of GER. Infants fed by gavage may have the duration of the feeding increased.

c. Apnea. Studies using pH probes and esophageal manometry have not shown an association between GER and apnea episodes.

d. Avoidance of tobacco smoke exposure. All families should be counseled to avoid exposing infants to tobacco smoke. A study found that perinatal tobacco smoke exposure was associated with more frequent reflux events on esophageal impedance testing.

e. Promotility agents. Treatment with promotility agents is often not efficacious and can pose health risks (QT prolongation, ventricular arrhythmias, tardive dyskinesia). These agents are not routinely recommended. Use of these agents should be in consultation with pediatric gastrointestinal specialists and with discussions of risks with the parents.

F. Potential complications associated with prolonged PN

1. **Cholestasis.** This is more often transient than progressive (see Chapter 26). Experimentally, even short-term PN can reduce bile flow and bile salt formation.
   - **a. Risk factors include the following:**
     - i. Prematurity
     - ii. Duration of PN administration
     - iii. Duration of fasting (lack of enteral feeding also produces bile inspissation and cholestasis)
     - iv. Infection
     - v. Narcotic administration
   - **b. Recommended management**
     - i. Attempt enteral feeding. Even minimal enteral feedings may stimulate bile secretion.
     - ii. Avoid excessive nutrition with PN.
     - iii. Consider a lipid-sparing strategy. When conjugated bilirubin is >1.5 mg/dL, pure soybean oil lipids may be decreased to 1 g/kg. If this change is made, the glucose infusion rate may need to be increased to 14 to 16 mg glucose/kg/minute to meet energy needs.
     - iv. Use of alternate lipid product. A pure fish oil triglyceride emulsion (Omegaven) is FDA approved for pediatric patients with PN-associated cholestasis. A multicomponent emulsion (SMOFlipid: soybean oil, medium-chain triglycerides, olive oil, and fish oil) is available for off-label use (see **Lipid** in section III.D.5), although their efficacy is prevention and/or treatment has not been established. Phytosterols are thought to be one of the main toxins involved in PN-associated cholestasis. Phytosterols are a component of the plasma membrane of plants, and they are present in soybean oil lipid emulsions. They are present in lower concentrations in multicomponent lipid emulsions but are only present in trace amounts in 100% fish oil lipid emulsions. Fish oil lipid emulsions are not recommended for *preventing* cholestasis or treating transient cholestasis. Laboratory monitoring for essential fatty acid deficiency, liver function, and bleeding diatheses is recommended.
2. **Metabolic abnormalities.** Azotemia, hyperammonemia, and hyperchloremic metabolic acidosis have become uncommon since introduction of the current crystalline amino acid solutions. These complications may occur, however, with amino acid intakes exceeding 4 g/kg/day.

G. Specialized formulas have been designed for a variety of congenital and neonatal disorders, including milk protein allergy, malabsorption syndromes, and several inborn errors of metabolism. Indications for the most commonly used of these specialized formulas are briefly reviewed in Table 21.6. Nutrient content of specialized formulas can be found on the manufacturer's website (Mead Johnson: https://www.hcp.meadjohnson.com/s/products, Abbott: https://abbottnutrition.com/infant-and-new-mother, Nestle Alfamino: https://www.alfamino.com/products, Nutricia Neocate: https://www.neocate.com/shop/hypoallergenic-formula-and-products/). However, it is important to note that **these formulas were not designed to meet the special nutritional needs of preterm infants**. These formulas are sometimes used for special indications, such as intestinal failure following NEC. Preterm infants who are fed these formulas require close nutritional assessment and monitoring for potential protein, mineral, and multivitamin supplementation (Table 21.7).

V. NUTRITIONAL CONSIDERATIONS IN DISCHARGE PLANNING.

Recent data describing postnatal growth in the United States suggest that a significant number of VLBW and ELBW infants continue to have catch-up growth requirements at the time of discharge from the hospital. However, there is a paucity of data regarding what to feed the preterm infant after discharge.

A. Growth monitoring. A discharge plan for every infant needs to include postdischarge monitoring of growth trajectory. Growth should be proportionate, so weight gain alone is an insufficient goal. Growth rate data obtained in the hospital is typically forwarded to infant follow-up clinics and the private pediatrician for VLBW and ELBW infants.

B. Human milk. The use of human milk and efforts to transition to full breastfeeding in former preterm infants who continue to require enhanced caloric density feedings poses a unique challenge. Individualized care plans are indicated in order to support the transition to full breastfeeding while continuing to allow for optimal rates of growth. Usually, this is accomplished by a combination of a specified number of nursing sessions per day, supplemented by two to three feedings of nutrient-enriched preterm formula. This method allows the infant to nurse and receive nutrient-dense feedings. Another approach is to continue use of HMF postdischarge. The use of ready-to-feed formula will help avoid the exposure to infant formula powder.

C. Infant formula. A meta-analysis of randomized controlled trials concluded that **nutrient-enriched postdischarge formulas** have limited benefits for growth and development up to 18 months after term compared with standard infant formulas. In some of the trials, infants on standard formula increased their volume of intake, therefore mostly compensating for any additional nutrients from the postdischarge formulas. The ESPGHAN suggested that preterm infants who demonstrate subnormal weight for age at discharge should be fed with fortified human milk or special formula fortified with high contents of protein, minerals, and trace elements as well as long-chain polyunsaturated fatty acids (LCPUFAs) until at least 40 weeks corrected age but possibly for another 3 months thereafter. In practice, preterm infants are considered to be appropriate candidates for the use of these formulas, either as

Table 21.6. Indications for Use of Infant Formulas

Clinical Condition	Suggested Type of Infant Formula	Rationale
Allergy to cow's milk protein or soy protein	Extensively hydrolyzed protein or free amino acids	Impaired digestion/ utilization of intact protein
Bronchopulmonary dysplasia	High-energy, nutrient-dense	Increased energy requirement, fluid restriction
Biliary atresia	Semi-elemental, containing reduced LCT (~45%), with supplemented MCT (~55%)	Impaired intraluminal digestion and absorption of long-chain fats
Chylothorax (persistent)	Significantly reduced LCT (~15%), with supplemented MCT (~84%)	Decreased lymphatic absorption of fats
Congestive heart failure	High-energy formula	Lower fluid and sodium intake; increased energy requirement
Cystic fibrosis	Semi-elemental formula, containing reduced LCT (~45%), with supplemented MCT (~55%) or standard formula with pancreatic enzyme supplementation	Impaired intraluminal digestion and absorption of long-chain fats
Galactosemia	Soy protein–based formula	Lactose-free
Gastroesophageal reflux	Standard formula, Enfamil AR	Consider small, frequent feedings.
Hepatic insufficiency	Semi-elemental formula, containing reduced LCT (~45%), with supplemented MCT (~55%)	Impaired intraluminal digestion and absorption of long-chain fats
Lactose intolerance	Low lactose formula	Impaired digestion or utilization of lactose
Lymphatic anomalies	Significantly reduced LCT (~15%), with supplemented MCT (~84%)	Impaired absorption of long-chain fats
Necrotizing enterocolitis	Preterm formula or semi-elemental formula, if indicated	Impaired digestion
Renal insufficiency	Standard formula	
	Similac PM 60/40	Low phosphate content, low renal solute load

LCT, long-chain triglyceride; MCT, medium-chain triglyceride.

Table 21.7. Oral Dietary Supplements Available for Use in Infants

Nutrient	Product	Source	Energy Content
Fat	MCT oil (Novartis)	Medium-chain triglycerides	8.3 kcal/g 7.7 kcal/mL
	Microlipid (Novartis)	Long-chain triglycerides	4.5 kcal/mL
	Corn oil	Long-chain triglycerides	8.6 kcal/g 8 kcal/mL
Carbohydrate	SolCarb (Solace) (for term infants only)	Maltodextrin	3.8 kcal/g 8 kcal/tsp (powder)
Protein	Abbott liquid protein	Extensively hydrolyzed casein protein	3.6 kcal/g 4 kcal/6 mL

an additive to human milk or as a sole formula choice, once they are >2,000 g and 35 weeks corrected age. However, the length of time after discharge these formulas should be continued remains unclear. Term formulas may also be used. Careful monitoring of growth is indicated with any feeding plan.

D. Vitamin and iron supplementation at discharge

1. Preterm infants who are >2,000 g and 35 weeks corrected gestational age, and **human milk–fed**, are supplemented daily with 1 mL pediatric multivitamin (M.V.I. Pediatric) without iron, and with ferrous sulfate drops administered separately. Often, M.V.I. Pediatric with iron will be given at discharge to infants who weigh >2,000 g to facilitate supplementation adherence by parents. This supplement provides 10 mg iron/mL, and the infant will quickly grow into a goal of 2 to 4 mg iron/kg/day.
2. Preterm infants who are >2,000 g and 35 weeks corrected gestational age, and **fed a combination** of human milk and formula, are supplemented with 1 mL vitamin D drops to provide 400 IU per day. Ferrous sulfate drops are administered separately, as needed. The upper limit of vitamin D intake for infants is 1,000 IU per day. The infant would need to consume >1 quart of formula with the 400 IU per day supplement to reach >1,000 IU per day of vitamin D.
3. Preterm infants who are >2,000 g and 35 weeks corrected gestational age, and **formula-fed**, are supplemented with 0.5 mL (400 IU/mL) vitamin D drops to provide a 200-IU/day vitamin D supplement + 200 IU/day from the formula. Ferrous sulfate drops are administered separately, if needed.

4. Term infants, who are exclusively human milk–fed, are supplemented daily with 1 mL (400 IU/mL) vitamin D drops, once feedings have been established. Iron supplementation is not indicated until 4 months of age. Earlier iron supplementation of 1 mg/kg is indicated for term infants who have received numerous blood drawings. Low birth weight infants should receive 2 mg/kg of iron.
5. Term infants, who are fed iron-fortified infant formula do not require vitamin D or iron supplements. In a few weeks, their formula volume intakes should provide goal intake of 400 IU per day of vitamin D.

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This chapter is dedicated to the memory of Diane Anderson, PhD, RD, LD. She was a pioneer in the field of neonatal nutrition and impacted the nourishment and growth of countless newborns through direct patient care, training neonatal dietitians, authoring multiple publications, and organizing a national conference. Her guidance and leadership immeasurably changed the field of neonatal nutrition, and she is greatly missed.

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22 Breastfeeding and Maternal Medications

Nancy Hurst, Margaret G. Parker, and Karen M. Puopolo

KEY POINTS

- Breastfeeding is beneficial for mothers and newborns.
- Hospital policies should include strategies to promote nonseparation of mothers and newborns and exclusive breastfeeding.
- All breastfeeding infants should be seen by their primary health provider at 3 to 5 days of age to ensure adequacy of milk intake.

I. RATIONALE FOR BREASTFEEDING. Breastfeeding enhances maternal involvement, interaction, and bonding; provides species-specific nutrients to support normal infant growth; provides nonnutrient growth factors, immune factors, hormones, and other bioactive components that can act as biologic signals; and can decrease the incidence and severity of infectious diseases, enhance neurodevelopment, decrease the incidence of childhood obesity and some chronic illnesses, and decrease the incidence and severity of atopic disease. Breastfeeding is beneficial for the mother's health because it has been shown to reduce risks of adverse cardiovascular health and type 2 diabetes and risk of maternal breast, ovarian, and endometrial cancer.

II. RECOMMENDATIONS ON BREASTFEEDING FOR HEALTHY TERM INFANTS INCLUDE THE FOLLOWING GENERAL PRINCIPLES (CENTERS FOR DISEASE CONTROL AND PREVENTION, AMERICAN ACADEMY OF PEDIATRICS)

A. Promote hospital policies that support exclusive breastfeeding and nonseparation of mother and infant during hospital stay, beginning with immediate skin-to-skin contact after birth.

B. Encourage frequent feeding (8 to 12 feeds per 24 hours) in response to early infant cues.

C. When direct breastfeeding is not possible, instruct mother to hand express and/or pump to promote milk production.

D. Supplements to breast milk (i.e., water or formula) should not be given unless medically indicated.

E. Breastfeeding should be well established (about 2 weeks postbirth) before pacifiers are used.

F. Complementary foods should be introduced around 6 months with continued breastfeeding up to and beyond the first year.

G. Oral vitamin D drops (400 IU daily) should be given to the infant beginning within the first few after birth.

H. Supplemental fluoride should not be provided during the first 6 months after birth.

III. MANAGEMENT AND SUPPORT ARE NEEDED FOR SUCCESSFUL BREASTFEEDING

A. Prenatal period. During pregnancy, all mothers should receive the following:

1. Information on the benefits of breastfeeding for mothers and infants
2. General information on the importance of exclusive breastfeeding during the maternity hospital stay in order to lay the foundation for adequate milk production

B. Early postpartum period. Prior to hospital discharge, all mothers should receive the following:

1. Breastfeeding assessment by a maternal–child nurse or lactation specialist
2. General breastfeeding information about the following:
   a. Basic positioning of infant to allow correct infant attachment at the breast
   b. Minimum anticipated feeding frequency (eight times per 24-hour period)
   c. Expected physiologically appropriate colostrum intakes (about 15 to 20 mL in first 24 hours)
   d. Infant signs of hunger and adequacy of milk intake
   e. Common breast conditions experienced during early breastfeeding and basic management strategies
   f. Postdischarge referral sources for breastfeeding support
   g. Postdischarge needs assessment for a breast pump and provision of education on the benefits of double electric breast pumps and pump use and cleaning.

C. All breastfeeding infants should be seen by a pediatrician or other health care provider within 1 to 3 days after discharge from the birth hospital to ensure appropriate milk intake, assessed by weight change from birth weight and urine and stool output. By 3 to 5 days of age, the infant should have yellow, seedy stools (approximately three times per day) and no more meconium stools and at least six wet diapers per day. A validated nomogram for assessing newborn weight loss can be accessed at http://www.newbornweight.org/.

1. Postdischarge lactation support should include ongoing education in infant latch and positioning, assessment of infant for signs of hunger and adequacy of milk intake, and information on expectations and treatment of minor breast/nipple conditions.
2. If mother does not have a breast pump, additional needs assessment should be made and information and education provide as in section III.B.2.g.

3. Expect a return to birth weight by 12 to 14 days of age and a continued rate of growth of at least 0.5 oz/day (~15 g/day) during the first month.
4. If infant growth is inadequate, after ruling out any underlying health conditions in the infant, breastfeeding assessment should include adequacy of infant attachment to the breast, presence or absence of signs of normal lactogenesis (i.e., breast fullness, leaking), and maternal history of conditions (i.e., endocrine, breast surgery) that may affect lactation.
   a. The ability of infants to transfer milk at breast can be measured by weighing the infant before and after feeding using the following guidelines:
      i. Weighing the diapered infant before and immediately after the feeding (without changing the diaper)
      ii. One-gram infant weight gain equals 1 mL milk intake.
5. If milk transfer is inadequate, supplementation (preferably with expressed breast milk) may be indicated.
6. If supplementation is indicated, instruct the mother to express her milk by hand and/or with a double electric breast pump following a feeding to allow additional breast stimulation to increase milk production.

IV. MANAGEMENT OF BREASTFEEDING PROBLEMS

A. Sore, tender nipples. Most mothers will experience some degree of nipple soreness commonly due to hormonal changes and increased friction caused by the infant's sucking action. A common description of this soreness includes an intense onset of pain during the initial latch-on with a rapid subsiding of discomfort as milk flow increases. Nipple tenderness should diminish during the first few weeks until no discomfort is experienced during breastfeeding. Purified lanolin and/or expressed breast milk applied sparingly to the nipples following feedings may hasten this process.

B. Traumatized, painful nipples (may include bleeding, blisters, and fissures). Possible causes include ineffective, poor latch-on to breast; improper infant sucking technique; removing infant from breast without first breaking suction; and an underlying nipple condition or infection (i.e., eczema, bacterial, fungal infection). Management of this degree of nipple injury includes (i) assessment of infant positioning and latch-on with correction of improper techniques and (ii) recognition and treatment of any underlying nipple condition. In cases of severely traumatized nipples, temporary cessation of breastfeeding may be indicated to allow for healing. In this scenario, it is important to instruct the mother to maintain lactation with mechanical/hand expression until direct breastfeeding is resumed.

C. Engorgement is a severe form of increased breast fullness that usually presents on days 3 to 5 postpartum signaling the onset of copious milk production. Engorgement may be caused by inadequate and/or infrequent breast stimulation resulting in swollen, hard breasts that are warm to the touch. The infant may have difficulty latching on to the breast until the engorgement is resolved. Treatment includes (i) application of warm, moist heat to the breast alternating with cold compresses to relieve edema of the breast tissue; (ii) gentle hand expression of milk to soften areola to facilitate infant

attachment to the breast; (iii) gentle massage of the breast during feeding and/or milk expression; and (iv) mild analgesic or anti-inflammatory for pain relief and/or reduction of inflammation.

D. Plugged milk ducts usually present as a palpable lump or area of the breast that does not soften during a feeding or pumping session. This can occur with missed or delayed feeding/pumping. Treatment includes (i) frequent feedings/pumpings beginning with the affected breast, (ii) application of moist heat and breast massage before and during feeding, and (iii) positioning infant during feeding to locate the chin toward the affected area to allow for maximum application of suction pressure to facilitate breast emptying.

E. Mastitis is an inflammatory and/or infectious breast condition—usually affecting only one breast. Signs and symptoms include rapid onset of fatigue; body aches; headache; fever; and tender, reddened breast area. Mothers should consult their health care providers for treatment of suspected mastitis. Treatment includes (i) continued breastfeeding on affected and unaffected breasts, (ii) frequent and efficient milk removal—using an electric breast pump when necessary (it is not necessary to discard expressed breast milk), (iii) appropriate antibiotics for a sufficient period (10 to 14 days), and (iv) comfort measures to relieve breast discomfort and general malaise (i.e., analgesics, moist heat/massage to breast).

F. Breast lumps or other abnormalities that do not respond to the general recommendations in section IV.A to E earlier should be discussed with mother's health care provider. Rarely, breast cancer can occur during lactation, often with delayed recognition due to the physiologic changes associated with pregnancy and lactation.

V. SPECIAL SITUATIONS.

Certain conditions in the infant, mother, or both may indicate specific strategies that require a delay and/or modification of the normal breastfeeding relationship. Whenever breastfeeding is delayed or suspended for a period of time, frequent breast emptying with an electric breast pump is recommended to ensure maintenance of lactation.

A. Infant conditions

1. **Hyperbilirubinemia** is not a contraindication to breastfeeding. Special attention should be given to ensuring infant is breastfeeding effectively in order to maintain adequate hydration, enhance gut motility, and facilitate bilirubin excretion.

2. **Congenital anomalies** may require special management.

   a. Craniofacial anomalies (i.e., cleft lip/palate, Pierre Robin) present challenges to the infant's ability to latch effectively to the breast. Modified positioning and special devices (e.g., nipple shield) may be used to achieve an effective latch. At times, special bottle systems with pumped milk may be needed.

   b. Cardiac or respiratory conditions may require fluid restriction and special attention to pacing of feeds to minimize fatigue during feeding.

   c. Restrictive lingual frenulum (ankyloglossia/tongue tie) may interfere with the infant's ability to effectively breastfeed. The inability of the infant to extend the tongue over the lower gum line and lift the tongue to

compress the underlying breast tissue may compromise effective milk transfer. Frenulectomy may be helpful in some cases.

3. **Premature infants** receive profound benefits from breastfeeding and the receipt of mother's own milk. Mothers should be encouraged to express their milk even if they do not plan on direct breastfeeding in order to provide their infant with the unique nutritional and nonnutritional components.

   Although mother's own milk imparts the greatest benefit to preterm and high-risk infants, pasteurized donor breast milk may be used when mother's milk is not available. When considering donor milk feeding, the product should be obtained from milk banks that are informed by guidelines established by the Human Milk Banking Association of North America (HMBANA). These guidelines ensure safe handling and maintain the maximum amount of active human milk components. We suggest obtaining parental assent prior to using donor milk.

   a. Special attention should be given to late preterm and near-term infants (35 to 37 weeks' gestation) who are often discharged from the hospital before they are breastfeeding effectively. Management considerations include (i) mechanical milk expression concurrent with breastfeeding until the infant is breastfeeding effectively, (ii) systematic assessment (and documentation) of breastfeeding by a trained observer, and (iii) weighing the infant before and after breastfeeding to evaluate adequacy of milk intake and determine need for supplementation.

   b. For premature infants who are separated from their infants soon after birth for intensive neonatal care, mothers should be encouraged to express their milk as soon as possible after birth, optimally within 6 to 8 hours, and continue milk expression at least every 3 to 4 hours. When the infant condition allows, mothers should be encouraged and supported to practice early and frequent skin-to-skin holding and place the infant at the breast to facilitate early nipple stimulation to enhance milk volume and ultimately enable infant oral feeding.

B. Maternal conditions associated with delayed lactogenesis II

1. Women with **diabetes** should be encouraged to breastfeed, and many find an improvement in their glucose metabolism during lactation. Early, close monitoring to ensure the establishment of lactation and adequacy of infant growth are recommended due to a well-documented delay (1 to 2 days) in the secretory phase of lactogenesis.
2. Women who have a **cesarean birth** or are **obese** have been observed to have a higher risk for delayed lactogenesis II.
3. Thyroid disease does not preclude breastfeeding, although without proper treatment of the underlying thyroid condition, poor milk production (hypothyroidism) or maternal loss of weight, agitation, and heart palpitations (hyperthyroidism) may negatively affect lactation. With proper pharmacologic treatment, the ability to lactate does not appear to be affected.
4. Mothers with a **history of breast or chest surgery** are able to breastfeed successfully. Prenatal assessment should include documenting the type of procedure (i.e., augmentation, reduction mammoplasty) and surgical

approach (i.e., submammary, periareolar, free nipple transplantation) used in order to determine the level of follow-up indicated in the early postpartum period. Attention should be directed to adequacy of milk production and infant growth.

VI. CARE AND HANDLING OF EXPRESSED BREAST MILK. When possible, direct breastfeeding provides the greatest benefit for mother and infant, providing maximal exposure to human milk components and the maternal microbiome and supporting maternal–infant interaction. However, when direct breastfeeding is not possible, breast milk should be expressed with proper attention to expression and storage techniques. Milk expression and storage techniques can affect the composition and bacterial content of mother's own milk. Guidelines for milk collection and storage vary depending on the condition of the infant: healthy term infant (Centers for Disease Control and Prevention [CDC]) or hospitalized preterm infant (HMBANA and American Diabetes Association [ADA]).

A. Breast milk expression and collection. Recommendations for initiation and maintenance of mechanical milk expression for pump-dependent mothers of hospitalized infants include (i) breast stimulation with a hospital-grade electric breast pump combined with hand expression/breast massage initiated within the first 6 to 8 hours following delivery, (ii) frequent pumping/hand expression (every 3 to 4 hours), (iii) pumping 10 to 15 minutes per session during the first few days until the onset of increased milk flow, and (iv) a target daily milk volume of 800 to 1,000 mL at the end of the second week following delivery is optimal and associated with greater duration of lactation.

B. Guidelines for breast milk collection include (i) performing hand hygiene with soap and water or waterless hand sanitizer prior to each milk expression; (ii) thorough cleaning of all milk collection equipment prior to and following each use with soap and hot water or by use of a dishwasher; (iv) collecting milk in sterile glass or hard plastic containers; and (v) labeling each milk container with infant's identifying information, date, and time of milk expression.

C. Guidelines for breast milk storage include (based on HMBANA/ADA recommendations for the hospitalized preterm infant with CDC recommendations for healthy term infants included in parenthesis) (i) use fresh, unrefrigerated milk within 4 hours of milk expression (CDC: 6 to 8 hours); (ii) refrigerate milk immediately following expression when the infant will be fed within 96 hours (CDC: 5 days); (iii) freeze milk when infant is not being fed or the mother is unable to deliver the milk to the hospital within 24 hours of expression; and (iv) in the event that frozen milk partially thaws, either complete thawing process and feed the milk or refreeze. Milk may be stored in a freezer compartment *within* a refrigerator compartment for 2 weeks, in a freezer compartment *separate from* the refrigerator compartment for 3 to 6 months, or a chest or upright deep freezer for up 6 to 12 months. Milk stored in these conditions for longer periods may be safe but will be of lower nutritional quality due to lipid degradation.

Environment	Temperature	Freshly Expressed Mother's Milk	Frozen Mother's Milk	Frozen Pasteurized Donor Milk
Room temperature	60°–85°F/ 16°–29°C	4 hours	4 hours	4 hours
Refrigerator	39°F/4°C	96 hours	48 hours	48 hours
Freezer (two-door fridge/freezer)	0°F/–18°C	9 months	9 months	6–8 months
Deep freezer	0°F/–18°C	12 months	12 months	6–12 months
Laboratory freezer	−94°F/–70°C	12 months	12 months	6–12 months

VII. CONTRAINDICATIONS AND CONDITIONS NOT CONTRAINDICATED TO BREASTFEEDING.

There are few contraindications to breastfeeding or expressed breast milk feeding. Maternal health conditions should be evaluated and appropriate treatments prescribed in order to support continued breastfeeding and/or minimal interruption of feeding when possible. Most maternal medications enter breast milk to some degree; however, with few exceptions, the concentrations of most are relatively low and the dose delivered to the infant often has no impact.

A. Contraindications to breastfeeding

1. An infant with **galactosemia** will be unable to breastfeed or receive breast milk.
2. A mother with **active untreated tuberculosis** will be isolated from her newborn for initial treatment. She can express her milk to initiate and maintain her milk volume during this period, and once it is deemed safe for her to have contact with her infant, she can begin breastfeeding.
3. The CDC recommends **women who test positive for HIV in the United States** not breastfeed. Some women with undetectable viral loads on stable HIV medication regimens may opt to breastfeed under the direction of their own infectious disease physician. Although we do not advocate for this practice, we have supported individual women who make this decision under medical supervision.
4. **Some maternal medications** are contraindicated during breastfeeding. Clinicians should maintain reliable resources for information on the transfer of drugs into human milk (see section VIII).

B. Conditions that are **not** contraindications to breastfeeding

1. Mothers who are positive for hepatitis B surface antigen. Infants should receive hepatitis B immune globulin and hepatitis B vaccine to minimize risk of perinatal transmission.
2. Although hepatitis C virus has been found in breast milk, transmission through breastfeeding has not been observed (see Chapter 48).

3. In full-term infants, the benefits of breastfeeding appear to outweigh the risk of transmission from cytomegalovirus (CMV)-positive mothers. Extremely preterm infants can acquire CMV through mother's own milk feeding. Freezing mother's milk can reduce the risk of CMV infection but has not shown to reduce the risk of sepsis-like syndrome. Currently, there is insufficient evidence to withhold mother's own milk to extremely preterm infants based on the risk of CMV infection.
4. Mothers who are febrile
5. Mothers who are exposed to or positive for COVID-19
6. Mothers exposed to low-level environmental chemical agents
7. Although tobacco smoking is not contraindicated, mothers should be advised to avoid smoking in the home and make every effort to stop smoking while breastfeeding.
8. Alcohol use should be avoided because it is concentrated in milk, and it can inhibit short-term milk production. Although an occasional, small alcoholic drink is acceptable, breastfeeding should be avoided for 2 hours after the drink.
9. Mothers who use marijuana should be advised to stop doing so while breastfeeding as it passes to infants through breast milk.

VIII. MATERNAL MEDICATIONS AND BREASTFEEDING.

Questions commonly arise regarding the safety of maternal medication use during breastfeeding. A combination of the biologic and chemical properties of the drug and the physiology of the mother and infant determine the safety of any individual medication. Consideration is given to the amount of drug that is found in breast milk, the half-life of the drug in the infant, and the biologic effect of the drug on the infant.

A. **Drug properties that affect entry into breast milk.** Molecular size, pH, pKa, lipid solubility, and protein-binding properties of the drug all affect the **milk-to-plasma (M/P) concentration ratio**, which is defined as the relative concentration of the protein-free fraction of the drug in milk and maternal plasma. Small molecular size, slightly alkaline pH, nonionization, high lipid solubility, and lack of binding to serum proteins all favor entry of a drug into breast milk. The half-life of the medication and frequency of drug administration are also important; the longer the cumulative time the drug is present in the maternal circulation, the greater the opportunity for it to appear in breast milk.

B. **Maternal factors.** The total maternal dose and mode of administration (intravenous vs. oral) as well as maternal illness (particularly renal or liver impairment) can affect the persistence of the drug in the maternal circulation. Medications taken in the first few days postpartum are more likely to enter breast milk as the mammary alveolar epithelium does not fully mature until the end of the first postpartum week.

C. **Infant factors.** The maturity of the infant is the primary factor determining the persistence of a drug in the infant's system. Preterm infants and term infants in the first month after birth metabolize drugs more slowly because of renal and hepatic immaturity. The total dose of drug that the infant is

exposed to is determined by the volume of milk ingested (per kilogram of body weight) as well as the frequency of feeding (or frequency of milk expression in the case of preterm infants) and the degree to which the medication can be absorbed by the infant's gastrointestinal system.

IX. DETERMINATION OF DRUG SAFETY DURING BREASTFEEDING.

A number of available resources evaluate the risk of individual medications to the breastfed infant. Ideally, judging the safety of a drug depends on the direct measurements of the entry of a drug into breast milk, the level and persistence of the drug in the breastfed infant, and experience with exposure of infants to the drug. This type of information is available for relatively few medications. In the absence of specific data, a judgment is made on the basis of both the known pharmacologic properties of the drug and the known or predicted effects of the drug on the developing infant. Clinicians providing advice to the nursing mother about the safety of a particular medication should be aware of the following points.

A. Resources may differ in their determination of drug safety during lactation. Different resources approach the question of medication use in breastfeeding with different perspectives. For example, drug manufacturers generally do not make a definitive statement about the safety of drugs in breastfeeding. Resources specifically designed to address breastfeeding will take the available data and make a recommendation about relative safety of the drug based on its biochemical properties.

B. The safety of a drug in pregnancy may not be the same as the safety of the drug during breastfeeding. Occasionally, a medication that is contraindicated in pregnancy (e.g., warfarin or ibuprofen) is safe to use while breastfeeding.

C. Definitive data are not available for most medications or for specific clinical situations. There is a need for individualized clinical judgment in many cases, taking into account the available information, the need of the mother for the medication, the combination of different medications taken, and the risk to the infant of both exposure to the drug and of exposure to breast milk substitutes.

D. The U.S. Food and Drug Administration (FDA) published in 2014 the ***Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling***, referred to as the **"Pregnancy and Lactation Labeling Rule"** (PLLR or final rule). "The PLLR requires changes to the content and format for information presented in prescription drug labeling in the Physician Labeling Rule (PLR) format to assist health care providers in assessing benefit versus risk and in subsequent counseling of pregnant women and nursing mothers who need to take medication, thus allowing them to make informed and educated decisions for themselves and their children. The PLLR removes pregnancy letter categories—A, B, C, D, and X. The PLLR also requires the label to be updated when information becomes outdated" (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm).

X. RESOURCES

A. LactMed is the drugs and lactation database, maintained by the U.S. National Library of Medicine's Toxicology Data Network (TOXNET). It is found at https://www.ncbi.nlm.nih.gov/books/NBK501922/. This database includes information on the expected transfer of substances in breast milk, anticipated absorption of substances by the infant, data on maternal and infant blood levels, and possible adverse effects in the nursing infant. Suggested therapeutic alternatives are listed where appropriate. This resource does not offer a specific rating system but provides summary guidance based on available data (or lack of data). All data are derived from the scientific literature and fully referenced; links to PubMed are provided for cited literature.

B. American Academy of Pediatrics, "The Transfer of Drugs and Therapeutics into Human Breast Milk: An Update on Selected Topics," *Pediatrics* 2013 (reaffirmed in 2018). The American Academy of Pediatrics no longer publishes safety ratings of medications, referring medical professionals to the LactMed web-based resource. This clinical report specifically addresses breastfeeding and the use of antidepressant medications, prescription pain medications, alcohol and drugs of abuse, medications used to treat substance dependence, substances used as galactogogues, common herbal supplements, vaccines, and radioactive substances used in diagnostic imaging.

C. Hale TW. *Hale's Medications & Mother's Milk*. 19th ed. New York, NY: Springer; 2021. This book is a comprehensive listing of hundreds of prescription and over-the-counter medications, radiopharmaceuticals, contrast agents, contraceptives, vitamins, herbal remedies, and vaccines, with primary references cited for most. The author provides a "Lactation Risk Category" rating for each entry as follows: **L1**: safest, **L2**: safer, **L3**: moderately safe, **L4**: possibly hazardous, and **L5**: contraindicated. Many drugs fall into the **L3 category**, which is defined as follows: "There are no controlled studies in breastfeeding women; however, the risk of untoward effects to a breastfed infant is possible, or controlled studies show only minimal, non-threatening adverse effects. Drugs should be given only if the potential benefit justifies the potential risk to the infant."

D. Briggs GG, Towers CV, Forinash AB, eds. *Briggs Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*. 12th ed. Philadelphia, PA: Wolters Kluwer Health; 2021. This book lists primary references and reviews data for medications with respect to the risk to the developing fetus and the risk in breastfeeding. For drug use in pregnancy, the book provides a recommendation from 17 potential categories based on available human and animal reproduction data. For drug use in lactation, the book provides a recommendation from seven potential categories based on available human and pharmacologic data.

E. Lawrence RA, Lawrence RM. *Breastfeeding: A Guide for the Medical Profession*. 8th ed. Philadelphia, PA: Elsevier; 2015. This book includes an extended discussion of the pharmacology of drug entry into breast milk. An appendix contains medications listed by category (analgesics, antibiotics, etc.) and provides available safety ratings as well as extensive pharmacokinetic data

for each drug, including values for the M/P ratio and maximum amount (milligram per milliliter) of drug found in breast milk.

F. The Breastfeeding and Human Lactation Study Center. The Study Center maintains a drug data bank that is regularly updated. Health professionals may call (585) 275-0088 to speak with staff members regarding the safety of a particular drug in breastfeeding. The Study Center will only take calls from health care professionals (not parents). The Study Center is part of the Division of Neonatology, Golisano Children's Hospital at the University of Rochester Medical Center.

G. InfantRisk Center—http://www.infantrisk.com. This center is staffed by knowledgeable personnel providing up-to-date evidence-based information on the use of medications during pregnancy and breastfeeding. They can be contacted at (806) 352-2519 Monday to Friday 8 am to 5 pm CST or online at the aforementioned address.

Suggested Readings

Hale TW. *Hale's Medications & Mother's Milk*. 19th ed. New York, NY: Springer; 2021.

Jones F. *Best Practice for Expressing, Storing and Handling Human Milk in Hospitals, Homes, and Child Care Settings*. 4th ed. Fort Worth, TX: Human Milk Banking Association of North America; 2019.

Lawrence RA, Lawrence RM. *Breastfeeding: A Guide for the Medical Profession*. 8th ed. Philadelphia, PA: Elsevier; 2015.

Parker MG, Stellwagen LM, Noble L, et al. Promoting human milk and breastfeeding for the very low birth weight infant. *Pediatrics* 2021;148(5):e2021054272.

Philipp BL. ABM Clinical Protocol #7: model breastfeeding policy (revision 2010). *Breastfeed Med* 2010;5(4):173–177.

Robbins ST, Meyers R, eds. *Infant Feedings: Guidelines for Preparation of Formula and Breast milk in Health Care Facilities*. 2nd ed. Arlington, VA: American Dietetic Association; 2011. https://safebabybmt.paragondsi.com/wp-content/uploads/2017/01/2011-ADA-Infant-Feedings-Guidelines-for-Preparation-of-Human-Milk-and-Formula-in-Health-Care-Facilities.pdf.

Sachs HC; and the Committee on Drugs. The transfer of drugs and therapeutics into human breast milk: an update on selected topics. *Pediatrics* 2013;132(3):e796–e809. http://pediatrics.aappublications.org/content/pediatrics/132/3/e796.full.pdf.

Section on Breastfeeding. Breastfeeding and the use of human milk. *Pediatrics* 2012;129(3):e827–e841.

Online Resources

Academy of Breastfeeding Medicine. http://www.bfmed.org/. Accessed September 16, 2021.

Baby-Friendly USA. http://www.babyfriendlyusa.org/. Accessed September 16, 2021.

Centers for Disease Control and Prevention. Breastfeeding. http://www.cdc.gov/breastfeeding/. Accessed September 16, 2021.

Human Milk Banking Association of North America. http://www.hmbana.org/. Accessed September 16, 2021.

InfantRisk Center. http://www.infantrisk.com. Accessed September 16, 2021.

International Lactation Consultant Association. http://www.ilca.org/. Accessed September 16, 2021.

LactMed database. http://www.ncbi.nlm.nih.gov/books/NBK501922/. Accessed September 16, 2021.

La Leche League International. http://www.llli.org/. Accessed September 16, 2021.

Newborn Weight Tool. Weight loss nomograms. http://www.newbornweight.org/. Accessed September 16, 2021.

U.S. Breastfeeding Committee. http://www.usbreastfeeding.org/. Accessed September 16, 2021.

Wellstart International. http://www.wellstart.org/. Accessed September 16, 2021.

23 Fluid and Electrolyte Management

Emily Whitesel

KEY POINTS

- Transition from fetal to neonatal life is associated with significant changes in water and electrolyte homeostatic control.
- Sources of water loss in the neonate include kidneys, skin, and lungs.
- Preterm infants are most vulnerable to fluid and electrolyte imbalance.
- Assessment and management of fluid requirements are essential components of newborn care.

Careful fluid and electrolyte management in term and preterm infants is an essential component of neonatal care. Developmental changes in body composition in conjunction with functional changes in skin, renal, and neuroendocrine systems account for the fluid balance challenges faced by neonatologists on a daily basis. Fluid management requires the understanding of several physiologic principles.

I. DISTRIBUTION OF BODY WATER

A. General principles. Transition from fetal to newborn life is associated with major changes in water and electrolyte homeostatic control. Before birth, the fetus has constant supply of water and electrolytes from the mother across the placenta. After birth, the newborn assumes responsibility for its own fluid and electrolyte homeostasis. The body composition of the fetus changes during gestation with a smaller proportion of body weight being composed of water as gestation progresses.

B. Definitions

1. Total body water (TBW) = intracellular fluid (ICF) + extracellular fluid (ECF) (Fig. 23.1)
2. ECF is composed of intravascular and interstitial fluid.
3. Insensible water loss (IWL) can be estimated by the following equation = fluid intake − urine output − (± Δ weight); however, unknown and unmeasurable factors also need to be considered.

C. Perinatal changes in TBW. A proportion of diuresis in both term and preterm infants (a decrease of 0.8 *z* scores) during the first days of life should be regarded as physiologic. However, excessive weight loss should be minimized and countered by providing appropriate nutritional support during this initial transition.

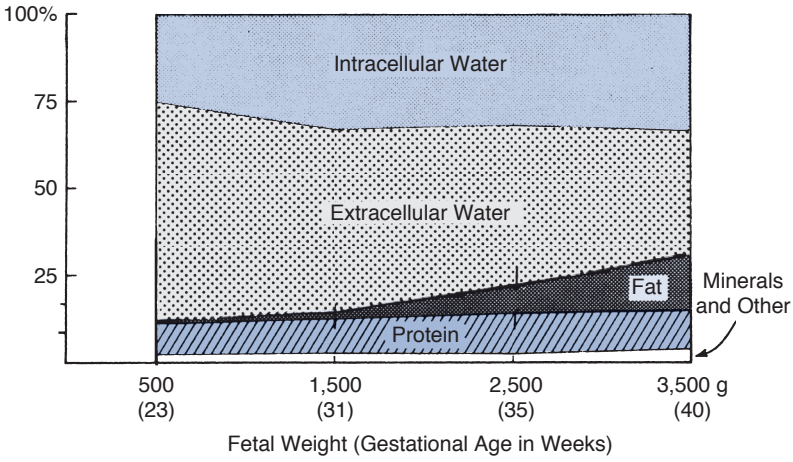


Figure 23.1. Body composition in relation to fetal weight and gestational age. (Reprinted from Dweck HS. Feeding the prematurely born infant. Fluids, calories, and methods of feeding during the period of extrauterine growth retardation. *Clin Perinatol* 1975;2[1]:183–202. Copyright © 1975 Elsevier. With permission. Data from Widdowson EM. Growth and composition of the fetus and newborn. In: Assali NS, ed. *Biology of Gestation*. Vol 2. New York, NY: Academic Press; 1968.)

At lower gestational ages, ECF accounts for a greater proportion of birth weight (see Fig. 23.1). Therefore, very low birth weight (VLBW) infants lose a greater percentage of birth weight to maintain ECF proportions equivalent to those of term infants. Although fluid overload is a potential concern for evolving chronic lung disease (CLD), nutritional support is necessary to optimize neurodevelopment, and a careful balance must be maintained between allowing appropriate physiologic diuresis and excessive weight loss.

D. Sources of water loss

1. **Renal losses.** Renal function matures with increasing gestational age. Immature sodium (Na) and water homeostasis is common in the preterm infant. Contributing factors leading to varying urinary water and electrolyte losses include the following:
   - **a.** Decreased glomerular filtration rate (GFR)
   - **b.** Reduced proximal and distal tubule Na reabsorption
   - **c.** Decreased capacity to concentrate or dilute urine
   - **d.** Decreased bicarbonate, potassium (K), and hydrogen ion secretion
2. **Extra renal losses.** In VLBW infants, IWL can exceed 150 mL/kg/day owing to increased environmental and body temperatures, skin breakdown, radiant warmers, phototherapy, and extreme prematurity (Table 23.1). Respiratory water loss increases with decreasing gestational age and with increasing respiratory rate; in intubated infants, inadequate humidification of the inspired gas may lead to increased IWL. Other fluid losses that should be replaced if amount is deemed significant include stool (diarrhea or ostomy drainage), cerebrospinal fluid (from ventriculotomy or serial lumbar punctures), and nasogastric tube or thoracostomy tube drainage.

Table 23.1. Insensible Water Loss (IWL)

Birth Weight (g)	IWL (mL/kg/day)
750–1,000	82
1,001–1,250	56
1,251–1,500	46
>1,501	26

Values represent mean IWL for infants in incubators during the first week of life. IWL is increased by phototherapy (up to 40%), radiant warmers (up to 50%), and fever. IWL is decreased by the use of humidified gas with respirators and heat shields in incubators.

Source: Bell EF, Gray JC, Weinstein MR, et al. The effects of thermal environment on heat balance and insensible water loss in low-birth-weight infants. *J Pediatr* 1980;96:452–459; Fanaroff AA, Wald M, Gruber HS, et al. Insensible water loss in low birth weight infants. *Pediatrics* 1972;50(2):236–245; and Okken A, Jonxis JH, Rispens P, et al. Insensible water loss and metabolic rate in low birthweight newborn infants. *Pediatr Res* 1979;13(9):1072–1075.

Incubators for newborn infants are being designed to improve maintenance of warmth and humidity and may lead to decreased IWL (e.g., the Giraffe Isolette).

II. ASSESSMENT OF FLUID AND ELECTROLYTE STATUS

A. History

1. **Maternal.** The newborn's fluid and electrolyte status partially reflects maternal hydration status and drug administration. Excessive use of oxytocin, diuretics, or hyponatremic intravenous (IV) fluid can lead to maternal and fetal hyponatremia. Antenatal steroids may increase skin maturation, subsequently decreasing IWL and the risk of hyperkalemia.
2. **Fetal/perinatal.** The presence of oligohydramnios may be associated with congenital renal dysfunction, including renal agenesis, polycystic kidney disease, or posterior urethral valves. Severe *in utero* hypoxemia or birth asphyxia may lead to acute tubular necrosis.

B. Physical examination

1. **Change in body weight.** Acute changes in an infant's weight generally reflect a change in TBW. The compartment affected will depend on the gestational age and clinical course of the infant. For example, long-term use of paralytic agents and peritonitis may lead to increased interstitial fluid volume and increased body weight but decreased intravascular volume. Therefore, weight should be measured at least daily with consideration for twice a day weights in the extremely low gestational age newborn.
2. **Skin and mucosal manifestations.** Altered skin turgor, sunken anterior fontanelle, and dry mucous membranes are essential to note on the physical exam but are not sensitive indicators of fluid or electrolyte balance.

3. **Cardiovascular.** Tachycardia can result from hypovolemia or from ECF excess (e.g., heart failure). Capillary refill time can be delayed with reduced cardiac output or peripheral vasoconstriction. Hepatomegaly can occur with increased ECF volume. Blood pressure changes occur late in the sequence of responses to reduced cardiac output.

C. Laboratory studies

1. **Serum electrolytes and plasma osmolarity** reflect the composition and tonicity of the ECF. Frequent monitoring, up to every 6 hours, should be done in the extremely low birth weight (ELBW) infants during the first few days of life owing to high IWL.
2. **Fluid balance** with input and output measurements should be monitored. Normal urine output is 1 to 3 mL/kg/hour. However, ELBW infants typically pass through three phases, with an initial prediuretic or oliguric phase, followed by a diuresis, before transitioning to a postdiuretic phase. With ECF depletion (dehydration), urine output may fall to <1 mL/kg/hour. However, in neonates with immature renal function, urine output may not decrease despite ECF volume depletion.
3. **Urine electrolytes and specific gravity (SG)** can reflect renal capacity to concentrate or dilute urine and reabsorb or excrete Na. Increases in SG can occur when the infant is receiving decreased fluids, has decreased urine output, or is spilling glucose. Neither urine electrolytes nor SG is very helpful when infant is on diuretics.
4. **Fractional excretion of Na (FENa)** reflects the balance between glomerular filtration and tubular reabsorption of Na. However, the utility is limited in preterm infants given decreased tubular Na reabsorption, and FENa increases with decreasing gestational age.

$$\text{FENa} = (\text{urine Na} \times \text{plasma creatinine}) / (\text{plasma Na} \times \text{urine creatinine}) \times 100$$

   a. Level of <1% indicates prerenal factors reducing renal blood flow.
   b. Level of 2.5% occurs with acute kidney injury (AKI).
   c. Level of >2.5% is frequently seen in infants of <32 weeks' gestation.
5. **Blood urea nitrogen (BUN) and serum creatinine (Cr)** values provide indirect information about ECF volume and GFR. However, these values can be challenging to interpret because initial levels are affected by maternal levels and placental clearance. Preterm infants have elevated values at birth that tend to fall over the first few weeks of life, making baseline levels hard to assess in the setting of physiologic change. Despite these challenges, neonates are at risk for AKI and serum Cr should be assessed initially and trended during any event that may carry an additional risk for AKI, such as a hemodynamically significant patent ductus arteriosus (PDA), sepsis, or necrotizing enterocolitis (NEC).
6. **Arterial pH, carbon dioxide tension (partial pressure of carbon dioxide [PCO_2]), and Na bicarbonate** determinations can provide indirect evidence of intravascular volume depletion because poor tissue perfusion leads to high anion gap metabolic acidosis (lactic acidosis).

Table 23.2. Initial Fluid Therapy*

Birth Weight (kg)	Dextrose (g/100 mL)	Fluid Rate (mL/kg/day)		
		<24 hours	24–48 hours	>48 hours
<1	5–10	100–150†	120–150	140–190
1–1.5	10	80–100	100–120	120–160
>1.5	10	60–80	80–120	120–160

*Infants in humidified incubators. Infants under radiant warmers usually require higher initial fluid rates.

†Very low birth weight infants frequently require even higher initial rates of fluid administration and frequent reassessment of serum electrolytes, urine output, and body weight.

III. MANAGEMENT OF FLUIDS AND ELECTROLYTES.

The goal of early management is to allow physiologic ECF loss over the several days of life, while minimizing weight loss, all while maintaining normal tonicity and intravascular volume as reflected by blood pressure, heart rate, urine output, serum electrolyte levels, and pH. Subsequent fluid management should maintain water and electrolyte balance, including requirements for body growth.

A. The term infant. Body weight decreases by 3% to 5% over the first 5 to 6 days. Subsequently, fluids should be adjusted so that changes in body weight are consistent with caloric intake. Clinical status should be monitored for maldistribution of water (e.g., edema). Na supplementation is not usually required in the first 24 hours unless ECF expansion is necessary. Small for gestational age term infants may require early Na supplementation to maintain adequate ECF volume.

B. The premature infant. Anticipate weight loss over the initial several days. Table 23.2 summarizes initial fluid therapy. Then, adjust fluids to maintain stable weight until an anabolic state is achieved and growth occurs. Frequently assess response to fluid and electrolyte therapy during the first 2 days of life. **Physical examination, urine output, SG, and serum electrolyte determinations may be required initially as frequently as every 6 hours in infants <1,000 g** (see section VIII.A).

Water loss through skin and urine may exceed 200 mL/kg/day, which can represent up to **one-third of TBW**. IV Na supplementation is not required for the first 24 hours unless ECF volume loss exceeds 5% of body weight per day (see Chapter 13).

IV. APPROACH TO DISORDERS OF NA AND WATER BALANCE.

Abnormalities can be grouped into disorders of **tonicity** or **ECF volume**. The conceptual approach to disorders of tonicity (e.g., hyponatremia) depends on whether the

newborn exhibits normal ECF (euvolemia), ECF depletion (dehydration), or ECF excess (edema).

A. Isonatremic disorders

1. Dehydration

a. Predisposing factors frequently involve equivalent losses of Na and water (through thoracostomy, nasogastric, or ventriculostomy drainage) or third-space losses that accompany peritonitis, gastroschisis, or omphalocele. Renal Na and water losses in the VLBW infant can lead to hypovolemia despite normal body tonicity.

b. Diagnosis. Dehydration is usually manifested by weight loss, decreased urine output, and increased urine SG. However, infants of <32 weeks' gestation may not demonstrate oliguria in response to hypovolemia. Poor skin turgor, tachycardia, hypotension, metabolic acidosis, and increasing BUN may coexist. A low FENa (<1%) is usually only seen in infants of >32 weeks' gestational age (see section II.C.4).

c. Therapy. Administer Na and water to first correct deficits and then adjust to equal maintenance needs plus ongoing losses. Acute isonatremic dehydration may require IV infusion of 10 mL/kg of NS if acute weight loss is >10% of body weight with signs of poor cardiac output.

2. Edema

a. Predisposing factors include excessive isotonic fluid administration, heart failure, sepsis, and neuromuscular paralysis.

b. Diagnosis. Clinical signs include periorbital and extremity edema, increased weight, and hepatomegaly.

c. Therapy includes **Na restriction** (to decrease total-body Na) and water restriction (depending on electrolyte response).

B. Hyponatremic disorders (Table 23.3). Consider **factitious hyponatremia** due to hyperlipidemia or **hypoosmolar hyponatremia** due to osmotic agents. True hypoosmolar hyponatremia can then be evaluated.

1. Hyponatremia due to ECF volume depletion

a. Predisposing factors include diuretic use, osmotic diuresis (glycosuria), VLBW with renal water and Na wasting, adrenal or renal tubular salt-losing disorders, gastrointestinal losses (vomiting, diarrhea), and third-space losses of ECF (skin sloughing, early NEC).

b. Diagnosis. Decreased weight, poor skin turgor, tachycardia, rising BUN, and metabolic acidosis are frequently observed. If renal function is mature, the newborn may develop decreased urine output, increased urine SG, and a low FENa.

c. Therapy. If possible, reduce ongoing Na loss. Administer Na and water to replace deficits and then adjust to match maintenance needs plus ongoing losses.

2. Hyponatremia with normal ECF volume

a. Predisposing factors include excess fluid administration and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion. Factors that cause SIADH include pain, opiate administration, intraventricular hemorrhage (IVH), asphyxia, meningitis, pneumothorax, and positive pressure ventilation.

Table 23.3. Hyponatremic Disorders

Clinical Diagnosis	Etiology	Therapy
Factitious hyponatremia/ pseudohyponatremia	Hyperlipidemia	
Hypertonic hyponatremia/ hyperosmolar hyponatremia	Mannitol	
	Hyperglycemia	
ECF volume normal	Syndrome of inappropriate antidiuretic hormone (SIADH)	Restrict water intake.
	Pain	
	Opiates	
	Excess intravenous fluids	
ECF volume deficit	Diuretics	Increase Na intake.
	Late-onset hyponatremia of prematurity	
	Congenital adrenal hyperplasia	
	Severe glomerulotubular imbalance (immaturity)	
	Renal tubular acidosis	
	Gastrointestinal losses	
	Necrotizing enterocolitis (third-space loss)	
ECF volume excess	Heart failure	Restrict water intake.
	Neuromuscular blockade (e.g., pancuronium)	
	Sepsis	

ECF, extracellular fluid; Na, sodium.

b. Diagnosis of SIADH. Weight gain usually occurs without edema. Excessive fluid administration without SIADH results in low urine SG and high urine output. In contrast, SIADH leads to **decreased urine output** and **increased urine osmolarity**. Urinary Na excretion in infants with SIADH varies widely and reflects Na intake. The diagnosis of SIADH presumes no volume-related stimulus to antidiuretic hormone (ADH)

release, such as reduced cardiac output or abnormal renal, adrenal, or thyroid function.

c. Therapy. Water restriction is therapeutic unless (i) serum Na concentration is less than approximately 120 mEq/L or (ii) neurologic signs such as obtundation or seizure activity develop. In these instances, **hypertonic Na chloride (NaCl) (3%) (1 to 3 mL/kg initial dose)** should be used. Fluid restriction alone can be used once serum Na concentration is >120 mEq/L and neurologic signs abate.

3. **Hyponatremia due to ECF volume excess**

a. Predisposing factors include sepsis with decreased cardiac output, late NEC, heart failure, abnormal lymphatic drainage, and neuromuscular paralysis.

b. Diagnosis. Weight increase with edema is observed. Decreasing urine output, increasing BUN and urine SG, and a low FENa are often present in infants with mature renal function.

c. Therapy. Treat the underlying disorder and **restrict water** to alleviate hypotonicity. Na restriction and improving cardiac output may be beneficial.

C. Hypernatremic disorders

1. **Hypernatremia with normal or deficient ECF volume**

a. Predisposing factors include increased renal and IWL in VLBW infants. Skin sloughing can accelerate water loss. ADH deficiency secondary to IVH can occasionally exacerbate renal water loss.

b. Diagnosis. Weight loss, tachycardia and hypotension, metabolic acidosis, decreasing urine output, and increasing urine SG may occur. Urine may be dilute if the newborn exhibits central or nephrogenic diabetes insipidus.

c. Therapy. Increase **free water administration** to reduce serum Na no faster than 1 mEq/kg/hour. If signs of ECF depletion or excess develop, adjust Na intake. **Hypernatremia does not necessarily imply excess total-body Na**. For example, **in the VLBW infant, hypernatremia in the first 24 hours of life is almost always due to free water deficits** (see section VIII.A.1).

2. **Hypernatremia with ECF volume excess**

a. Predisposing factors include excessive isotonic or hypertonic fluid administration, especially in the face of reduced cardiac output.

b. Diagnosis. Weight gain associated with edema is observed. The infant may exhibit normal heart rate, blood pressure, and urine output and SG but an elevated FENa.

c. Therapy. Restrict Na administration.

V. OLIGURIA. Oliguria exists if urine flow is <1 mL/kg/hour. Although delayed micturition in a healthy infant is not of concern until 24 hours after birth, urine output in a critically ill infant should be assessed by 8 to 12 hours of life, using urethral catheterization if indicated. Diminished urine output may reflect abnormal prerenal, renal parenchymal, or postrenal factors (Table 23.4). Neonatal AKI is often multifactorial, with prerenal causes being the most common, including hypotension, hypovolemia, intravascular volume depletion,

Table 23.4. Etiologies of Oliguria

Prerenal	Renal Parenchymal	Postrenal
Decreased inotropy	Acute tubular necrosis	Posterior urethral valves
	Ischemia (hypoxia, hypovolemia)	
Decreased preload	Disseminated intravascular coagulation	Neuropathic bladder
	Renal artery or vein thrombosis	
Increased peripheral resistance	Nephrotoxin	Prune belly syndrome
	Congenital malformation	Uric acid nephropathy
	Polycystic disease	
	Agenesis	
	Dysplasia	

and sepsis. It is important to exclude other potentially treatable etiologies (see Chapter 28). In VLBW infants, oliguria may be normal in the first 24 hours of life (see section VIII.A.1).

A. History and physical examination. Screen the maternal and infant history for maternal diabetes (renal vein thrombosis), birth asphyxia (acute tubular necrosis), and oligohydramnios (Potter syndrome). Force of the infant's urinary stream (posterior urethral valves), rate and nature of fluid administration and urine output, and nephrotoxic drug use (aminoglycosides, indomethacin, furosemide) should be evaluated. **Physical examination** should determine blood pressure and ECF volume status; evidence of cardiac disease, abdominal masses, or ascites; and the presence of any congenital anomalies associated with renal abnormalities (e.g., Potter syndrome, epispadias).

B. Diagnosis

1. **Initial laboratory examination** should include urinalysis, BUN, Cr, and FENa determinations. These aid in diagnosis and provide baseline values for further management.
2. **Fluid challenge**, consisting of a total of 20 mL/kg of NS, is administered as two infusions at 10 mL/kg/hour if no suspicion of structural heart disease or heart failure exists. Decreased cardiac output not responsive to ECF expansion may require the institution of inotropic/chronotropic pressor agents. Some may consider low-dose dopamine to attempt to augment renal blood flow and urine output (see Chapter 40).

3. **If no response to fluid challenge occurs**, one may induce diuresis with **furosemide 1 to 2** mg/kg IV.
4. Patients who are unresponsive to increased cardiac output and diuresis should be evaluated with an **abdominal ultrasonography** to define renal, urethral, and bladder anatomy. Other forms of imaging such as a voiding cystourethrography, IV pelography, or angiography may be required (see Chapter 28).

C. **Management.** **Prerenal** oliguria should respond to increased cardiac output. **Postrenal** obstruction requires urologic consultation, with possible urinary diversion and surgical correction. If parenchymal **AKI** is suspected, minimize excessive ECF expansion and electrolyte abnormalities. If possible, eliminate reversible causes of declining GFR, such as nephrotoxic drug use.

1. **Monitor** daily weight, input and output, and BUN, Cr, and serum electrolytes.
2. **Fluid restriction.** Replace insensible fluid loss plus urine output. **Withhold K supplementation** unless hypokalemia develops. Replace urinary Na losses unless edema develops.
3. **Adjust dosage and frequency of drugs** eliminated by renal excretion. Monitor serum drug concentrations to guide drug-dosing intervals.
4. **Peritoneal or hemodialysis** may be indicated in patients whose GFR progressively declines causing complications related to ECF volume or electrolyte abnormalities (see Chapter 28).

VI. METABOLIC ACID–BASE DISORDERS

A. **Normal acid–base physiology.** Normal sources of acid production include the metabolism of amino acids containing sulfur and phosphate as well as hydrogen ion released from bone mineralization. Intravascular buffers include bicarbonate, phosphate, and intracellular hemoglobin. Maintenance of normal pH depends on excretion of volatile acid (e.g., carbonic acid) from the lungs, skeletal exchange of cations for hydrogen, and renal regeneration and reclamation of bicarbonate. Kidneys contribute to maintenance of acid–base balance by reabsorbing the filtered load of bicarbonate, secreting hydrogen ions as titratable acidity (e.g., H_2PO_4), and excreting ammonium ions.

B. **Metabolic acidosis** (see Chapter 60). Metabolic acidosis results from excessive loss of buffer or from an increase of volatile or nonvolatile acid in the extracellular space.

1. **Anion gap.** Metabolic acidosis can result from accumulation of acid or loss of buffering equivalents. Anion gap determination will suggest mechanism. Na, Cl, and bicarbonate are the primary ions of the extracellular space and exist in approximately electroneutral balance. The **anion gap**, calculated as the difference between the Na concentration and sum of the Cl and bicarbonate concentrations, reflects the unaccounted-for anion composition of the ECF. An increased anion gap indicates an accumulation of organic acid, whereas a normal anion gap indicates a loss of buffer equivalents. Normal values for the neonatal anion gap are 5 to 15 mEq/L and vary directly with serum albumin concentration.

Table 23.5. Metabolic Acidosis

Increased Anion Gap (>15 mEq/L)	Normal Anion Gap (<15 mEq/L)
Acute renal failure	Renal bicarbonate loss
Inborn errors of metabolism	Renal tubular acidosis
Lactic acidosis	Acetazolamide
Late metabolic acidosis	Renal dysplasia
Toxins (e.g., benzyl alcohol)	Gastrointestinal bicarbonate loss
	Diarrhea
	Cholestyramine
	Small-bowel drainage
	Dilutional acidosis
	Hyperalimentation acidosis

2. **Metabolic acidosis associated with an increased anion gap (>15 mEq/L).** Disorders (Table 23.5) include renal failure, inborn errors of metabolism, lactic acidosis, late metabolic acidosis, and toxin exposure. Lactic acidosis results from diminished tissue perfusion and resultant anaerobic metabolism in infants with asphyxia or severe cardiorespiratory disease. Late metabolic acidosis typically occurs during the second or third week of life in premature infants who ingest high casein-containing formulas, where intake is in excess of renal clearance. Although no longer common now that infant formulas are not casein based, it still may occur, particularly with IV nutrition.
3. **Metabolic acidosis associated with a normal anion gap (<15 mEq/L)** results from bicarbonate loss through the gastrointestinal system or the kidneys (see Table 23.5). Premature infants <32 weeks' gestation frequently manifest a proximal or distal renal tubular acidosis (RTA). Urine pH persistently >7 in an infant with metabolic acidosis suggests a distal RTA, with an inability to secrete hydrogen ions. Proximal RTAs results from reduced bicarbonate reabsorption, although urinary pH for a proximal RTA may vary.
4. **Therapy.** Whenever possible, **treat the underlying cause**. Lactic acidosis due to low cardiac output or due to decreased peripheral oxygen delivery should be treated with specific measures. Treat normal anion gap metabolic acidosis by decreasing the rate of bicarbonate loss (e.g., decreased small-bowel drainage) or providing buffer equivalents. **IV Na bicarbonate or Na acetate** (which is compatible with calcium [Ca] salts) is more commonly used to treat severe acidosis. Oral buffer supplements can include citric acid (Bicitra) or Na citrate

(1 to 3 mEq/kg/day). Estimate bicarbonate deficit from the following formula:

$$\text{Deficit} = 0.4 \times \text{body weight} \times (\text{desired bicarbonate} - \text{actual bicarbonate})$$

The premature infant's acid–base status can change rapidly, and frequent monitoring is warranted. The infant's ability to tolerate an increased Na load and to metabolize acetate is an important variable that influences acid–base status during treatment.

C. Metabolic alkalosis. Metabolic alkalosis is characterized by an elevation in serum bicarbonate. Major causes of metabolic alkalosis can be categorized as hydrogen loss through the gastrointestinal tract (e.g., emesis, gastric suctioning, congenital chloride diarrhea), renal hydrogen loss (loop or thiazide diuretics, primary mineralocorticoid excess, Bartter/Gitelman syndrome, chronic hypercarbia), severe hypokalemia resulting in intracellular hydrogen shift, alkali administration in the setting of impaired renal function, and contraction alkalosis. The etiology of metabolic alkalosis can be clarified by determining urinary Cl concentration. Alkalosis accompanied by ECF depletion is associated with decreased urinary Cl, whereas states of mineralocorticoid excess are usually associated with increased urinary Cl (Table 23.6). Treat the underlying disorder.

VII. DISORDERS OF K BALANCE.

K is the fundamental intracellular cation. Serum K concentrations do not necessarily reflect total-body K because extracellular and intracellular K distribution also depends on the pH of body compartments. **An increase of 0.1 pH unit in serum results in approximately 0.6 mEq/L fall in serum K concentration due to an intracellular shift of K ions**. Total-body K is regulated by balancing K

Table 23.6. Metabolic Alkalosis

Low Urinary Cl (<10 mEq/L)	High Urinary Cl (>20 mEq/L)
Diuretic therapy (late)	Bartter syndrome with mineralocorticoid excess
Acute correction of chronically compensated respiratory acidosis	Alkali administration
Nasogastric suction	Massive blood product transfusion
Vomiting	Diuretic therapy (early)
Secretory diarrhea	Hypokalemia

Cl, chloride.

intake (normally 1 to 2 mEq/kg/day) and excretion through urine and the gastrointestinal tract.

A. Hypokalemia is usually asymptomatic; however, it can lead to arrhythmias, ileus, renal concentrating defects, and lethargy in the newborn.

1. **Predisposing factors** include nasogastric or ileostomy drainage, chronic diuretic use, and renal tubular defects.
2. **Diagnosis.** Obtain serum electrolytes, BUN, Cr, as well as urine electrolytes, pH, and an electrocardiogram (ECG) to detect possible conduction defects (prolonged QT interval and U waves).
3. **Therapy.** Reduce renal or gastrointestinal losses of K. Gradually increase intake of K as needed.

B. Hyperkalemia. The normal serum K level in a nonhemolyzed blood specimen at normal pH is 3.5 to 5.5 mEq/L; symptomatic hyperkalemia may begin at a serum K level >6 mEq/L.

1. **Predisposing factors.** Hyperkalemia can occur unexpectedly in any patient but should be **anticipated** and **screened** for in the following scenarios:
   a. Increased K release secondary to tissue destruction, trauma, cephalhematoma, hypothermia, bleeding, intravascular or extravascular hemolysis, asphyxia/ischemia, and IVH
   b. Decreased K clearance due to renal failure, oliguria, hyponatremia, and congenital adrenal hyperplasia
   c. Miscellaneous associations including dehydration, birth weight <1,500 g (see section VIII.A.2), blood transfusion, inadvertent excess (KCl) administration, CLD with KCl supplementation (see section VIII.B), and exchange transfusion.
2. **Diagnosis.** Up to 50% of VLBW infants born before 25 weeks' gestation manifest serum K levels >6 mEq/L in the first 48 hours of life (see section VIII.A.2). However, with sudden unexpected hyperkalemia in the neonatal intensive care unit (NICU), medication error must be considered. Obtain serum and urine electrolytes, serum pH, and Ca concentrations. The hyperkalemic infant may be asymptomatic or may present with a spectrum of signs including bradyarrhythmias or tachyarrhythmias, cardiovascular instability, or collapse. The ECG findings progress with increasing serum K from peaked T waves (increased rate of repolarization), flattened P waves and increasing PR interval (suppression of atrial conductivity), to QRS widening and slurring (conduction delay in ventricular conduction tissue as well as in the myocardium itself), and finally, supraventricular/ventricular tachycardia, bradycardia, or ventricular fibrillation. The ECG findings may be the first indication of hyperkalemia (see Chapter 41).
3. **Management. Once hyperkalemia is diagnosed, remove all sources of exogenous K (change all IV solutions and analyze for K content), rehydrate the patient if necessary, and eliminate arrhythmia-promoting factors.** Although limited studies are available addressing the pharmacology and treatment of neonatal hyperkalemia, the approach consists of three components:
   a. Goal 1: stabilization of cardiac membrane. This can be accomplished by Ca administration. **Ca gluconate (10%) given carefully at a**

starting dose of 60 to 100 mg/kg/dose may be the most useful in the NICU. Dosing may be repeated as needed. Treatment with hypertonic NaCl solution has also been reported in patients who are both hyperkalemic and hyponatremic but is not done routinely. Use of antiarrhythmic agents may be considered for refractory ventricular tachycardia (see Chapter 41).

b. Goal 2: dilution and intracellular shifting of K

i. Increased serum K in the setting of dehydration should respond to fluid resuscitation.

ii. **Insulin** enhances intracellular K uptake by direct stimulation of the membrane-bound Na–K ATPase. Neonates are sensitive to the effects of insulin requiring concomitant glucose administration to maintain normal blood glucose concentration and frequent monitoring of serum or blood glucose levels. This therapy may begin with a bolus of insulin and glucose or may start with an insulin and glucose infusion. **A continuous IV infusion of insulin should be started within the range of 0.01 to 0.1 units/kg/hour. The usual ratio is 1 unit of insulin for every 2 to 4 g of dextrose for a continuous infusion. If considering an initial bolus of insulin, typical dosing is 0.05 units/kg of human regular insulin in combination with dextrose bolus. The usual ratio is 1 unit of insulin for every 5 g of dextrose for intermittent IV doses of insulin.** To minimize the effect of binding to IV tubing, insulin diluted in dextrose 10% in water ($D_{10}W$) may be flushed through the tubing. Adjustments in infusion rate of either glucose or insulin in response to hyperglycemia or hypoglycemia may be simplified if the two solutions are prepared individually (see Chapter 24).

iii. **β2-Adrenergic stimulation** works by driving the K intracellularly by stimulating the Na–K ATPase. Although a paucity of neonatal/preterm data exists, β stimulation can be an effective and readily available therapy in the treatment of acute hyperkalemia, which appears to be well tolerated.

iv. Acidosis may increase serum K by shifting the balance of the intracellular K-for-hydrogen-ion exchange, leading to K movement extracellularly and worsening hyperkalemia. In theory, when acidosis is corrected, the opposite will occur, shifting K back intracellularly. If acidosis is present, **Na bicarbonate 1 to 2 mEq/kg IV** may be used, although the resultant pH change may not be sufficient to markedly shift K ions. Theoretically, every 0.1 pH unit increase leads to a decrease of 0.6 mEq/L in serum K. However, little evidence exits to support efficacy in neonates, with known risks of Na bicarbonate administration, including the risk of IVH in premature neonates.

c. Goal 3: enhanced K excretion. As the therapies earlier are transient, steps should be taken to remove K as the infant is being stabilized.

i. Diuretic therapy (e.g., **furosemide 1 mg/kg IV**) may increase K excretion by increasing flow and Na delivery to the distal tubules. This is a potentially effective way to eliminate K from the body.

ii. Double volume **exchange transfusion** is another potentially lifesaving option (see Chapter 26) that has been reported in the past. However, it comes with its own risks, requires expertise, and takes time to prepare.

iii. Cation exchange resins such as sodium polystyrene sulfonate (Kayexalate) provide another mechanism through which K may be excreted. It works by enhancing K excretion through the gut through the exchange of Na for K ions. These resins can be administered orally or rectally. However, they have been studied primarily in adults, and raise a number of safety concerns in the neonatal population. Overall, the efficacy in the neonate is questionable, and despite animal studies showing improved safety in updated suspensions (sorbitol-free), there continues to be an increased risk for NEC as well as possible bowel obstruction due to plug formation. Therefore, any use of Kayexalate in preterm infants must be done with extreme caution. **Oral/PG administration of Kayexalate is not recommended in preterm infants because they are prone to hypomotility and are at risk for NEC. Should the use of Kayexalate be deemed necessary, then rectal administration of Kayexalate (1 g/kg/dose) with a retention time of 15 to 30 minutes is recommended.** This may be effective in lowering serum K levels by approximately 1 mEq/L. Of note, due to its delayed onset of action, it should not be used in a situation that requires emergent intervention.

The clinical condition, ECG, and actual serum K level all affect the choice of therapy for hyperkalemia. Figure 23.2 contains guidelines for treatment of hyperkalemia.

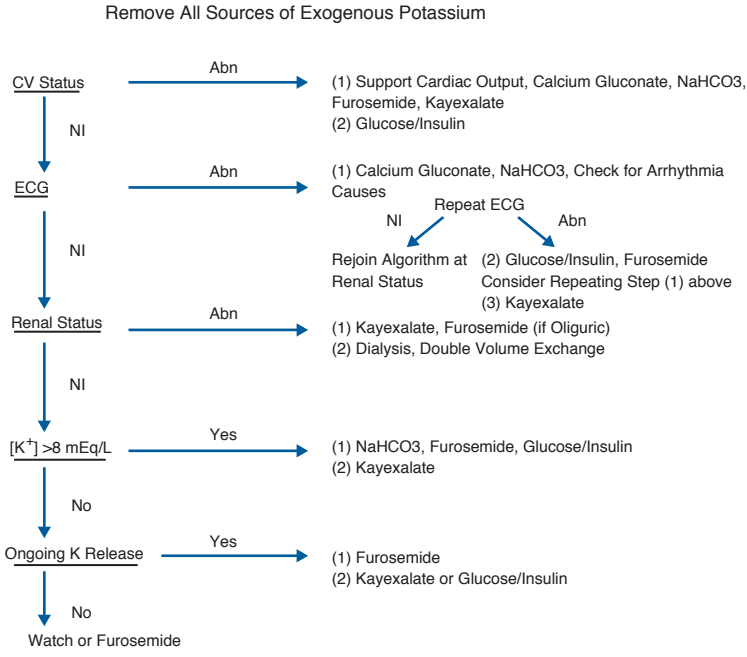
VIII. COMMON CLINICAL SITUATIONS

A. VLBW infant

1. **VLBW infants undergo three phases of fluid and electrolyte homeostasis:** prediuretic (first day of life), diuretic (second to third day of life), and postdiuretic (fourth to fifth day of life). Marked diuresis can occur during the diuretic phase leading to **hypernatremia** and the need for frequent serum electrolyte determinations (q6–8h) and increased rates of parenteral fluid administration. Increased free water loss through skin and dopamine-associated natriuresis (due to increased GFR) can further complicate management. Hypernatremia often occurs despite a total-body Na deficit. Lack of a brisk diuretic phase has been associated with increased CLD incidence.

   In addition, **impaired glucose tolerance** can lead to hyperglycemia, requiring reduced rates of parenteral glucose infusion (see Chapter 24). This combination frequently leads to administration of reduced dextrose concentrations in parenteral solutions. Avoid the infusion of parenteral solutions containing <200 mOsmol/L (i.e., D_3W), to minimize local osmotic hemolysis and thereby reduce renal K load.

2. **VLBW infants often develop a nonoliguric hyperkalemia** in the first few days of life. This is caused by a relatively low GFR combined with



In General, if [K^+] Acceptable for 6 h Cease Therapy but Continue Monitoring

Drug Doses:			
	Calcium Gluconate	1–2 mL/kg IV	
	NaHCO3	1–2 mEq/kg IV	
	Furosemide	1 mg/kg IV	
	Glucose/Insulin	Bolus:	D10W 2 mL/kg Humulin 0.05 U/kg
		Infusion:	D10W 2–4 mL/kg/h Humulin, 10 U/100 mL D10W or 5% albumin, 1 mL/kg/h
	Kayexalate	1 g/kg PR, Used Cautiously in the Setting of an Immature Ischemic GI Tract	

Figure 23.2. Treatment of hyperkalemia. CV, cardiovascular; Nl, normal; Abn, abnormal; $NaHCO_3$, sodium bicarbonate; ECG, electrocardiogram; IV, intravenous; $D_{10}W$, dextrose in 10% water; GI, gastrointestinal. For a given algorithm outcome, proceed by administering the entire set of treatments labeled (1). If unsuccessful in lowering [K^+] or improving clinical condition, proceed to the next set of treatments, for example, (2) and then (3).

an intracellular to extracellular K shift due to decreased Na–K ATPase activity. Postnatal glucocorticoid use may further inhibit Na–K ATPase activity. Insulin infusion to treat hyperkalemia may be necessary but elevates the risk of iatrogenic hypoglycemia (see section VII.B for additional treatment details).

3. **Late-onset hyponatremia of prematurity** is defined as hyponatremia that occurs after the second week of life in the growing premature infant in the setting of a negative Na balance. Failure of the immature renal

tubules to reabsorb filtered Na in a rapidly growing infant contributes to this condition as well as low Na intake due to the low Na content in breast milk. Diuretic therapy for babies with CLD may compound these losses. Late-onset hyponatremia has been reported in up to half of all preterm infants who are predominately human milk fed by 3 to 4 weeks of life. Periodic electrolyte measurements should be obtained, starting 2 weeks after achieving full volume enteral feeds. If affected, treatment with simple Na supplementation (start with 2 mEq/kg/day).

B. Severe CLD (see Chapter 34). CLD requiring **diuretic** therapy often leads to **hypokalemic, hypochloremic metabolic alkalosis**. Affected infants frequently have a chronic respiratory acidosis with partial metabolic compensation. Subsequently, vigorous diuresis can lead to total-body K and ECF volume depletion, causing a superimposed metabolic alkalosis. If the alkalosis is severe, alkalemia (pH >7.45) can supervene and result in central hypoventilation. If possible, gradually reduce urinary Na and K loss by reducing the diuretic dose and/or increase K intake by administration of KCl (starting at 1 mEq/kg/day). Rarely, administration of ammonium Cl (0.5 mEq/kg) is required to treat the metabolic alkalosis. Long-term use of loop diuretics such as furosemide promotes excessive urinary Ca losses and nephrocalcinosis. Urinary Ca losses may be reduced through concomitant thiazide diuretic therapy (see Chapter 34).

Suggested Readings

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24 Hypoglycemia and Hyperglycemia

Alejandra Barrero-Castillero and Rebecca Simmons

KEY POINTS

- Neonatal hypoglycemia is common in the newborn period but remains controversial due to the difficulty in defining hypoglycemia and the clinical thresholds for treatment.
- The American Academy of Pediatrics (AAP) recommends screening asymptomatic at-risk infants (preterm, small for gestational age [SGA], large for gestational age [LGA], and infants of diabetic mothers [IDMs]) and treating hypoglycemia once it is recognized.
- The Pediatric Endocrine Society (PES) states that by 48 to 72 hours of life, *plasma* glucose levels should be similar to that of older children and adults (70 to 100 mg/dL).
- *Plasma* glucose is the gold standard, and whole blood glucoses (often measured at bedside) may be approximately 15% lower than plasma levels.
- Hyperglycemia is very rarely seen in the newborn nursery but frequently occurs in very low birth weight (VLBW) infants in the neonatal intensive care unit (NICU).

Hypoglycemia is one of the most common metabolic problems seen in both the newborn nursery and neonatal intensive care unit (NICU). Confirming a diagnosis of clinically significant hypoglycemia requires interpretation of blood glucose values within the clinical context. The definition of hypoglycemia as well as its clinical significance and management remain controversial. Blood glucose levels in the first hours of life are typically lower than normal values of older children or adults. In healthy infants, blood glucose levels can often be maintained in the appropriate range by initiating feeding soon after birth. Most cases of neonatal hypoglycemia are transient, respond readily to treatment, and are associated with an excellent prognosis. Persistent hypoglycemia is more likely to be associated with abnormal endocrine conditions most commonly due to hyperinsulinemia, less frequently resulting from genetic or congenital defects in the metabolism of glucose, glycogen, and fatty acids. Possible neurologic sequelae associated to hypoglycemia is concerning; however, long-term follow-up studies assessing neurodevelopmental outcomes are conflicting and is not possible to validly quantify the effects of neonatal hypoglycemia on subsequent neurodevelopment.

Hyperglycemia is very rarely seen in the newborn nursery but frequently occurs in very low birth weight (VLBW) infants in the NICU.

I. HYPOGLYCEMIA. Glucose provides approximately 60% to 70% of fetal energy needs. Almost all fetal glucose derives from the maternal circulation by the process of transplacental-facilitated diffusion that maintains fetal glucose levels at approximately two-thirds of maternal levels. The severing of the umbilical cord at birth abruptly interrupts the source of glucose. Subsequently, the newborn must rapidly respond by glycogenolysis of hepatic stores, inducing gluconeogenesis, and using exogenous nutrients from feeding to maintain adequate glucose levels. During this normal transition and adaptation to postnatal life, newborn glucose levels fall to a low point in the first 1 to 2 hours of life (to as low as 30 mg/dL) and then increase to >45 mg/dL, stabilizing at mean levels of 65 to 70 mg/dL by 3 to 4 hours of age. Glucose concentrations in the first 48 hours of life are expected to be lower that later in life.

A. Incidence. The incidence of hypoglycemia varies by population and definition used. Furthermore, blood glucose levels change markedly within the first hours of life, and it is necessary to know the infant's exact age to interpret the glucose level and diagnose hypoglycemia. However, a prospective New Zealand study of infants at risk for hypoglycemia (defined as a blood glucose <2.6 mOsm [<46.8 mg/dL]) demonstrated that 47% of large for gestational age (LGA) infants, 52% of small for gestational age (SGA) infants, 48% of infants of diabetic mothers (IDMs), and 54% of late-preterm infants were found to be hypoglycemic.

B. Definition. In 2011, the American Academy of Pediatrics (AAP) published a clinical report by the Committee on Fetus and Newborn focused on postnatal glucose homeostasis in late-preterm and term infants. The report provides a practical guideline for screening and management of neonatal hypoglycemia in the first 24 hours of life. In the absence of consensus in the literature of exact definitions of hypoglycemia (glucose values or duration), the report guides clinicians to develop hypoglycemia screening protocols to avoid prolonged hypoglycemia in symptomatic infants and asymptomatic at-risk newborns. The Pediatric Endocrine Society (PES) also released hypoglycemia guidelines in 2015, which specify that glucose levels after 48 hours of life in newborns should be comparable to adult levels (70 to 100 mg/dL) and at-risk infants should be evaluated for hypoglycemia with higher thresholds (<60 mg/dL) specifically of ***plasma*** glucose, which is approximately 15% higher than whole blood glucose. The thresholds for treating hypoglycemia depend on the presence of symptoms, the age of the infant in hours, and the persistence of hypoglycemia.

In the AAP report, the authors recommend measuring **blood glucose levels** and treatment for the following:

1. **Symptomatic** infants with blood glucose <40 mg/dL with intravenous (IV) glucose (For symptoms, see section I.D.1.)
2. **Asymptomatic** infants at risk for hypoglycemia defined as late preterm (34 to 36 6/7 weeks of gestation), term SGA, IDM, or LGA
   a. **First 4 hours of life**
      i. Initial screen <25 mg/dL (should be done within first hours after birth), infant should be fed and rechecked, and if the next level, 1 hour later, is <25 mg/dL, treatment with IV glucose should be administered.
      ii. If the second check is 25 to 40 mg/dL, feeding may be considered as an alternative to IV glucose.

b. Four to 24 hours of life

i. Glucose <35 mg/dL, infants should be fed and glucose rechecked in 1 hour.

ii. If glucose continues to be <35 mg/dL, IV glucose should be administered.

iii. If recheck after initial feeding is 35 to 45 mg/dL, feeding may be attempted.

iv. Recommendation is to target glucose >45 mg/dL.

c. According to the PES, by **48 to 72 hours** of life, glucose control should be similar to that of older children and adults. ***Plasma*** glucose levels should be 70 to 100 mg/dL. Bedside reagent strips will be within ±10 to 15 mg/dL and less accurate in the hypoglycemic range. Furthermore, typically bedside whole blood glucose measurements are ~15% lower than plasma levels.

C. Etiology

1. **Hyperinsulinemic** hypoglycemia causes persistent, recurrent hypoglycemia in newborns, and it may be associated with an increased risk of brain injury because it not only decreases serum glucose levels but also prevents the brain from using secondary fuel sources by suppressing fatty acid release and ketone body synthesis. Some cases of hyperinsulinemic hypoglycemia are transient and resolve over the course of several days, whereas others require more aggressive and prolonged treatment.

a. The most common example of hyperinsulinism is the **IDM** (see Chapter 62). Additionally, LGA infants are at risk for hyperinsulinism. Although women are screened for gestational diabetes during pregnancy, some women either have mild glucose intolerance that is subthreshold for diagnosis or develop late-onset glucose intolerance, and their infants are sometimes LGA and hypoglycemic.

b. Congenital genetic. Hyperinsulinism is seen in mutations of genes encoding the pancreatic beta cell adenosine triphosphate (ATP)-sensitive potassium channel, such as ABCC8 and KCNJ11, which encode for SUR1 and Kir6.2. Elevated insulin levels are also associated with loss of function mutations in HNF4A gene. Additional mutations continue to be identified.

c. Secondary to other conditions

i. Birth asphyxia

ii. Syndromes such as Beckwith-Wiedemann syndrome (macrosomia, mild microcephaly, omphalocele, macroglossia, hypoglycemia, and visceromegaly)

iii. Congenital disorders of glycosylation and other metabolic conditions

iv. Erythroblastosis (hyperplastic islets of Langerhans) (see Chapter 26)

v. Maternal tocolytic therapy with beta-sympathomimetic agents (terbutaline)

vi. Malpositioned umbilical artery catheter used to infuse glucose in high concentration into the celiac and superior mesenteric arteries T11–T12, stimulating insulin release from the pancreas

vii. Abrupt cessation of high glucose infusion

viii. After exchange transfusion with blood containing high glucose concentration

ix. Insulin-producing tumors (nesidioblastosis, islet cell adenoma, or islet cell dysmaturity)

2. **Decreased production/stores**
   - **a. Prematurity** (Among 193 late-preterm infants in a prospective New Zealand study, 54% were hypoglycemic.)
   - **b.** Intrauterine growth restriction (**IUGR**) or **SGA**. Among 152 SGA infants in New Zealand study, 52% were hypoglycemic.
   - **c.** Inadequate caloric intake
   - **d.** Delayed onset of feeding

3. **Increased utilization and/or decreased production.** Any infant with one of the following conditions should be evaluated for hypoglycemia; parenteral glucose may be necessary for the management of these infants.
   - **a. Perinatal stress**
     - **i.** Sepsis
     - **ii.** Shock
     - **iii.** Asphyxia
     - **iv.** Hypothermia (increased utilization)
     - **v.** Respiratory distress
     - **vi.** Postresuscitation
   - **b.** After exchange transfusion with heparinized blood that has a low glucose level in the absence of a glucose infusion; reactive hypoglycemia after exchange with relatively hyperglycemic citrate-phosphate-dextrose (CPD) blood
   - **c.** Defects in carbohydrate metabolism (see Chapter 60)
     - **i.** Glycogen storage disease
     - **ii.** Fructose intolerance
     - **iii.** Galactosemia
   - **d.** Endocrine deficiency
     - **i.** Adrenal insufficiency
     - **ii.** Hypothalamic deficiency
     - **iii.** Congenital hypopituitarism
     - **iv.** Glucagon deficiency
     - **v.** Epinephrine deficiency
   - **e.** Defects in amino acid metabolism (see Chapter 60)
     - **i.** Maple syrup urine disease
     - **ii.** Propionic acidemia
     - **iii.** Methylmalonic acidemia
     - **iv.** Tyrosinemia
     - **v.** Glutaric acidemia type II
     - **vi.** Ethylmalonic adipic aciduria
   - **f. Polycythemia.** Hypoglycemia may be due to higher glucose utilization by the increased mass of red blood cells. Additionally, decreased amount of serum per drop of blood may cause a reading consistent with hypoglycemia on whole blood measurements but may yield a normal glucose level on laboratory analysis of serum (see Chapter 46).
   - **g.** Maternal or infant therapy with **β-blockers** (e.g., labetalol or propranolol). Possible mechanisms include the following:
     - **i.** Prevention of sympathetic stimulation of glycogenolysis
     - **ii.** Prevention of recovery from insulin-induced decreases in free fatty acids and glycerol
     - **iii.** Inhibition of epinephrine-induced increases in free fatty acids and lactate after exercise

D. Diagnosis

1. **Symptoms** that have been attributed to hypoglycemia are nonspecific.
   - **a.** Irritability
   - **b.** Tremors
   - **c.** Jitteriness
   - **d.** Exaggerated Moro reflex
   - **e.** High-pitched cry
   - **f.** Seizures
   - **g.** Lethargy
   - **h.** Hypotonia
   - **i.** Cyanosis
   - **j.** Apnea
   - **k.** Poor feeding
   - **l.** Many infants have no symptoms.
2. **Screening.** Serial blood glucose levels should be routinely measured in infants who have risk factors for hypoglycemia and in infants who have symptoms that could be due to hypoglycemia (see section I.B).
3. **Reagent strips with reflectance meter.** Although in widespread use as a bedside point-of-care screening tool, reagent strips are of unproven reliability in documenting hypoglycemia in neonates.
   - **a.** Reagent strips measure whole blood glucose, which is 15% lower than plasma levels.
   - **b.** Reagent strips are subject to false-positive and false-negative results as a screen for hypoglycemia, even when used with a reflectance meter.
   - **c.** Results may be affected by other intrinsic factors like polycythemia or extrinsic factors such as poor sampling techniques.
   - **d.** A valid confirmatory laboratory glucose determination is required before one can diagnose hypoglycemia; however, if the sample awaits analysis in the laboratory, the glucose level can be falsely low (see section I.D.4.a).
   - **e.** If a reagent strip reveals a concentration <45 mg/dL, treatment should not be delayed while one is awaiting confirmation of hypoglycemia by laboratory analysis. If an infant has either symptom that could be due to hypoglycemia and/or a low glucose level as measured by a reagent strip, treatment should be initiated immediately after the confirmatory blood sample is obtained.
4. **Laboratory diagnosis**
   - **a.** The laboratory sample of plasma must be obtained and analyzed promptly to avoid the measurement being falsely lowered by glycolysis. The glucose level can fall up to 6 mg/dL per hour in a blood sample that awaits analysis.
5. **Subcutaneous continuous glucose monitoring (CGM)** has been shown to be accurate but has not been approved for use in newborns and has primarily been used in research settings.
6. **Additional evaluation** for persistent hypoglycemia. Most hypoglycemia will resolve in 2 to 3 days. A glucose infusion rate (GIR) of more than 8 to 10 mg of glucose per kilogram per minute suggests increased utilization due to hyperinsulinism. This condition is usually transient, but if

it persists, endocrine evaluation may be necessary to specifically evaluate for hyperinsulinism or other rare causes of hypoglycemia as listed in section I.D.1. Many evaluations are not productive because they are done too early in the course of a transient hypoglycemic state or the samples to determine hormone levels are drawn when the glucose level is normal.

a. Critical lab sample. Diagnosing hyperinsulinemia requires measuring an insulin level that is inappropriately high for a simultaneous serum glucose. Evaluation requires drawing blood for insulin, cortisol, and amino acids at a time when the glucose level is <40 mg/dL. The typical critical lab sample includes the following:

- **i.** Glucose
- **ii.** Insulin
- **iii.** Cortisol. Cortisol levels can be used to screen for the integrity of the hypothalamic-pituitary-adrenal axis.
- **iv.** β-Hydroxybutyrate and free fatty acid levels. Measurement of plasma β-hydroxybutyrate and free fatty acid levels can be useful because decreased levels of these substances can indicate excessive insulin action even if insulin levels are not significantly elevated.

b. If the insulin level is normal for the blood glucose level, consider additional testing as indicated below to evaluate for other causes of persistent hypoglycemia such as defects in carbohydrate metabolism (see section I.C.3.c), endocrine deficiency (see section I.C.3.d), and defects in amino acid metabolism (see section I.C.3.e).

- **i.** Growth hormone
- **ii.** Adrenocorticotropic hormone (ACTH)
- **iii.** Thyroxine (T4) and thyroid-stimulating hormone (TSH)
- **iv.** Glucagon
- **v.** Plasma amino acids
- **vi.** Urine ketones
- **vii.** Urine-reducing substance
- **viii.** Urine amino acids
- **ix.** Urine organic acids
- **x.** Genetic testing for various mutations such as SUR1 and KiR6.2.

7. **Differential diagnosis.** The symptoms mentioned in section I.D.1 can be due to many other causes with or without associated hypoglycemia. If symptoms persist after the glucose concentration is in the normal range, other etiologies should be considered. Some of these are as follows:
   - **a.** Sepsis
   - **b.** Central nervous system (CNS) disease
   - **c.** Toxic exposure
   - **d.** Metabolic abnormalities
     - **i.** Hypocalcemia
     - **ii.** Hyponatremia or hypernatremia
     - **iii.** Hypomagnesemia
     - **iv.** Pyridoxine deficiency
   - **e.** Adrenal insufficiency
   - **f.** Heart failure
   - **g.** Renal failure
   - **h.** Liver failure

E. Management. Anticipation and prevention, when possible, are key to the management of infants at risk for hypoglycemia (see section I.B.2).

1. **Feeding.** Some asymptomatic infants with early glucose levels in the 30s (mg/dL) will respond to feeding (breast milk or formula). Infants at risk should start feeding within 1 hour of life. A follow-up blood glucose should be measured 1 hour after the start of the feeding. If the glucose level does not rise, IV glucose infusions are required. Feeding of glucose water is not recommended. The early introduction of milk feeding is preferable and will often result in raising glucose levels to normal, maintaining normal stable levels, and avoiding problems with rebound hypoglycemia. For persistent hypoglycemia, feeding strategies that may assist with management include decreasing the interval between feedings and/or adding calories or carbohydrate supplements (e.g., SolCarb for term infants only) to feedings. These strategies may sometimes be useful in infants who feed well but have marginal glucose levels when weaning off IV fluids. These recommendations are from clinical experience and have not been formally studied. Returning to a typical feeding interval and weaning off of additional calories before discharge is preferred, particularly in LGA infants.

2. **Breastfeeding.** Breastfed infants have lower glucose levels but higher ketone body levels than those who are formula fed. The use of alternate fuels may be an adaptive mechanism during the first days of life as the maternal milk supply and the infant's feeding ability both increase. Early breastfeeding enhances gluconeogenesis and increases the production of gluconeogenic precursors. Some infants will have difficulty in adapting to breastfeeding, and symptomatic hypoglycemia has been reported to develop in breastfed infants after hospital discharge. Late-preterm infants will sometimes have a delay in achieving adequate oral feeding volumes and should have glucose levels measured. It is important to document that breastfed infants are latching on and appear to be sucking milk, but there is no need to routinely monitor glucose levels in healthy full-term breastfed infants who do not have additional risk factors and are asymptomatic. Although data are emerging about the potential benefits of hand expression of colostrum for IDM for storage prior to delivery, this practice remains controversial and not yet standard of care.

3. **Dextrose gel.** Since 2013 after the Sugar Babies randomized placebo-controlled trial, many units have incorporated to their practice the use of 40% dextrose gel (0.5 mL/kg) administration to treat mild hypoglycemia in infants at risk for hypoglycemia, which has shown to decrease NICU admissions for hypoglycemia minimizing separation of mother and infant, lower formula use, and lower formula feeding rates at 2 weeks of life. Additionally, is noninvasive, safe, and well tolerated at a low cost.
   a. Dose is 40% dextrose gel 0.5 mL/kg (200 mg/kg) massaged into buccal mucosa and encourage infant to feed (breastfeeding or formula).
   b. Monitor glucose level after 30 minutes of gel administration and feed.
   c. If glucose below threshold may give an additional dextrose gel administration. There is unit variation in the number of dextrose gel administrations accepted before NICU admission for IV therapy.

4. IV therapy

a. Indications

i. Inability to tolerate oral feeding

ii. Persistent symptoms of hypoglycemia after feeding

iii. Oral feedings do not maintain normal glucose levels.

iv. Severe hypoglycemia (see section I.B.2)

b. Urgent treatment

i. Two-hundred milligrams per kilogram of glucose over 1 minute; to be followed by continuing therapy below. This initial treatment is equivalent to 2 mL/kg of dextrose 10% in water ($D_{10}W$) infused intravenously.

c. Continuing therapy

i. Infusion of glucose at a rate of 6 to 8 mg of glucose per kilogram per minute (Fig. 24.1)

ii. GIR may be calculated using the following formula:

$$\text{GIR in mg/kg/minute} = \frac{(\text{dextrose \% concentration} \times \text{mL/kg/day})}{144}$$

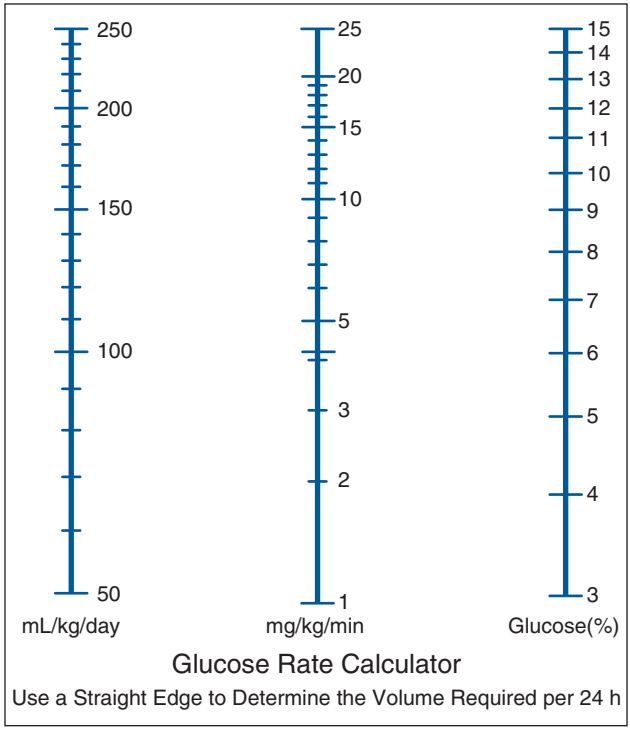

Figure 24.1. Interconversion of glucose infusion units. (Reprinted from Klaus MH, Faranoff AA, eds. *Care of the High-Risk Neonate*. 2nd ed. Philadelphia, PA: WB Saunders; 1979:430. Copyright © 1979 Elsevier. With permission.)

For example, in an infant receiving $D_{10}W$ at 80 mL/kg/day, the GIR would be $\frac{(10 \times 80)}{144} = 5.6$ mg/kg/minute.

Another way to calculate the GIR can be easily remembered (as it rhymes):

$$\frac{D \times \text{rate}}{6 \times \text{weight}}$$

This is equivalent to (dextrose % concentration × mL/hour on the pump) / (6 × weight [kg]).

For example, for a 4-kg infant receiving 13.3 mL/hour (80 mL/kg/day) of $D_{10}W$, the GIR would be

$$\frac{10 \times 13.33}{6 \times 4} = 5.6 \text{ mg/kg/minute}$$

Many hospitals now have computerized provider order entry systems that automatically calculate the GIR.
Additionally, Figure 24.1 helps visualize the GIR depending on total fluid goal and dextrose concentration.

iii. Recheck glucose level 20 to 30 minutes after IV bolus and then hourly until stable to determine if additional therapy is needed.

iv. Additional bolus infusions of 2 mL/kg of $D_{10}W$ may be needed.

v. If glucose is stable and in acceptable range, feedings may be continued and the glucose infusion tapered as permitted by glucose measurements prior to feeding.

vi. For most infants, IV $D_{10}W$ at daily maintenance rates will provide adequate glucose. The required concentration of dextrose in the IV fluids will depend on the daily water requirement. It is suggested that calculation of both glucose intake (i.e., milligrams of glucose per kilogram per minute) and water requirements be done each day or more frequently if glucose levels are unstable. For example, on the first day, the fluid requirement is generally about 80 mL/kg/day or 0.055 mL/kg/minute; therefore, $D_{10}W$ provides about 5.6 mg of glucose per kilogram per minute, and $D_{15}W$ at 80 mL/kg/day provides 8.25 mg of glucose per kilogram per minute.

vii. Some infants with hyperinsulinism and infants with IUGR will require 12 to 15 mg of dextrose per kilogram per minute (often as $D_{15}W$ or $D_{20}W$).

viii. The concentration of glucose and the rate of infusion are increased as necessary to maintain a normal blood glucose level. A central venous catheter may be necessary to give higher glucose concentrations ($D_{15}W$ to $D_{20}W$) in an acceptable fluid volume. After glucose levels have been stable in the normal range, it is appropriate to taper the GIR and concentration while monitoring glucose levels before feeding. IV fluids should be weaned slowly while feedings are advanced.

5. Historically, providers have administered **hydrocortisone**, 10 mg/kg/day intravenously in two divided doses, if it is difficult to maintain glucose

values in the normal range despite 12 to 15 mg of glucose per kilogram per minute. Hydrocortisone reduces peripheral glucose utilization, increases gluconeogenesis, and increases the effects of glucagon. The hydrocortisone will usually result in stable and adequate glucose levels, and it can then be rapidly tapered over the course of a few days. Before administering hydrocortisone, providers might consider drawing a cortisol level. We do not use hydrocortisone routinely for hypoglycemia.

6. **Diazoxide** (5 to 15 mg/kg/day in divided doses every 8 to 12 hours) may be given orally for infants who are persistently hyperinsulinemic under pediatric endocrinology guidance. This drug inhibits insulin release by acting as a specific ATP-sensitive potassium channel agonist in normal pancreatic beta cells and decreases insulin release. It can take up to 5 days for a positive effect to be seen. Side effects include fluid retention that may lead to respiratory decompensation and pulmonary hypertension. Coadministration with a diuretic such as hydrochlorothiazide is recommended as well as an assessment of the cardiopulmonary health (including baseline echocardiogram and electrocardiogram [ECG]) prior to initiating diazoxide. Remains the only drug U.S. Food and Drug Administration (FDA) approved for hyperinsulinemic hypoglycemia.
7. **Glucagon** (0.2 mg/kg intramuscularly, subcutaneously [SC], or intravenously, maximum 1.0 mg) is rarely used. It may be given to hypoglycemic infants with good glycogen stores, but it is only a temporizing measure to mobilize glucose for 2 to 3 hours in an emergency until IV glucose can be given. The glucose level will often fall after the effects of glucagon have worn off, and it remains important to obtain IV access to adequately treat these infants. For IDMs, the dose is 0.3 mg/kg (maximum dose is 1.0 mg) (see Chapter 62).
8. If medical treatment does not control the blood glucose level, 18F-fluoro-L-DOPA positron emission tomography (PET) scan should be considered to identify focal lesions in the pancreas and consider surgical treatment by subtotal **pancreatectomy**. Referral to a subspecialty center with experience in these procedures should be considered if a genetic defect of glucose control is suspected or confirmed.

F. Discharge readiness. Infants should be able to maintain plasma glucose above the threshold blood glucose goal after 48 hours of life even if a feeding is missed (>60 mg/dL or >70 mg/dL in high-risk infants with other risk factors [e.g., known hypoglycemic disorder]). To ensure infants maintain fasting glucose levels >60 mg/dL, PES recommends *prolonged fasting period* of minimum 6 to 8 hours that should be done close to discharge.

G. Long-term follow-up and evaluation. Infants with hypoglycemia have been reported to exhibit a typical pattern of CNS injury particularly in the parietooccipital cortex and subcortical white matter. However, it is often difficult clinically to separate isolated hypoglycemia from hypoxic-ischemic encephalopathy plus hypoglycemia. Some clinicians believe it is useful to obtain a magnetic resonance imaging **(MRI) scan** on infants with symptomatic hypoglycemia, but this is not yet standard of care. Close follow-up of neurodevelopmental status is warranted.

II. HYPERGLYCEMIA. Definition varies but generally defined as a whole blood glucose level >125 mg/dL or plasma glucose values >150 mg/dL or >180 mg/dL. The prevalence of hyperglycemia in preterm infants has been described between 43% and 80% in VLBW infants in studies using CGM in the first week after birth. This problem is not only commonly encountered in low gestational age and low birth weight preterm infants receiving parenteral glucose but is also seen in other term critically ill infants. Hyperglycemia has been associated with increased mortality and morbidity in the neonatal period, and there is limited data of the long-term effects. There are usually not any specific symptoms associated with neonatal hyperglycemia, but the major clinical problems associated with hyperglycemia are hyperosmolarity and osmotic diuresis. Osmolarity of more than 300 mOsm/L usually leads to osmotic diuresis (each 18 mg/dL rise in blood glucose concentration increases serum osmolarity 1 mOsm/L). Subsequent dehydration may occur rapidly in small preterm infants with large insensible fluid losses.

The hyperosmolar state, an increase of 25 to 40 mOsm or a glucose level of >400 mg/dL, can cause water to move from the intracellular compartment to the extracellular compartment. The resultant contraction of the intracellular volume of the brain may be a cause of cerebral edema, seizures, and intracranial hemorrhage.

A. Etiology

1. **Iatrogenic.** Exogenous parenteral glucose administration of more than 4 to 6 mg/kg/minute of glucose in preterm infants weighing <1,000 g may be associated with hyperglycemia.
2. **Drugs.** The most common association is with glucocorticoids. Other drugs associated with hyperglycemia are caffeine, theophylline, phenytoin, and diazoxide.
3. **Extremely low birth weight infants** (<1,000 g), possibly due to variable insulin response, to persistent endogenous hepatic glucose production despite significant elevations in plasma insulin, or to insulin resistance that may in part be due to immature glycogenolysis enzyme systems. Extremely low birth weight infants sometimes must be administered fluids in excess of 200 mL/kg/day, and a minimum glucose concentration of dextrose 5% must be used to avoid infusing a hypotonic solution. When this amount of fluid is administered, the infant is presented with a large glucose load. Modifications to the physical environment (i.e., humidified incubators; see Chapters 15 and 23) that decrease free water loss help limit the amount of IV fluid needed to treat these infants.
4. **Lipid infusion.** Free fatty acids are gluconeogenic and thus associated with higher glucose levels. Lipid emulsions are an important element to a balanced delivery of nutrition. Reduction or discontinuation of lipid infusions should only be considered after other potential drivers of hyperglycemia are addressed (i.e., adjustments to total dextrose infusion and GIR).
5. **Sepsis**, possibly due to depressed insulin release, cytokines, or endotoxin, resulting in decreased glucose utilization. Stress hormones such as cortisol and catecholamines are elevated in sepsis. In an infant who

has normal glucose levels and then becomes hyperglycemic without an excess glucose load, sepsis should be the prime consideration.

a. "Stressed" preterm infants requiring mechanical ventilation or other painful procedures, from persistent endogenous glucose production due to catecholamines and other "stress hormones." Insulin levels are usually appropriate for the glucose level.

6. **Hypoxia**, possibly due to increased glucose production in the absence of a change in peripheral utilization
7. **Surgical procedures.** Hyperglycemia in this setting is possibly due to the secretion of epinephrine, glucocorticoids, and glucagon as well as excess administration of glucose-containing IV fluids.
8. **Neonatal diabetes mellitus.** In this rare disorder (1 in 400,000 births), infants present with significant hyperglycemia and severe clinical symptoms including polyuria, dehydration, and ketoacidosis that require prompt treatment with insulin. It may be present as part of a syndrome or as an isolated finding in the first months of life, usually <6 months of life. They characteristically are SGA term infants, without gender predilection, and a third have a family history of diabetes mellitus. They present with marked glycosuria, hyperglycemia (240 to 2,300 mg/dL), polyuria, severe dehydration, acidosis, mild or absent ketonuria, reduced subcutaneous fat, and failure to thrive. Insulin values are either absolutely or relatively low for the corresponding blood glucose elevation. Approximately half of the infants have a transient need for insulin treatment and are at risk for recurrence of diabetes in the second or third decade. Many of the patients with permanent diabetes have mutations involving regulation of the ATP-sensitive potassium channels of the pancreatic beta cells. Activating mutations of either the KCNJ11 gene that encodes the Kir6.2 subunit or the ABCC8 gene that encodes the sulfonylurea receptor (SUR1) have been implicated in the cause of neonatal diabetes. Repeated plasma insulin values are necessary to distinguish transient from permanent diabetes mellitus. Molecular genetic diagnosis can help distinguish the infants with transient diabetes from those with permanent diabetes, and it can also be important for determining which infants are likely to respond to treatment with sulfonylureas.
9. Diabetes due to **pancreatic lesions** such as pancreatic aplasia or hypoplastic or absent pancreatic beta cells is usually seen in SGA infants who may have other congenital defects. They usually present soon after birth, and survival has been rare.
10. Transient hyperglycemia associated with ingestion of **hyperosmolar formula**. Clinical presentation may mimic transient neonatal diabetes with glycosuria, hyperglycemia, and dehydration. A history of inappropriate formula dilution is key. Treatment consists of rehydration, discontinuation of the hyperosmolar formula, and appropriate instructions for mixing concentrated or powder formula.
11. **Hepatic glucose production** can persist despite normal or elevated glucose levels.
12. **Immature development of glucose transport proteins**, such as GLUT-4

B. Treatment. The primary goal is prevention and early detection of hyperglycemia by carefully adjusting GIRs and frequent monitoring of blood glucose levels and urine for glycosuria. If present, evaluation and possible intervention are indicated.

1. Measure glucose levels in preterm infants or infants with abnormal symptoms.
2. Extremely low birth weight preterm infants (<1,000 g) should start and maintain a GIR of at least 4 to 6 mg/kg/minute to match the basal glucose requirement. Glucose levels and fluid balance need to be followed closely to provide data for adjusting the concentration and/or the rate of glucose infusion. Hypotonic fluids (dextrose solutions with concentrations <5%) should be avoided.
   a. As appropriate, decrease the GIR and closely follow the blood glucose levels.
3. Begin parenteral nutrition as soon as possible in low birth weight infants. Some amino acids (higher protein intake) promote insulin secretion.
   a. Feed if condition allows. Feeding can promote the secretion of hormones that promote insulin secretion.
   b. Many small infants will initially be unable to tolerate a certain glucose load (e.g., 6 mg/kg/minute) but will eventually develop tolerance if they are presented with just enough glucose to keep their glucose level high yet not enough to cause glycosuria.
4. **Exogenous insulin.** There is no consensus when to start insulin therapy but has been used when glucose values exceed 250 mg/dL despite efforts to lower the amount of glucose delivered or when prolonged restriction of parenterally administered glucose would substantially decrease the required total caloric intake. Neonates may be extremely sensitive to the effects of insulin. It is desirable to decrease the glucose level gradually to avoid rapid fluid shifts. Very small doses of insulin are used, and the actual amount delivered may be difficult to determine because some of the insulin is adsorbed on the plastic surfaces of the IV tubing. Unlike in adult intensive care units (ICUs) where insulin and tight glucose control has been shown to increase survival, the routine use of insulin is not recommended in the NICU. The 2011 Cochrane Report on routine strategies to prevent hyperglycemia among VLBW infants reported that prophylactic insulin use was associated with higher risk of death by 28 days and no improvements in long-term outcomes among survivors. We use insulin on a limited basis when even low GIRs (~4 mg/kg/minute) are ineffective at reducing blood glucose levels below approximately 250 mg/dL.
   a. Insulin infusion
      i. The standard dilution is 15 units regular human insulin (0.15 mL) added to 30 mL normal saline for a concentration of 0.5 units/mL.
      ii. Prior to starting the infusion, purge the IV tubing with a minimum of 2 times the volume of the connecting tubing using the insulin-containing solution to saturate the plastic binding sites.
      iii. Bolus insulin infusion
         a) Dose 0.05 to 0.1 units/kg every 4 to 6 hours as needed (PRN)
         b) Infuse over 15 minutes via syringe pump.

c) Monitor glucose every 30 minutes to 1 hour for a target level of 180 mg/dL and not <100 mg/dL.

d) If glucose remains >200 mg/dL after three doses, consider continuous infusion of insulin.

iv. Continuous insulin infusion

a) Rate of infusion is 0.05 to 0.2 units/kg/hour (usual starting dose is 0.05 units/kg/hour).

$$\text{Flow rate (mL/hour)} = \frac{\text{(dose [units/kg/hour]} \times \text{weight [kg])}}{\text{concentration (units/mL)}}$$

For example:
Ordered dose is 0.05 units/kg/hour, and infant weighs 600 g (0.6 kg).
0.05 units/kg/hour × 0.6 kg = 0.03 units/hour
Concentration is 0.5 units/mL.

$$\text{Infusion rate is: } \frac{0.03 \text{ units/hour}}{0.5 \text{ mL}} = (0.06 \text{ mL/hour})$$

b) Check glucose levels every 30 minutes until stable to adjust the infusion rate.

c) If glucose remains >180 mg/dL, titrate in increments of 0.01 unit/kg/hour.

d) If hypoglycemia occurs, discontinue insulin infusion and administer IV bolus of $D_{10}W$ at 2 mL/kg × 1 dose.

e) Monitor potassium level.

f) Monitor for rebound hyperglycemia.

b. Subcutaneous insulin lispro

i. This is rarely used except in neonatal diabetes. A typical dose is 0.03 unit/kg PRN for glucose >200 mg/dL.

ii. Do not administer more frequently than every 3 hours to avoid hypoglycemia.

iii. Rotate administration sites.

iv. Monitor glucose level frequently.

v. Monitor electrolytes including potassium level every 6 hours initially.

vi. Insulin lispro has a rapid onset of action (15 to 30 minutes) and peak effect is 30 minutes to 2.5 hours.

c. Oral sulfonylureas have been used in the long-term management of infants with Kir6.2 and SUR1 defects.

Suggested Readings

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25 Abnormalities of Serum Calcium and Magnesium

Steven A. Abrams

KEY POINTS

- Hypocalcemia is common in preterm infants, but clinical symptoms including seizure activity are more likely to occur at a higher ionized calcium level in full-term or late-preterm infants than in very low birth weight (VLBW) infants.
- Intravenous treatment of hypocalcemia must be done cautiously with continuous cardiac monitoring in neonates.
- Hypomagnesemia is commonly seen with hypocalcemia and should be treated.
- Hypercalcemia is also common especially in extremely small preterm infants and requires adjustment of calcium intake when severe in the first days of life, although clinical symptoms are uncommon.

I. HYPOCALCEMIA

A. General principles

1. **Definition.** Neonatal hypocalcemia is defined as a total serum calcium concentration of <7 mg/dL or an ionized calcium concentration of <4 mg/dL (1 mmol/L). In very low birth weight (VLBW) infants, ionized calcium values of 0.8 to 1 mmol/L are common and not usually associated with clinical symptoms. Even values as low as 0.7 mmol/L are uncommonly associated with seizure activity in VLBW infants. In larger infants such as those >32 weeks' gestation, clinical symptoms, including seizures, may occur more readily with an ionized calcium concentration of 0.8 to 1.0 mmol/L.

2. **Pathophysiology**

   a. Calcium ions (Ca^{2+}) in cellular and extracellular fluid (ECF) are essential for many biochemical processes. Significant aberrations of serum calcium concentrations are frequently observed in the neonatal period.

      i. Hormonal regulation of calcium homeostasis. Regulation of serum and ECF-ionized calcium concentration within a narrow range is critical for blood coagulation, neuromuscular

excitability, cell membrane integrity and function, and cellular enzymatic and secretory activity. The principal calciotropic or calcium-regulating hormones are parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D ($1,25(OH)_2D$, also referred to as *calcitriol*).

ii. When the ECF-ionized calcium level declines, parathyroid cells secrete PTH. PTH mobilizes calcium from bone, increases calcium resorption in the renal tubule, and stimulates renal production of $1,25(OH)_2D$. PTH secretion causes the serum calcium level to rise and the serum phosphorus level to either be maintained or fall.

iii. Vitamin D is synthesized from provitamin D in the skin after exposure to sunlight and is also ingested in the diet. Vitamin D is transported to the liver, where it is converted to 25(OH)D (also called calcidiol) which is the major storage form of the hormone. This is transported to the kidney, where it is converted to the biologically active hormone $1,25(OH)_2D$ (calcitriol). Calcitriol increases intestinal calcium and phosphate absorption and mobilizes calcium and phosphate from bone.

3. Etiology

a. Prematurity. Preterm infants are capable of mounting a PTH response to hypocalcemia, but target organ responsiveness to PTH may be diminished.

b. Infants of diabetic mothers (IDMs) have a 25% to 50% incidence of hypocalcemia if maternal control is poor. Hypercalcitoninemia, hypoparathyroidism, abnormal vitamin D metabolism, and hyperphosphatemia have all been implicated, but the etiology remains uncertain.

c. Severe neonatal birth depression is frequently associated with hypocalcemia, hypomagnesemia, and hyperphosphatemia. Decreased calcium intake and increased endogenous phosphate load are likely causes.

d. Congenital. Parathyroid function may be absent in DiGeorge sequence (hypoplasia or absence of the third and fourth branchial pouch structures) as an isolated defect in the development of the parathyroid glands or as part of the Kenny-Caffey syndrome.

e. Pseudohypoparathyroidism

f. Maternal hyperparathyroidism

g. Magnesium deficiency (including inborn error of intestinal magnesium transport) impairs PTH secretion.

h. Severe vitamin D deficiency (frequency in newborn period is uncertain)

i. Alkalosis and bicarbonate therapy

j. Rapid infusion of citrate-buffered blood (exchange transfusion) chelates ionized calcium.

k. Shock or sepsis

l. Phototherapy may be associated with hypocalcemia by decreasing melatonin secretion and increasing uptake of calcium into the bone.

m. For late-onset hypocalcemia, high phosphate intakes lead to excess phosphorus and decreased serum calcium.

B. Diagnosis

1. Clinical presentation

a. Hypocalcemia increases both cellular permeability to sodium ions and cell membrane excitability. The signs are usually nonspecific: apnea, seizures, jitteriness, increased extensor tone, clonus, hyperreflexia, and stridor (laryngospasm).

b. Early-onset hypocalcemia in preterm newborns is often asymptomatic but may show apnea, seizures, or abnormalities of cardiac function, although identifying these as primarily due to the calcium level is often difficult.

c. Late-onset syndromes, in contrast, frequently presents as hypocalcemic seizures. Often, they must be differentiated from other causes of newborn seizures, including "fifth-day" fits and infections including those caused by herpes simplex virus (HSV).

2. History

a. For late-onset presentation, infant formula feeding is most common. Parents may report partial breastfeeding but rarely, if ever, exclusive breastfeeding. Abnormal movements and lethargy may precede obvious seizure activity. Rarely, use of goat's milk or cow's milk use may be reported. Symptoms are usually described beginning from the third to fifth days of life.

b. Overfeeding may also be identified in the history, although this can be difficult to ascertain.

3. Physical examination

a. General physical findings associated with seizure disorder in the newborn may be present in some cases. Usually, there are no apparent physical findings.

4. Laboratory studies

a. There are three definable fractions of calcium in serum: (i) ionized calcium (~50% of serum total calcium); (ii) calcium bound to serum proteins, principally albumin (~40%); and (iii) calcium complexed to serum anions, mostly phosphates, citrate, and sulfates (~10%). Ionized calcium is the only biologically available form of calcium.

b. Assessment of calcium status using ionized calcium is preferred, especially in the first week of life. Correction nomograms, used to convert total calcium into ionized calcium, are not reliable in the newborn period.

c. Calcium concentration reported as milligrams per deciliter can be converted to molar units by dividing by 4 (e.g., 10 mg/dL converts to 2.5 mmol/L).

d. Postnatal changes in serum calcium concentrations. At birth, the umbilical serum calcium level is elevated (10 to 11 mg/dL). In healthy term babies, calcium concentrations decline for the first 24 to 48 hours; the nadir is usually 7.5 to 8.5 mg/dL. Thereafter, calcium concentrations progressively rise to the mean values observed in older children and adults.

e. Although an association with vitamin D deficiency is uncommon, an assessment of both maternal and neonatal serum 25-hydroxyvitamin D

level may be warranted. Values <10 to 12 ng/dL are suggestive of severe deficiency that may be associated with clinical symptoms in some, but probably not most, infants.

f. Hypomagnesemia is often seen in association with late-onset hypocalcemia.

5. Monitoring

a. Suggested schedule for monitoring calcium levels in infants such as VLBW, IDM, and birth depression who are at risk for developing hypocalcemia:

i. Ionized calcium: at 12, 24, and 48 hours of life

ii. Total serum phosphorus and total serum magnesium for infants with hypocalcemia

iii. Other lab tests, including serum concentrations of PTH, 25(OH) D, and $1,25(OH)_2D$ are not routinely needed unless neonatal hypocalcemia does not readily resolve with calcium therapy or DiGeorge sequence is suspected. It is extremely rare that $1,25(OH)_2D$ is ever measured in neonates.

iv. A prolonged electrocardiographic QTc interval is a traditional indicator that is typically not clinically useful in the newborn period.

6. Imaging

a. Absence of a thymic shadow on a chest radiograph and the presence of conotruncal cardiac abnormalities may suggest a diagnosis of 22q11 syndrome, also known as *CATCH22* or *DiGeorge sequence*. Genetic consultation and evaluation may be of value if this is suspected.

C. Treatment

1. Medications

a. Therapy with calcium is usually adequate for most cases. In some cases (see the following text), concurrent therapy with magnesium is indicated.

b. Rapid intravenous infusion of calcium can cause a sudden elevation of serum calcium level, leading to bradycardia or other dysrhythmias. Intravenous calcium should be given for treatment of hypocalcemic crisis (e.g., seizures) with careful cardiovascular monitoring.

c. Infusion by means of the umbilical vein may result in hepatic necrosis if the catheter is lodged in a branch of the portal vein.

d. Rapid infusion by means of the umbilical artery can cause arterial spasms and, at least experimentally, intestinal necrosis and thus is not indicated.

e. Intravenous calcium solutions are incompatible with sodium bicarbonate because calcium carbonate will precipitate.

f. Extravasation of calcium solutions into subcutaneous tissues can cause severe necrosis and subcutaneous calcifications.

i. Calcium preparations. Calcium gluconate 10% solution is preferred for intravenous use. Calcium glubionate syrup (Neo-Calglucon) is a convenient oral preparation. When not available, intravenous calcium gluconate may be given orally. Use of calcium carbonate is generally avoided as the relatively high stomach pH of the neonate does not allow for solubilization of the calcium and absorption.

ii. If the ionized calcium level drops to 1 mmol/L or less (for infants ≥1,500 g) or 0.8 mmol/L or less (for infants <1,500 g), a continuous intravenous calcium infusion may be commenced. For infants with asymptomatic early hypocalcemia, this may be done using total parenteral nutrition (TPN). For use without other TPN components, a dose of 40 to 50 mg/kg/day of elemental calcium is typical.

iii. It may be desirable to prevent the onset of hypocalcemia for newborns who exhibit cardiovascular compromise (e.g., severe respiratory distress syndrome, asphyxia, septic shock, and persistent pulmonary hypertension of the newborn). Use a continuous calcium infusion, preferably by means of a central catheter, to maintain an ionized calcium 1.0 to 1.4 mmol/L (<1,500 g) or 1.2 to 1.5 mmol/L (≥1,500 g).

iv. Emergency calcium therapy (for active seizures or profound cardiac failure thought to be associated with severe hypocalcemia) consists of 100 to 200 mg/kg of 10% calcium gluconate (9 to 18 mg of elemental calcium per kilogram) by intravenous infusion over 10 to 15 minutes.

g. Monitor heart rate and rhythm and the infusion site throughout the infusion.

h. Repeat the dose in 10 to 20 minutes if there is no clinical response.

i. Following the initial dose(s), maintenance calcium should be given through continuous intravenous infusion.

j. Hypocalcemia associated with hyperphosphatemia presenting after day of life (DOL) 3

i. The goal of initial therapy is to reduce renal phosphate load while increasing calcium intake. Reduce phosphate intake by feeding the infant human milk or a low-phosphorus formula (Similac PM 60/40 is most widely used, but other relatively low mineral formulas, including Nestlé Good Start group of formulas, may be used).

ii. Avoid the use of preterm formulas, lactose-free or other special formulas, or transitional formulas (NeoSure and EnfaCare). These often have high levels of phosphorus or may be more limited in calcium bioavailability.

iii. Increase the oral calcium intake using supplements (e.g., 20 to 40 mg/kg/day of elemental calcium added to Similac PM 60/40). This approach may also be helpful for IDMs who are symptomatic and do not have an intravenous line in place. Phosphate binders are generally not necessary and may not be safe for use, especially in premature infants.

iv. Gradually wean calcium supplements over 2 to 4 weeks. Monitor serum calcium and phosphorus levels one to two times weekly.

v. The use of vitamin D or active vitamin D ($1,25(OH)_2D$) in this circumstance is not usually necessary. If a serum 25-hydroxyvitamin D level is obtained and is <20 ng/mL, then 1,000 IU of vitamin D should be given daily and the value rechecked in 14 to 21 days. Rarely are higher doses needed by neonates.

k. Rare defects in vitamin D metabolism are treated with vitamin D analogues, for example, dihydrotachysterol (Hytakerol) and calcitriol (Rocaltrol). The rapid onset of action and short half-life of these drugs lessen the risk of rebound hypercalcemia. Endocrine evaluation is usually indicated if these are suspected clinically.

II. HYPERCALCEMIA

A. General principles

1. Definition

a. Neonatal hypercalcemia (serum total calcium level >11 mg/dL, serum ionized calcium level >1.45 mmol/L) may be asymptomatic and discovered incidentally during routine screening. Alternatively, the presentation of severe hypercalcemia (>16 mg/dL or ionized calcium >1.8 mmol/L) can require immediate medical intervention. Very mild hypercalcemia (serum calcium 11 to 12 mg/dl or ionized calcium 1.45 to 1.60 mmol/L) is common and does not require any intervention at all.

2. Etiology

a. Imbalance in intake or use of calcium

b. Clinical adjustment of TPN by completely removing the phosphorus (due to, e.g., concern about excess sodium or potassium intake) can rapidly lead to hypercalcemia, especially in VLBW infants. This commonly leads to ionized calcium values from 1.45 to 1.6 mmol/L.

c. Extreme prematurity. Moderate to extreme hypercalcemia is not uncommon in infants <750 g birth weight on usual TPN mineral intakes. Values up to 2.2 mmol/L of ionized calcium occur. This is likely due to inability to use calcium in these infants and may or may not be associated with a high serum phosphorus.

d. Hyperparathyroidism

- **i.** Congenital hyperparathyroidism associated with maternal hypoparathyroidism usually resolves over several weeks.
- **ii.** Neonatal severe primary hyperparathyroidism (NSPHP). The parathyroids are refractory to regulation by calcium, producing marked hypercalcemia (frequently 15 to 30 mg/dL).
- **iii.** Self-limited secondary hyperparathyroidism associated with neonatal renal tubular acidosis

e. Hyperthyroidism. Thyroid hormone stimulates bone resorption and bone turnover.

f. Hypophosphatasia, an autosomal recessive bone dysplasia, produces severe bone demineralization and fractures.

g. Increased intestinal absorption of calcium

h. Hypervitaminosis D rarely may result from excessive vitamin D ingestion by the mother (during pregnancy) or the neonate. Because vitamin D is extensively stored in fat, intoxication may persist for weeks to months (see Chapter 21).

i. Decreased renal calcium clearance

j. Familial hypocalciuric hypercalcemia, a clinically benign autosomal dominant disorder, can present in the neonatal period. The gene mutation is on chromosome 3q21–24.

k. Idiopathic neonatal/infantile hypercalcemia occurs in the constellation of Williams syndrome (hypercalcemia, supravalvular aortic stenosis or other cardiac anomalies, "elfin" facies, psychomotor retardation) and in a familial pattern lacking the Williams phenotype. Increased calcium absorption has been demonstrated; increased vitamin D sensitivity and impaired calcitonin secretion are proposed as possible mechanisms.

l. Subcutaneous fat necrosis is a sequela of trauma or asphyxia. Only the more generalized necrosis seen in asphyxia is associated with significant hypercalcemia. Granulomatous (macrophage) inflammation of the necrotic lesions may be a source of unregulated $1,25(OH)_2D_3$ synthesis.

m. Acute renal failure usually during the diuretic or recovery phase

B. Diagnosis

1. Clinical presentation

a. Hyperparathyroidism—includes hypotonia, encephalopathy, poor feeding, vomiting, constipation, polyuria, hepatosplenomegaly, anemia, and extraskeletal calcifications, including nephrocalcinosis

b. Milder hypercalcemia may present as feeding difficulties or poor linear growth.

2. History

a. Maternal/family history of hypercalcemia or hypocalcemia, parathyroid disorders, and nephrocalcinosis

b. Family history of hypercalcemia or familial hypocalciuric hypercalcemia

c. Manipulations of TPN

3. Physical examination

a. Small for dates (hyperparathyroidism, Williams syndrome)

b. Craniotabes, fractures (hyperparathyroidism), or characteristic bone dysplasia (hypophosphatasia)

c. Elfin facies (Williams syndrome)

d. Cardiac murmur (supravalvular aortic stenosis and peripheral pulmonic stenosis associated with Williams syndrome)

e. Indurated, bluish-red lesions (subcutaneous fat necrosis)

f. Evidence of hyperthyroidism

4. Laboratory evaluation

a. The clinical history, serum and urine mineral levels of phosphorus, and the urinary calcium:creatinine ratio (U_{Ca}/U_{Cr}) should suggest a likely diagnosis.

- **i.** A very elevated serum calcium level (>16 mg/dL) usually indicates primary hyperparathyroidism or, in VLBW infants, phosphate depletion or the inability to use calcium for bone formation.
- **ii.** Low serum phosphorus level indicates phosphate depletion, hyperparathyroidism, or familial hypocalciuric hypercalcemia.
- **iii.** Very low U_{Ca}/U_{Cr} suggests familial hypocalciuric hypercalcemia.

b. Specific serum hormone levels (PTH, 25(OH)D) may confirm the diagnostic impression in cases where obvious manipulations of diet/TPN are not apparent. Measurement of $1,25(OH)_2D$ is rarely indicated unless hypercalcemia persists in infants ≥1,500 g with no other apparent etiology.

c. A very low level of serum alkaline phosphatase activity suggests hypophosphatasia (confirmed by increased urinary phosphoethanolamine level).
d. Radiography of hand/wrist may suggest hyperparathyroidism (demineralization, subperiosteal resorption) or hypervitaminosis D (submetaphyseal rarefaction).

C. Treatment

1. Emergency medical treatment (symptomatic or calcium >16 mg/dL, ionized Ca >1.8 mmol/L) in infants >1,500 g. Smaller VLBW infants should usually be treated less aggressively regardless of serum calcium or ionized calcium.
2. Discontinue all sources of calcium intake including parenteral nutrition for ionized Ca >1.8.
   a. Volume expansion with isotonic saline solution. Hydration and sodium promote urinary calcium excretion. If cardiac function is normal, infuse normal saline solution (10 to 20 mL/kg) over 15 to 30 minutes.
   b. Furosemide (1 mg/kg intravenously) induces calciuria.
3. Inorganic phosphate may lower serum calcium levels in hypophosphatemic patients by inhibiting bone resorption and promoting bone mineral accretion.
   a. Glucocorticoids are effective in hypervitaminosis A and D and subcutaneous fat necrosis by inhibiting both bone resorption and intestinal calcium absorption; they are ineffective in hyperparathyroidism.
   b. Low-calcium, low-vitamin D diets are an effective adjunctive therapy for subcutaneous fat necrosis and Williams syndrome.
   c. Calcitonin is a potent inhibitor of bone resorption. The antihypercalcemic effect is transient but may be prolonged if glucocorticoids are used concomitantly. There is little reported experience in neonates.
   d. Parathyroidectomy with autologous reimplantation may be indicated for severe persistent neonatal hyperparathyroidism.

III. DISORDERS OF MAGNESIUM: HYPOMAGNESEMIA AND HYPERMAGNESEMIA

A. Etiology

1. Hypermagnesemia is usually due to an exogenous magnesium load exceeding renal excretion capacity.
   a. Magnesium sulfate therapy for maternal preeclampsia or preterm labor
   b. Administration of magnesium-containing antacids to the newborn
   c. Excessive magnesium in parenteral nutrition
   d. Hypomagnesemia is uncommon but is often seen with late-onset hypocalcemia.

B. Diagnosis

1. Elevated serum magnesium level (>3 mg/dL) suggests hypermagnesemia, although symptoms are uncommon with serum values <4 to 5 mg/dL. Values of 2.2 to 3 are commonly reported by laboratories as outside the normal range but are nonpathologic. Low serum magnesium level of <1.6 mg/dL suggests hypomagnesemia.

2. Severe hypermagnesemic symptoms are unusual in neonates with serum magnesium level <6 mg/dL. The common curariform effects include apnea, respiratory depression, lethargy, hypotonia, hyporeflexia, poor suck, decreased intestinal motility, and delayed passage of meconium.
3. Hypomagnesemia is usually seen along with hypocalcemia in the newborn. Hypomagnesemic symptoms can also include apnea and poor motor tone.
4. Hypomagnesemia may be seen with therapeutic cooling in the newborn.
5. Mild to moderate asymptomatic hypermagnesemia does not require daily measurement of serum magnesium. Frequent monitoring of serum magnesium is generally only needed for values >5 mg/dL.

C. Treatment

1. Hypocalcemic seizures with concurrent hypomagnesemia should include treatment for the hypomagnesemia.
   a. The preferred preparation for treatment is magnesium sulfate. The 50% solution contains 500 mg or 4 mEq/mL
   b. Correct severe hypomagnesemia (<1.6 mg/dL) with 50 mg/kg of magnesium sulfate intravenously given over 1 to 2 hours. When administering intravenously, infuse slowly and monitor heart rate. The dose may be repeated after 12 hours. Obtain serum magnesium levels before each dose.
2. Often, the only intervention necessary for hypermagnesemia is removal of the source of exogenous magnesium.
3. Exchange transfusion, peritoneal dialysis, and hemodialysis are not used in the newborn period.
4. For hypermagnesemic babies, begin feedings only after suck and intestinal motility are established. Rarely, respiratory support may be needed.
5. Mild hypermagnesemia (serum magnesium <4.0) should not lead to withholding of physiologic magnesium from intravenous parenteral nutrition.

Suggested Readings

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26 Neonatal Hyperbilirubinemia

Vinod K. Bhutani and Ann R. Stark

KEY POINTS

- Visual inspection is **not** a reliable measure of bilirubin level.
- Jaundice before age 24 hours is a medical emergency and may result from excessive bilirubin production.
- Measurement of bilirubin and identification of risk factors, especially gestational age, during birth hospitalization predicts need for phototherapy and guides timing of follow-up after discharge.
- Identification of clinical risk factors for bilirubin neurotoxicity and recognition of early signs of acute bilirubin encephalopathy promotes timely escalation of treatment.
- Evaluation of infants with prolonged elevated unconjugated and/or conjugated bilirubin levels after 7 days of age ensures prompt intervention for treatable disorders.

I. BACKGROUND. Almost all newborn infants have a serum or plasma total bilirubin (TB) level >1 mg/dL in contrast to adults in whom the normal TB level is <1 mg/dL. Approximately 85% of all term newborns and most preterm infants develop clinical jaundice or progressive hyperbilirubinemia. A peak TB level >12.9 mg/dL occurs in 6.1% of well term newborns and a TB level >15 mg/dL occurs in only ~3% of normal term infants.

II. BILIRUBIN METABOLISM. Changes in the TB level result from changes in the balance of bilirubin production and excretion.

A. Bilirubin production. Bilirubin is derived from the breakdown of heme-containing proteins in the reticuloendothelial system. A normal newborn produces 6 to 10 mg of bilirubin/kg/day, greater than the adult production of 3 to 4 mg/kg/day. Physiologic bilirubin production is distinguished from that due to hemolysis and increased red cell destruction.

1. **Red blood cell (RBC) hemoglobin** is the major heme-containing protein. Hemoglobin released from senescent RBCs in the reticuloendothelial system or from ineffective erythropoiesis accounts for 80% to 90% of bilirubin production. One gram of hemoglobin produces 34 mg of bilirubin. Breakdown of other heme-containing proteins such as cytochromes and catalase contributes the remaining 10% to 20% of bilirubin.

2. **Bilirubin metabolism.** The microsomal enzyme heme oxygenase located in the liver, spleen, and nucleated cells oxidizes the heme ring from heme-containing proteins to **biliverdin** (transient) and **carbon monoxide (CO)** (exhaled from the lung); the **iron** that is released is recycled. The enzyme **biliverdin reductase** rapidly reduces biliverdin to bilirubin. Because heme breakdown yields equimolar amounts of CO and biliverdin, bilirubin production can be indirectly assessed by measuring CO production.

B. Bilirubin clearance and excretion

1. **Transport.** Bilirubin is nonpolar, insoluble in water, and transported to liver cells bound to serum **albumin**. Bilirubin bound to albumin is thought to be nontoxic to the central nervous system (CNS). It is the unconjugated bilirubin not bound to albumin (unbound bilirubin or "free" bilirubin) that is considered neurotoxic to targeted CNS sites. Displacement of bilirubin from albumin by acidosis, drugs such as ceftriaxone, benzoyl alcohol (a preservative), or free fatty acids (FFAs) at high molar ratios of FFA to albumin may further increase bilirubin toxicity.
2. **Hepatic uptake.** Nonpolar, fat-soluble unconjugated bilirubin (dissociated from albumin) crosses the hepatocyte plasma membrane and is bound mainly to cytoplasmic **ligandin** (Y protein) for transport to the smooth endoplasmic reticulum for conjugation to a water-soluble entity.
3. **Conjugation.** In hepatocytes, the enzyme **uridine diphosphoglucuronate glucuronosyltransferase (UGT)** catalyzes the conjugation process of bilirubin with glucuronic acid, resulting in mostly bilirubin diglucuronides and some monoglucuronides that are more water soluble than unconjugated bilirubin and mostly nontoxic to the CNS. Both glucuronide forms of conjugated bilirubin are excreted into the bile canaliculi against a concentration gradient.
   a. Inherited deficiencies and polymorphisms of the conjugating enzyme gene can cause severe hyperbilirubinemia in newborns. Polymorphisms in the UGT1A1 gene due to differences in the number of thymine-adenine repeats in the promotor gene diminish the expression of the UGT1A1 enzyme and result in increased TB levels (**Gilbert syndrome**). Differences in these polymorphisms in individuals of different ancestry contribute to the variation in conjugating ability and neonatal hyperbilirubinemia among Caucasian, Asian, and African populations. In addition, a mutation in the UGT1A1 gene that is common in East Asians contributes to an increased risk of severe neonatal hyperbilirubinemia in that population.
4. **Excretion.** Conjugated bilirubin is secreted into the bile and then excreted into the gastrointestinal (GI) tract where it is eliminated in the stool. Conjugated bilirubin is not reabsorbed from the bowel unless it is deconjugated by the intestinal enzyme β-glucuronidase present in the neonatal intestinal mucosa. Resorption of bilirubin from the GI tract and delivery back to the liver for reconjugation is called the enterohepatic circulation. Intestinal bacteria, present in adults but to

a limited extent in newborns, can prevent enterohepatic circulation of bilirubin by reducing conjugated bilirubin to urobilin, which is not a substrate for β-glucuronidase.

5. **Fetal bilirubin metabolism.** Most unconjugated bilirubin formed by the fetus is cleared by the placenta into the maternal circulation. In the event of severe fetal hemolysis, unconjugated bilirubin is elevated in the cord blood. Rates of bilirubin rise of >0.20 to >0.5 mg/dL/hour have been observed after separation from the placental circulation (e.g., in infants severely affected due to Rh incompatibility). Formation of conjugated bilirubin is limited in the fetus because of decreased fetal hepatic blood flow, decreased hepatic ligandin, and decreased UGT1A1 activity. The small amount of conjugated bilirubin excreted into the fetal gut is usually hydrolyzed by β-glucuronidase and resorbed. Bilirubin is normally found in amniotic fluid by 12 weeks' gestation and is usually absent by 37 weeks' gestation. Increased amniotic fluid bilirubin is found in fetal hemolytic disease and fetal intestinal obstruction below the bile ducts.

III. NONPATHOLOGIC (BENIGN) HYPERBILIRUBINEMIA. The serum TB level of most term and late-preterm newborn infants rises to >2 mg/dL during the first week after birth. This level usually rises in healthy full-term infants to an average peak of 6 to 8 mg/dL by 3 to 5 days of age and then resolves. A rise to 12.9 mg/dL is within the "physiologic range," not neurotoxic, and is considered benign. In late-preterm infants, average TB peak may range from 10 to 12 mg/dL on the fifth day after birth and may continue to rise without treatment and without a specific abnormality of bilirubin metabolism. This level may not be benign due to the infant's gestational age especially in low birth weight infants. In both full-term and late-preterm infants, TB levels may not be <2 mg/dL until 4 to 6 weeks of age. TB levels >20 mg/dL are unusual, occurring in <2% of the screened population. Exaggerated hyperbilirubinemia is "nonphysiologic jaundice" and is attributed to the following mechanisms:

A. **Increased bilirubin production due to the following:**
   1. Increased RBC volume per kilogram and decreased RBC survival (90 vs. 120 days) in infants compared to adults
   2. Increased ineffective erythropoiesis and increased turnover of nonhemoglobin heme proteins

B. **Defective bilirubin uptake** from plasma caused by decreased ligandin and binding of ligandin by other anions

C. **Decreased bilirubin clearance** due to decreased UGT1A1 activity. In term infants at 7 days of age, UGT activity is approximately 1% that of adults and does not reach adult levels until at least 3 months of age.

D. **Decreased hepatic excretion** (elimination) of bilirubin. Factors that lead to decreased elimination of bilirubin include increased enterohepatic circulation caused by high levels of intestinal β-glucuronidase, a greater portion of bilirubin monoglucuronide than diglucuronide, decreased intestinal bacteria, and decreased gut motility with poor evacuation of bilirubin-laden meconium.

IV. SIGNIFICANT HYPERBILIRUBINEMIA during the first week after birth occurs when the TB is within 2 mg/mL of the phototherapy level for the infant's age, gestational age, and presence of neurotoxicity risk factors. This is often associated with an increased rate of bilirubin rise (≥0.3 mg/dL/hour in the first 24 hours or ≥0.2 mg/dL/hour thereafter).

A. Further evaluation for significant hyperbilirubinemia is required for any of the following (Table 26.1):

1. Onset of jaundice before 24 hours of age
2. Elevation of TB to a level that may require phototherapy and closer follow-up (Table 26.2)
3. Rate of rise that may reach "severe" levels (>20 mg/dL) during the first week
4. Associated signs of illness such as poor feeding, emesis, lethargy, excessive weight loss, apnea, respiratory instability, or temperature instability that may suggest incipient signs of acute bilirubin neurotoxicity
5. Cholestatic hyperbilirubinemia is defined by direct serum bilirubin level >1.0 mg/dL or conjugated bilirubin ≥0.3 mg/dL
6. Prolonged unconjugated or conjugated hyperbilirubinemia at age younger than 7 days in a term infant as manifested by persistent jaundice

Table 26.1. Clinical Risk Factors for Developing Significant Hyperbilirubinemia

■ Lower gestational age (i.e., each additional week of prematurity)
■ Jaundice at age <24 hours
■ Predischarge TcB/TSB level that anticipates phototherapy
■ Risk of neonatal hemolysis as suggested by rapid rate of rise in the TSB or TcB (>0.3 mg/dL/hour at age <24 hours and >0.2 mg/dL/hour thereafter).
■ Use of phototherapy before discharge
■ Parent or sibling requiring phototherapy or exchange transfusion
■ Family history or genetic ancestry suggestive of inherited RBC disorders, including G6PD deficiency
■ Exclusive breastfeeding with suboptimal intake
■ Scalp hematoma or significant bruising
■ Down syndrome
■ Macrosomic infant of a diabetic mother

TcB, transcutaneous bilirubin; TSB, total serum bilirubin; RBC, red blood cell; G6PD, glucose-6-phosphate dehydrogenase.

Table 26.2. Guidelines to Time of Discharge and Follow-up

Phototherapy Threshold Minus TcB/TSB		AAP Recommended Action at Discharge
0.1–1.9	Postnatal age <24 hours	Delay. Consider phototherapy; repeat TSB in 4–8 hours.
	Postnatal age ≥24 hours	Measure TSB in 4–24 hours. Options: ■ Delay discharge; consider phototherapy. ■ Consider home phototherapy (as per Table 26.6). ■ Discharge without phototherapy; close follow-up
2.0–3.4	Regardless of gestational age or postnatal age	TSB or TcB in 4–24 hours
3.5–5.4	Regardless of gestational age or postnatal age	TSB or TcB in 1–2 days
5.4–6.9	Discharge postnatal age <72 hours.	Follow-up within 2 days; TcB or TSB as per clinical judgment
	Discharge age ≥72 hours.	Clinical judgment
≥7	Discharge age <72 hours.	Follow-up within 3 days; TcB or TSB as per clinical judgment
	Discharge age ≥72 hours.	Follow-up as per clinical judgment

TcB, transcutaneous bilirubin; TSB, transcutaneous bilirubin; AAP, American Academy of Pediatrics.

Source: Reproduced with permission from Kemper AR, Newman TB, Slaughter JL, et al. Clinical practice guideline revision: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 2022:e2022058859. Copyright © 2022 by the American Academy of Pediatrics.

B. Causes of hyperbilirubinemia

1. **Increased bilirubin production.** Hemolytic disease is the most common cause of hyperbilirubinemia (see Chapter 45). This includes RBC disorders such as isoimmunization (e.g., Rh ABO and minor blood group incompatibility), erythrocyte biochemical abnormalities such as glucose-6-phosphate dehydrogenase (G6PD) or pyruvate kinase deficiencies, or abnormal erythrocyte morphology such as hereditary spherocytosis (HS). Other causes of increased RBC breakdown are sepsis (bacterial, viral, protozoal), breakdown of sequestered blood due to bruising or cephalohematoma, and polycythemia.
2. **Decreased bilirubin clearance**
   a. Mutations in the gene that encodes UGT1A1 decrease bilirubin conjugation, reducing hepatic clearance and increasing total serum bilirubin (TSB) levels.

b. Crigler-Najjar syndrome due to either absent UGT activity (type I) or reduced UGT activity (type II) results in severe hyperbilirubinemia.

c. Gilbert syndrome results from a mutation in the promoter region of the UGT1A1 gene, reducing production of UGT, and is the most common inherited disorder of bilirubin glucuronidation. Although the Gilbert genotype alone is not associated with increased hyperbilirubinemia, severe hyperbilirubinemia can result when an affected newborn also has increased bilirubin production or increased enterohepatic circulation.

d. Polymorphisms of the organic anion transporter protein may lead to severe hyperbilirubinemia, especially when combined with a UGT1A1 gene mutation.

e. Decreased clearance may occur in infants of diabetic mothers and with congenital hypothyroidism, galactosemia, and other inherited metabolic disorders.

3. **Increased enterohepatic circulation.** Disorders leading to increased enterohepatic circulation include decreased enteral intake, including breastfeeding failure; "breast milk jaundice" (a misnomer for prolonged unconjugated hyperbilirubinemia in a breast-fed infant); or impaired GI motility due to intestinal atresias, meconium ileus, or Hirschsprung disease.

   a. Breastfeeding jaundice (suboptimal intake hyperbilirubinemia). Infants who are breastfed have higher bilirubin levels on day 3 of age compared to formula-fed infants. Breastfeeding jaundice typically occurs with suboptimal lactation during the first postnatal week that leads to insufficient intake, with weight loss, decreased stool frequency, and sometimes hypernatremia. Hyperbilirubinemia is attributed mainly to the decreased intake of milk that leads to slower bilirubin elimination and increased enterohepatic circulation.

   b. Breast milk jaundice (prolonged unconjugated hyperbilirubinemia with adequate intake) is a condition that may be due to genetic predisposition and occurs in about 2.4% of all infants. It typically begins after the first 3 to 5 postnatal days, peaks within 2 weeks of age, and, if breastfeeding is continued, gradually returns to normal levels over 3 to 12 weeks. If breastfeeding is interrupted, the bilirubin level may fall rapidly in 48 hours. If nursing is then resumed, the bilirubin may rise by 2 to 4 mg/dL but usually will not reach the previous high level. Affected infants have good weight gain, normal liver function test (LFT) results, and no evidence of hemolysis. The mechanism of breast milk jaundice is uncertain and may be associated with Gilbert disease or perhaps a factor in human milk, possibly β-glucuronidase, that deconjugates intestinal bilirubin and promotes its absorption.

4. **Hyperbilirubinemia in preterm infants (<35 weeks' gestational age).** Preterm neonates are more vulnerable to hyperbilirubinemia than term infants. Historically, without access to phototherapy or exchange transfusion, the incidence of kernicterus was very high. With effective phototherapy, the need for exchange transfusion is rare; however, the potential oxidant side effects of phototherapy in extremely low birth weight infants are under investigation. Suggested management of hyperbilirubinemia in preterm infants is based on expert consensus (Table 26.3).

Table 26.3. Suggested Bilirubin Thresholds for Use of Phototherapy and Exchange Transfusion in Preterm Infants <35 Weeks' Gestational Age

	Phototherapy	Exchange Transfusion
Gestational Age (weeks)	**Initiate Phototherapy Total Serum Bilirubin (mg/dL)**	**Total Serum Bilirubin (mg/dL)**
<28 0/7	5–6	11–14
28 0/7–29 6/7	6–8	12–14
30 0/7–31 6/7	8–10	13–16
32 0/7–33 6/7	10–12	15–18
34 0/7–34 6/7	12–14	17–19

Source: Reprinted by permission from Nature: Maisels MJ, Watchko JF, Bhutani VK, et al. An approach to the management of hyperbilirubinemia in the preterm infant less than 35 weeks of gestation. *J Perinatol* 2012;32:660–664.

V. PREVENTION OF HYPERBILIRUBINEMIA IN HEALTHY TERM AND LATE-PRETERM INFANTS. The American Academy of Pediatrics (AAP) clinical practice guideline (CPG) for the treatment of unconjugated hyperbilirubinemia in healthy newborn infants at 35 weeks' gestation age and older is based on these general principles: to reduce the occurrence of severe hyperbilirubinemia (and possible risk of bilirubin neurotoxicity) while also reducing unintended harm of overtreatment: prevention (including maternal antibody screening), feeding support, systematic infant assessment before discharge, close follow-up, and prompt intervention when indicated.

A. Prenatal maternal evaluation for risk of fetal hemolysis, mostly due to isoimmunization, is a key prevention strategy. If the maternal antibody screen is positive or unknown because the mother did not have prenatal antibody screening, a direct antiglobulin test (DAT; previously known as a Coombs test) should be performed on the infant at the time of birth.

B. Assessment for progression of jaundice at least every 12 hours after delivery should be done for all babies until discharge and continued at follow-up. This should be supported by family education.

C. Predischarge bilirubin levels should be measured between 24 and 48 hours after birth or prior to discharge if that occurs earlier. Visual inspection is not a reliable measure of bilirubin level.

1. TB can be assayed directly on blood, serum or, plasma (TSB) that can be collected by heel stick sampling at the time of the metabolic screen.
2. TB can be estimated based on measurements of transcutaneous testing (transcutaneous bilirubin [TcB]). TcB testing relies on spectrophotometric correlation of subdermal bilirubin reflectance. This estimate provides a valid and reliable screening test to identify infants who require a TSB measurement and may reduce the number of blood draws.

3. When more than one TcB or TSB measure is available, the rate of rise can be used as a possible index of hemolysis. Hemolysis is suggested by a rate of rise ≥0.3 mg/dL/hour in the first 24 hours or ≥0.2 mg/dL/hour after 24 hours.
4. TcB measurements may not be reliable in circumstances such as during or after phototherapy, after direct sunlight exposure, or at TSB levels ≥15 mg/dL. TcB can overestimate TSB in darkly pigmented infants and underestimate TBS in light-skinned infants. As a result, a confirmatory TSB should be measured if TcB is ≥13 mg/dL.
5. **Increased screening and treatment** of severe hyperbilirubinemia in otherwise healthy newborns ≥35 weeks' gestational age is based on the hour-specific bilirubin, the gestational age, and whether the infant has risk factors for bilirubin neurotoxicity. Plotting the infant's bilirubin level on the 2022 AAP CPG for the need of phototherapy (see Section VI below) can be used to chart an infant's progression of hyperbilirubinemia and ascertain the timing for closer follow-up (see Table 26.2). The rate of rise of bilirubin may provide additional information regarding severity.

D. Clinical risk factors for hyperbilirubinemia are listed in Table 26.1. Infants with risk factors require closer monitoring than those without risk factors. Determining the presence of these specific risk factors requires examining the infant, assessing laboratory data, and obtaining a family history of blood disorders or neonatal jaundice.

E. Bilirubin neurotoxicity risk factors. The presence of hyperbilirubinemia neurotoxicity risk factors lowers the threshold for treatment with phototherapy and the level at which care should be escalated (Table 26.4). Clinical signs of hemodynamic instability, sepsis, and acidemia indicate potential increased neurotoxicity risk. Lower gestational age and isoimmune hemolytic disease are risk factors for both significant hyperbilirubinemia and bilirubin neurotoxicity. Other risk factors are conditions that result in greater availability of unbound bilirubin (i.e., bilirubin not bound to albumin) and include signs of serious illness and low serum albumin (<3.0 g/dL).

Table 26.4. Hyperbilirubinemia Neurotoxicity Risk Factors

■ Gestational age <38 weeks and this risk increases with the degree of prematurity
■ Albumin <3.0 g/dL
■ Isoimmune hemolytic disease (i.e., positive DAT), G6PD deficiency, or other hemolytic conditions
■ Sepsis
■ Significant clinical instability in the previous 24 hours

DAT, direct antiglobulin test; G6PD, glucose-6-phosphate dehydrogenase.

Source: Reproduced with permission from Kemper AR, Newman TB, Slaughter JL, et al. Clinical practice guideline revision: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 2022:e2022058859. Copyright © 2022 by the American Academy of Pediatrics.

F. Bilirubin follow-up. Because the peak bilirubin level typically occurs at 72 to 96 hours, after healthy newborns are discharged from their birth hospital, follow-up is essential. Management and follow-up are guided by the predischarge bilirubin level and risk factors including gestational age (see Table 26.2). Parents should receive written and verbal instructions about the need for follow-up. A TSB gradient >7 mg/dL between measured TSB and TSB threshold should be reassuring for the resolution of elevated bilirubin level.

G. End-tidal carbon monoxide (ETCO), corrected to ambient CO, does not improve the sensitivity or specificity of predicting severe hyperbilirubinemia over TB alone. However, ETCO can identify infants with exaggerated bilirubin production due to hemolytic conditions that need closer monitoring and likely earlier intervention.

VI. EVALUATION OF INFANTS WITH HYPERBILIRUBINEMIA

A. History

1. Family history

a. A family history of jaundice, anemia, splenectomy, or early gallbladder disease suggests hereditary hemolytic anemia (e.g., spherocytosis, G6PD deficiency).

b. A family history of liver disease may suggest galactosemia, α1-antitrypsin deficiency, tyrosinosis, hypermethioninemia, Gilbert disease, Crigler-Najjar syndrome types I and II, or cystic fibrosis.

c. Ethnic or geographic origin (East Asian, South Asian, Greek, Mediterranean, Arab, African American, Hispanic, and American Indian) may suggest conditions associated with hyperbilirubinemia. A sibling with jaundice or anemia may suggest blood group incompatibility or breast milk jaundice.

2. Pregnancy history

a. Illness during pregnancy may suggest congenital viral or toxoplasmosis infection.

b. Infants of diabetic mothers are more likely to develop hyperbilirubinemia (see Chapter 2).

c. Maternal drugs may interfere with bilirubin binding to albumin, making bilirubin toxic at relatively low levels (sulfonamides, intravenous medications with benzoyl alcohol), or may trigger hemolysis in a G6PD-deficient infant (sulfonamides, nitrofurantoin, antimalarials).

3. Labor and delivery history

a. Birth trauma may be associated with extravascular bleeding and hemolysis.

b. Oxytocin use may be associated with neonatal hyperbilirubinemia, although this is controversial.

c. Infants with hypoxic-ischemic insult may have elevated bilirubin levels; causes include inability of the liver to process bilirubin and intracranial hemorrhage, and both are potential mechanisms for neurologic impairment.

d. Delayed cord clamping may be associated with neonatal polycythemia and increased bilirubin load.

4. **Infant history**
   a. Delayed or infrequent stooling may be caused by poor caloric intake or intestinal obstruction and lead to increased enterohepatic circulation of bilirubin.
   b. Poor caloric intake may decrease bilirubin uptake by the liver.
   c. Vomiting can be due to sepsis, pyloric stenosis, or galactosemia and some inborn errors of metabolism.

B. Physical examination. Jaundice results from deposition of bilirubin in the skin, mucous membranes, conjunctiva, sclera, and subcutaneous tissues. Blanching the skin with finger pressure makes it easier to observe jaundice. However, visual inspection is not a reliable indicator of serum TB level or the detection of rapidly rising levels, especially in infants with dark skin. Jaundice typically progresses in a cephalocaudal direction, starting in the face. The highest bilirubin levels are typically associated with jaundice below the knees and in the hands, although there is substantial overlap of bilirubin levels associated with jaundice progression. Comparison of skin color of the face and the leg (by flexing the hip and bringing the knees close to the face) could suggest progression of jaundice. All infants should be visually assessed for jaundice at least every 12 hours following delivery until discharge and thereafter by parents and clinicians for about 7 to 10 days until resolution. Infants with jaundice should have a bilirubin measurement and be examined for the following contributing factors:

1. Lower gestational age (<38 weeks' gestational age)
2. Small for gestational age may be associated with polycythemia and intrauterine infections. Microcephaly may be associated with congenital infections.
3. Extravascular blood including bruising, cephalohematoma, or other enclosed hemorrhage
4. Pallor associated with hemolytic anemia or extravascular blood loss
5. Petechiae may suggest congenital infection, sepsis, or erythroblastosis.
6. Hepatosplenomegaly may be associated with hemolytic anemia, congenital infection, or liver disease.
7. Omphalitis or other sign of infection
8. Congenital infection, sometimes associated with chorioretinitis
9. Evidence of hypothyroidism (see Chapter 61)
10. Down syndrome

C. Additional laboratory tests should be performed when TSB is at or near the threshold for initiation of phototherapy.

1. **The mother's blood type, Rh, and antibody screen** done during pregnancy should be reviewed, and the antibody screen should be repeated at delivery.
2. **The infant's blood type, Rh, and DAT (Coombs test)** to assess for isoimmune hemolytic disease. Infants of Rh-negative women should have a blood type, Rh, and DAT (Coombs test) performed at birth. Routine blood typing and DAT of infants born to O Rh-positive mothers to determine risk for ABO incompatibility is unnecessary. Such testing is

indicated in infants with clinically significant hyperbilirubinemia and can be considered in those in whom follow-up is difficult or whose increased skin pigmentation may limit recognition of jaundice.

3. **Serial TSB/TcB measurements** will document a natural progression of neonatal bilirubinemia to either resolution or benign hyperbilirubinemia (Fig. 26.1) or, to a significant level requiring intervention (thresholds for phototherapy). TSB should be measured if the TcB is within 3.0 mg/dL of the designated phototherapy treatment threshold, if the TcB exceeds the phototherapy treatment threshold, or if the TcB is ≥13 to 15 mg/dL. If more than one TcB or TSB measure is available, the rate of rise may be used to identify possible hemolysis. A rapid rate of rise (≥0.3 mg/dL/hour in the first 24 hours or ≥0.2 mg/dL/hour thereafter) is exceptional and indicates increased bilirubin production most often due to hemolysis. In such situations, a DAT should be determined if not previously done and may include an elution search for specific isoimmune antibodies. If an infant is at high risk of developing significant hyperbilirubinemia and needing phototherapy, but the threshold has not been met and appropriate follow-up cannot be assured, it may be reasonable to delay discharge until appropriate follow-up can be assured or the period of greatest risk has passed (i.e., 72 to 96 hours) and the rate of rise of TSB has decreased.
4. **Peripheral smear for RBC morphology and reticulocyte count** to detect causes of Coombs-negative hemolytic disease (e.g., HS). HS occurs in about 1 per 2,000 births and may be missed if family history alone is used for screening, as many cases are *de novo*, and HS may be autosomal recessive in infants of Japanese ancestry. In one report, a mean corpuscular hemoglobin concentration of ≥36.0 g/dL had 82% sensitivity and 98% specificity for diagnosing HS.

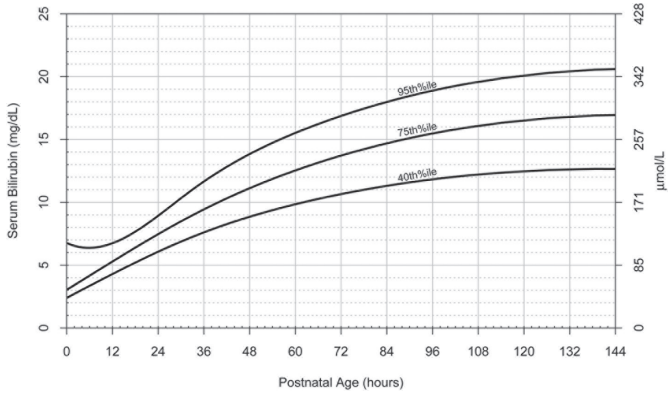

Figure 26.1. Hour-specific bilirubin percentile curves at 40th, 75th, and 95th percentiles (0 to 144 postnatal hours) that represent a natural bilirubin profile in 397,395 otherwise healthy term and late preterm neonates without overt hemolysis.

5. **Hematocrit** or hemoglobin measurement will identify polycythemia or suggest blood loss from occult hemorrhage.
6. **Identification of specific antibody** on the infant's RBCs (if result of direct DAT test is positive)
7. **Direct or conjugated bilirubin** should be measured with significant hyperbilirubinemia and prior to an intervention. Total and direct (or conjugated) bilirubin levels (see section IV.A.5) should be measured in breastfed infants who remain jaundiced at 3 to 4 weeks of age and in formula-fed infants who remain jaundiced at 2 weeks or with signs of cholestasis (light-colored stools and bilirubin in urine). If direct bilirubin is elevated, urinalysis and urine culture should be obtained; state newborn screen should be checked for hypothyroidism, tyrosinemia, and galactosemia; and urine should be checked for reducing substances (see section X, neonatal cholestasis).
8. **Other tests** for liver disease, congenital infections, sepsis, metabolic defects, or hypothyroidism are indicated for infants with prolonged jaundice.
9. **G6PD measurement** may be helpful when family history is suggestive of African, East/South Asian, Mediterranean, or Middle Eastern/Arab descent; nonphysiologic hyperbilirubinemia; or at a threshold to likely need phototherapy. The incidence of G6PD deficiency among African Americans males is 11% to 13%, comprising the most affected subpopulation among the non-white population in the United States. G6PD activity should be measured in any infant with jaundice of unknown cause whose TSB rises despite effective phototherapy, whose TSB rises suddenly or rises after an initial decline, or who requires escalation of care. If G6PD deficiency is strongly suspected but the measurement of G6PD activity is normal or close to normal, especially in a female newborn, the G6PD activity should be measured again at least 3 months later.

D. Prolonged indirect (unconjugated) hyperbilirubinemia (7 days or longer) should be confirmed by measuring both TB and serum direct-reacting or conjugated bilirubin (i.e., a fractionated bilirubin measure) to determine the indirect bilirubin level (the difference between the total and the direct-reacting or conjugated bilirubin). Direct bilirubin and unconjugated bilirubin are not synonymous assays, and each has its normal range values. Most of these infants have breast milk jaundice, but other causes include hemolytic disease, hypothyroidism, extravascular blood, pyloric stenosis with Gilbert disease, and Crigler-Najjar syndrome. Limited studies suggest that prolonged exposure to indirect hyperbilirubinemia might be associated with an increased risk of neurotoxicity, although other studies have not found this association.

VII. FAMILY AND CAREGIVER EDUCATION.

Clinical care emphasizes the continual implementation of universal systematic assessment for the risk of severe hyperbilirubinemia, close follow-up, and prompt intervention. Prior to hospital discharge, all caregivers should receive institutional guidance with written and verbal instruction about jaundice and the risk of kernicterus. Clinicians should ensure that caregivers are educated and understand information that facilitates individualized postdischarge care including the date, time, and place of the follow-up appointment and, when necessary, any prescriptions and appointments for follow-up testing.

Table 26.5. Clinical Signs of Progressive Bilirubin Neurotoxicity

Clinical Signs	Early	Moderate	Advanced	Neurologic Outcomes
Mental status	Sleepy but arousable	Lethargy, poor suck, irritable or jittery	Semicoma, apneic spells, seizures, unable to feed, coma	Often reversible with timely and effective phototherapy
Muscle tone	Mild to moderate hypotonia	Persistent hypotonia during sleep; hypertonia with neck and back arching	Persistent retrocollis or opisthotonus; bicycling	Often reversible with timely intervention with exchange transfusion
Cry pattern (attributed to painful spasms)	High pitched when aroused	Shrill; difficult to control	Inconsolable, weak cry or absent cry	Interventions can be critical and lifesaving procedures.

Note: A recently referred test result for automated auditory brainstem response during the acute phase of acute bilirubin encephalopathy is a sign of progressive bilirubin neurotoxicity.

Source: Johnson L, Bhutani VK, Karp K, et al. Clinical report from the pilot USA Kernicterus Registry (1992 to 2004). *J Perinatol* 2009;29(suppl 1):S25–S45. doi:10.1038/jp.2008.211.

VIII. CLINICAL MANAGEMENT

A. Management of unconjugated hyperbilirubinemia is directed at prevention of severe hyperbilirubinemia, defined as TSB >20 g/dL in term and late-preterm infants, and presumably lower values in more immature infants. Supplementation with enteral intake of water or dextrose water does not prevent hyperbilirubinemia and does not decrease TSB levels. TSB is used to guide all interventions and is modified by the presence of clinical **neurotoxicity risk factors** (see Table 26.4) that increase the risk of neurologic injury because they interfere with binding of bilirubin to albumin, increase permeability of the blood–brain barrier, or make brain cells more susceptible to damage by bilirubin. Lower gestational age also increases risk of toxicity. Intervention in preterm infants is guided by gestational and postmenstrual age.

1. Decisions to initiate phototherapy or escalate care are guided by the gestational age, the hour-specific TB, and the identification of clinical bilirubin neurotoxicity as manifested by signs of encephalopathy (Tables 26.4 and 26.5). The presence of hyperbilirubinemia neurotoxicity risk factors or clinical signs lowers the threshold for treatment with phototherapy and the TSB level at which intervention should be escalated.

Other considerations include clinical (hemodynamic) instability, sepsis, or acidemia (recent or antecedent).

2. Lower gestational age and isoimmune hemolytic disease are risk factors both for developing significant hyperbilirubinemia and for bilirubin neurotoxicity. Low serum albumin can increase the risk of neurotoxicity because of the greater availability of unbound bilirubin (bilirubin not bound to albumin). Currently, data are insufficient to guide clinical care using specific unbound bilirubin levels. Experts consider an albumin level <3.0 g/dL to be a key hyperbilirubinemia neurotoxicity risk factor. Measuring albumin is recommended to evaluate the need for escalation of care.

B. Phototherapy is the initial intervention used to treat and prevent severe hyperbilirubinemia in asymptomatic infants. Effective phototherapy is recommended by the 2022 AAP CPG at the TSB thresholds in Figures 26.2, and 26.3. These thresholds are based on gestational age, neurotoxicity risk

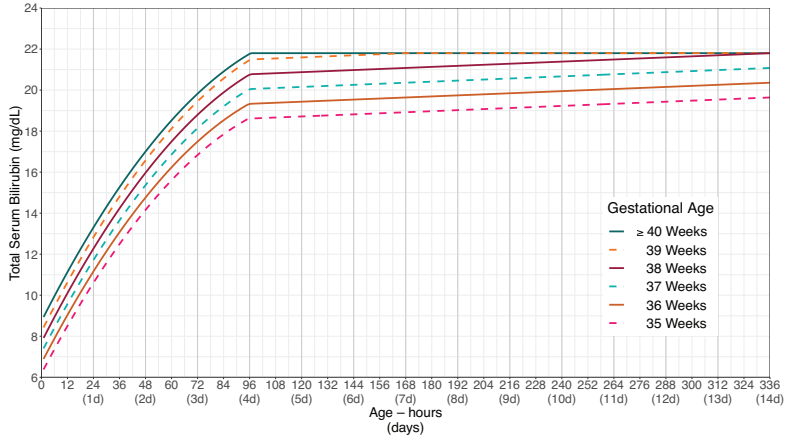

Figure 26.2. Phototherapy thresholds* by gestational age and age in hours for infants with **NO** recognized hyperbilirubinemia neurotoxicity risk factors† other than gestational age. *These thresholds are based on expert opinion rather than strong evidence on when the potential benefits of phototherapy exceed its potential harms. Use total serum bilirubin (TSB) levels; do not subtract direct-reacting or conjugated bilirubin from the TSB. In rare cases of severe hyperbilirubinemia, where the direct-reacting or conjugated bilirubin exceeds 50% of the TSB, consult an expert. Note that infants younger than 24 hours old with a TSB at or above the phototherapy threshold are likely to have a hemolytic process and should be evaluated for hemolytic disease as described in recommendation 14. †Hyperbilirubinemia neurotoxicity risk factors include gestational age <38 weeks; albumin <3.0 g/dL; isoimmune hemolytic disease; glucose-6-phosphate dehydrogenase deficiency; possibly other hemolytic conditions, sepsis; or any significant clinical instability in the previous 24 hours. (Reproduced with permission from Kemper AR, Newman TB, Slaughter JL, et al. Clinical practice guideline revision: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 2022:e2022058859.)

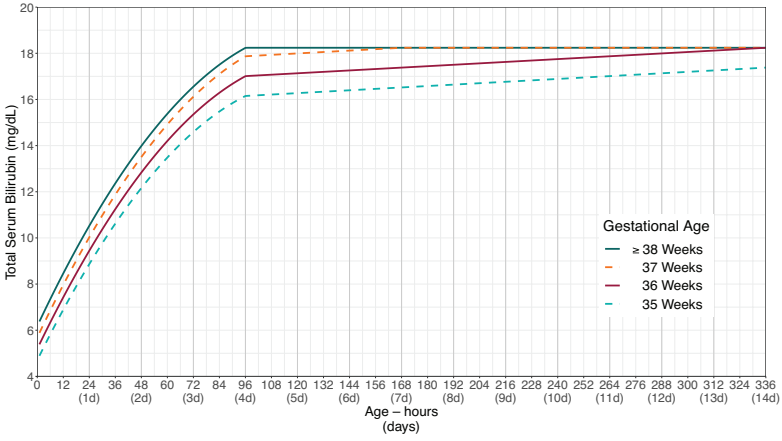

Figure 26.3. Phototherapy thresholds* by gestational age and age in hours for infants with ANY recognized hyperbilirubinemia neurotoxicity risk factors† other than gestational age. *These thresholds are based on expert opinion rather than strong evidence on when the potential benefits of phototherapy exceed its potential harms. Use total serum bilirubin (TSB) levels; do not subtract the direct-reacting or conjugated bilirubin from the TSB. In rare cases of severe hyperbilirubinemia, where the direct-reacting or conjugated bilirubin exceeds 50% of the TSB, consult an expert. †Hyperbilirubinemia neurotoxicity risk factors include gestational age <38 weeks; albumin <3.0 g/dL; isoimmune hemolytic disease; glucose-6-phosphate dehydrogenase deficiency; possibly other hemolytic conditions, sepsis; or any significant clinical instability in the previous 24 hours. (Reproduced with permission from Kemper AR, Newman TB, Slaughter JL, et al. Clinical practice guideline revision: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 2022:e2022058859. Copyright © 2022 by the American Academy of Pediatrics.)

factors, and age of the infant in hours. Phototherapy is provided to infants with clinical risk factors of bilirubin neurotoxicity or with any signs of acute bilirubin encephalopathy (ABE) while preparations are made for escalation of care (see Table 26.5 and Figure 26.4). TSB typically declines within a few hours of treatment initiation. The rate of decline is increased by increased irradiance and more exposed surface area.

1. **Mechanisms of bilirubin reduction by phototherapy.** Photons of light in the blue-green spectrum reach circulating bilirubin in the cutaneous and subcutaneous structures and alter the structure of bilirubin.

   a. Structural isomerization of bilirubin is induced by light (photons) that irreversibly converts bilirubin to lumirubin, a more soluble substance that can be excreted into bile and urine without conjugation.

   b. Photoisomerization rapidly converts about 15% of the 4Z,15Z bilirubin isomer to the less toxic 4Z,15E form. Although the less toxic isomer can be excreted into bile without conjugation, the process is reversible and clearance is slow. Standard laboratory tests do not

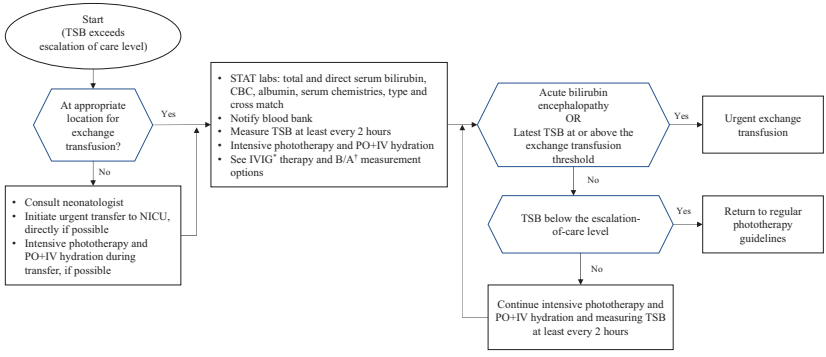

Figure 26.4. Approach to escalation of care. The escalation-of-care threshold is 2 mg/dL below the exchange transfusion threshold. (Reproduced with permission from Kemper AR, Newman TB, Slaughter JL, et al. Clinical practice guideline revision: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 2022:e2022058859. Copyright © 2022 by the American Academy of Pediatrics.)

distinguish between the isomers, so TB levels may not change, although may be less toxic.

c. Photo-oxidation is a slower process that converts bilirubin to small polar products that are excreted in the urine and is the least important mechanism of bilirubin elimination.

2. **Characteristics of phototherapy delivery devices.** Among the multiple devices available for phototherapy, the most effective are characterized by the following:

a. Light emission in the narrow blue-green spectrum to the skin surface (460 to 490 nm; ideal peak at 478 nm), which includes the region (460 nm) where bilirubin most strongly absorbs light

b. Irradiance of at least 30 $\mu W/cm^2/nm$ (range, 25 to 35 $\mu W/cm^2/nm$) in term and late-preterm babies

c. Illumination of maximal exposure of the body surface area (orbits and genital area protected)

d. Shown to decrease TSB during first 4 to 6 hours of exposure

3. **Features of light sources**

a. Blue light-emitting diodes (LEDs) provide optimal high-intensity light in the absorption spectrum of bilirubin, available as either overhead or underneath (mattress or fiberoptic pad) devices effectively lower circulating TSB.

b. Fiberoptic blankets or pads can be placed directly under the infant and are sometimes used as adjuvants to enhance body surface exposure. Due to their small size, they rarely cover enough surface area to be effective when used alone in term infants and thus are typically used together with overhead lights when escalation of care is indicated.

c. U.S. Food and Drug Administration-approved devices that meet International Electrotechnical Commission standards filter the light sources for radiation and ultraviolet light exposures.

4. **Initiation of phototherapy administration**
   a. Exposure during phototherapy should be as extensive as possible, minimizing the area covered by a diaper.
   b. An opaque mask should shield the eyes, avoid occlusion of the nose, and provide comfort.
5. **Sunlight exposure.** Although sunlight exposure effectively lowers TSB level, safety concerns, including exposure to ambient ultraviolet light, potential sunburn, and thermal effects, preclude use of sunlight as a reliable therapeutic tool. In low-resource settings, use of appropriate filters and thermal monitoring may allow use of filtered sunlight for phototherapy.
6. **Bilirubin monitoring.** **TSB level** is monitored during phototherapy to document response to therapy. For hospitalized infants, TSB should be measured within 12 hours after starting phototherapy. The timing of this measurement and the frequency of TSB monitoring during phototherapy is guided by the infant's age, the presence of neurotoxicity risk factors, the TSB level, and the trajectory of TSB. Although exposure to phototherapy results in immediate degradation of bilirubin, clinicians may measure TB 2 to 3 hours after initiation of phototherapy to ensure that TB is decreasing. TB is also measured 1 to 2 days after discontinuation of phototherapy to assess for rebound of the TB level.
7. **Adverse effects of phototherapy.** Phototherapy is generally considered safe in term and late-preterm neonates. Risk–benefit analysis favors its use, and the known potential adverse effects are avoidable or transient. Temperature is monitored to avoid temperature instability. Monitoring of urine output and weight allows early detection of increased insensible water loss that may lead to dehydration. Occurrence of loose stools or any erythematous rash, if present, is typically transient. Due to a potential risk of retinal injury or degeneration seen in animals after 24 hours of fluorescent phototherapy exposure and for reasons of infant comfort, eyes are covered in all newborns undergoing phototherapy.
   a. "Bronze baby" syndrome. Some infants with direct hyperbilirubinemia (cholestatic jaundice) undergoing phototherapy may develop nontoxic transient dark bronze discoloration of the skin thought to be related to impaired excretion of photoproducts of bile pigment.
8. **Hydration and urine output** should be maintained to promote urinary excretion of lumirubin. Transition from meconium to increasing yellow-colored stool is reassuring that bilirubin metabolites are being eliminated. Feedings by breast or bottle should continue during phototherapy unless TSB is approaching the level for exchange transfusion; in that case, feeding should not interrupt phototherapy until TB has fallen below 20 mg/dL. Breastfed infants with inadequate intake or excessive weight loss should be supplemented with expressed breast milk or formula. Breastfeeding, if interrupted, should resume as soon as possible.

Table 26.6. Potential Eligibility of Discharged Infants for Home Phototherapy

■ Gestational age ≥38 weeks, postnatal age >48 hours
■ Clinically well with adequate oral feeding
■ No known clinical risk for significant hyperbilirubinemia other than TSB level (see Table 26.1)
■ No discernible bilirubin neurotoxicity risk factors (see Table 26.2)
■ No previous use of phototherapy
■ TSB level no more than 1 mg/dL above the phototherapy treatment threshold (see Figures 26.2 and 26.3)
■ An LED-based phototherapy device implemented at home without delay
■ Capacity for daily TSB measurement.

TSB, total serum bilirubin; LED, light-emitting diode.

Source: Data from Kemper AR, Newman TB, Slaughter JL, et al. Clinical practice guideline revision: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 2022:e2022058859.

9. **Home phototherapy** is an effective (Table 26.6), less expensive option than hospital phototherapy, and easy to implement with the use of LED fiberoptic blankets. However, it may not have the same irradiance or surface area exposure as hospital phototherapy. According to the AAP CPG, for infants who develop a TSB above the phototherapy threshold after hospital discharge, treatment with a home LED-based phototherapy device rather than readmission to the hospital is an option for those who meet the following criteria: (i) gestational age ≥38 weeks, (ii) postnatal age ≥48 hours old, (iii) clinically well with adequate feeding, (iv) no known hyperbilirubinemia neurotoxicity risk factors (see Table 26.4), (v) no previous phototherapy, (vi) TSB level no more than 1 mg/dL above the phototherapy treatment threshold (see Figs. 26.2, 26.3, and 26.4), (vii) an LED-based phototherapy device will be available in the home without delay, and (viii) TSB can be measured daily. However, its cost-effectiveness and safety for use in infants with unpredictable rate of bilirubin rise with hemolytic hyperbilirubinemia has not been adequately validated.

C. Pharmacologic therapy. No validated chemopreventive agents currently exist for neonatal hyperbilirubinemia. Intravenous immunoglobulin (IVIG) (0.5 to 1 g/kg IVIG over 2 hours, repeated in 12 hours, if needed) has been used in infants with isoimmune hemolytic diseases, especially Rh disease. For ABO incompatibility, it may be used when TSB continues to rise despite intensive phototherapy and is within 2 or 3 mg/dL of the threshold

recommended for exchange transfusion. The mechanism of its protective action is unknown, and an association IVIG use and necrotizing enterocolitis has been reported.

D. Excessive hyperbilirubinemia. TSB rising to exchange thresholds is a medical emergency and escalation of care needs to be initiated, including preparation for an exchange transfusion. Escalation of care refers to the intensive care of infants with rapidly rising bilirubin levels who are likely to need an exchange transfusion in order to possibly prevent kernicterus (Figures 26.5 and 26.6 and Tables 26.4, 26.5, and 26.6). The TSB threshold for escalated care is 2 mg/dL below the exchange transfusion threshold. The direct-reacting or conjugated bilirubin value should not be subtracted from the TB value when determining management.

1. The escalation-of-care period continues until the TSB is below the escalation of care threshold.
2. Optimal management occurs in a neonatal intensive care unit (NICU). If the current facility is unable to perform an emergency exchange transfusion, a neonatologist should be consulted emergently and the

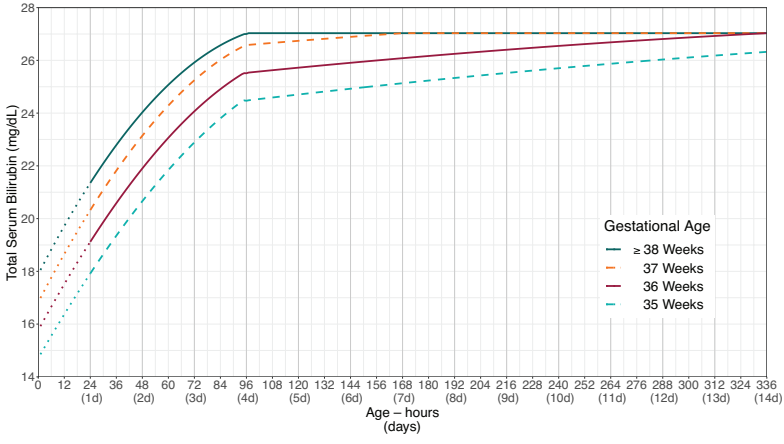

Figure 26.5. Exchange transfusion thresholds* by gestational age for infants with NO recognized hyperbilirubinemia neurotoxicity risk factors† other than gestational age. *These thresholds are based on expert opinion rather than strong evidence on when the potential benefits of escalation of care exceed its potential harms. The *stippled lines* for the first 24 hours indicate uncertainty due to the wide range of clinical circumstances and responses to intensive phototherapy. Use total serum bilirubin (TSB) levels; do not subtract direct bilirubin from the TSB. In rare cases of severe hyperbilirubinemia, where the direct-reacting or conjugated bilirubin exceeds 50% of the TSB, consult an expert. †See Table 26.4. (Reproduced with permission from Kemper AR, Newman TB, Slaughter JL, et al. Clinical practice guideline revision: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 2022:e2022058859. Copyright © 2022 by the American Academy of Pediatrics.)

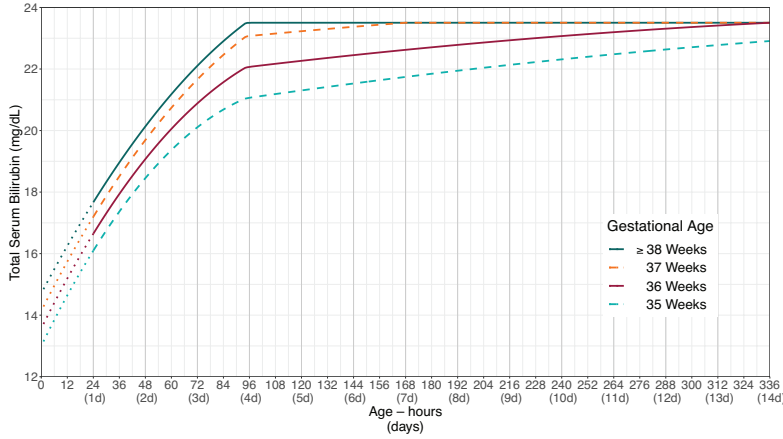

Figure 26.6. Exchange transfusion thresholds* by gestational age for infants with **ANY** recognized hyperbilirubinemia neurotoxicity risk factors† other than gestational age. *See text which describes escalation of care. These thresholds are based on expert opinion rather than strong evidence on when the potential benefits of escalation of care exceed its potential harms. The *stippled lines* for the first 24 hours indicate uncertainty due to the wide range of clinical circumstances and responses to intensive phototherapy. Use total serum bilirubin (TSB) levels; do not subtract direct bilirubin from the TSB. In rare cases of severe hyperbilirubinemia, where the direct-reacting or conjugated bilirubin exceeds 50% of the TSB, consult an expert. †Hyperbilirubinemia neurotoxicity risk factors include albumin <3.0 g/dL; isoimmune hemolytic disease; glucose-6-phosphate dehydrogenase deficiency; possibly other hemolytic conditions, sepsis; or any significant clinical instability in the previous 24 hours. (Reproduced with permission from Kemper AR, Newman TB, Slaughter JL, et al. Clinical practice guideline revision: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 2022:e2022058859. Copyright © 2022 by the American Academy of Pediatrics.)

infant should be immediately transferred to a NICU that can perform the exchange transfusion with continued escalated phototherapy.

3. Intensive phototherapy and intravenous hydration should be initiated and continued during a hospital transfer.
4. Whenever possible, the infant should be admitted directly to the NICU rather than through the emergency department to avoid delay in care.
5. Blood should be sent STAT for total and direct-reacting serum bilirubin, a complete blood count, serum albumin, serum chemistries, and type and cross-match. A TcB obtained prior to use of phototherapy may guide the urgency of initial care while TSB results are awaited. Note that most TcB devices will report an "error" value for bilirubin levels >20 mg/dL.
6. TSB should be measured at least every 2 hours from the start until the end of the escalation-of-care period.
7. When the TSB is lower than the escalation-of-care threshold, management should proceed according to routine guidelines.

Table 26.7. Use of Bilirubin to Albumin Ratio with Gestational Age and Risk of Neurotoxicity to Consider Exchange Transfusion

Gestational Age (weeks)	Bilirubin Neurotoxicity Risk Factor	Bilirubin/Albumin Ratio (mg/dL/g/dL)
≥38	None	≥8.0
≥38	+ 1, or more	≥7.2
35–37	None	≥7.2
35–37	+ 1, or more	≥6.8
<35*	There is no current evidence that bilirubin/albumin ratios are predictive of bilirubin neurotoxicity. Both bilirubin binding capacity and unbound bilirubin are proposed as biomarkers in research studies.*	

*From Götze T, Blessing H, Grillhösl C, et al. Neonatal cholestasis—differential diagnoses, current diagnostic procedures, and treatment. *Front Pediatr* 2015;3:43.

Source: Data from Kemper AR, Newman TB, Slaughter JL, et al. Clinical practice guideline revision: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 2022:e2022058859.

E. Exchange transfusion is now a rare but life-saving measure that rapidly removes bilirubin when escalated phototherapy fails to prevent a rise in bilirubin to potentially toxic levels or when infants have progressive neurologic signs to moderate or advanced acute bilirubin toxicity (see Figures 26.5 and 26.6). Exchange transfusion is the most effective method for immediate, rapid removal of bilirubin and can be life-saving. In cases of isoimmune hemolytic disease, exchange transfusion also removes antibody and sensitized RBCs which are replaced with donor RBCs lacking the sensitizing antigen. Bilirubin/albumin ratio may be considered prior to an exchange transfusion based on gestational age and association of clinical bilirubin neurotoxicity risk factors (Table 26.7).

1. Immediately after a double volume exchange transfusion (about 160 to 180 mL/kg), TSB values are typically half the value prior to the procedure. After 30 to 60 minutes, extravascular bilirubin rapidly equilibrates with the reduced vascular level, so that TSB levels return to approximately two-thirds of preexchange levels. Following blood volume equilibration, approximately 85% of the circulating RBCs are replaced.
2. The ideal donor product is fresh type O Rh-negative irradiated packed RBCs that are resuspended in AB plasma and cross-matched against maternal plasma and cells. The unit is reconstituted to a hematocrit of 50% to 55%. In isoimmune non-ABO hemolytic disease, the blood should not contain the sensitizing antigen.
3. The volume ordered should account for tubing losses (~30 mL) plus twice the infant's estimated blood volume (i.e., 2 times 80 to 90 mL/kg).

4. During blood administration, a thermal monitored blood warmer is used to maintain donor blood temperature at 37°C. The blood reservoir is stirred to avoid infusion of pooled or sludged blood product. The entire duration of the exchange procedure rarely exceeds 2 hours.

5. Ideally, an expert skilled in exchange transfusions should lead the procedure. It is usually performed through an umbilical venous catheter using a push–pull technique in which aliquots of the patient's blood are removed and replaced with the donor blood. Individual aliquots should be approximately 10% or less of the infant's blood volume, with a maximum volume of 20 mL for a term baby who weighs more than 3 kg and smaller volumes in babies with physiologic instability. Alternatively, in a very small or unstable baby, blood can be steadily withdrawn from an umbilical artery catheter at a rate of 2 to 4 mL/kg/minute while an equivalent volume is slowly infused at the same rate through a venous catheter (an isovolumic procedure). Other central vascular access may be used if the umbilical vessels cannot be accessed.

6. Albumin. Some clinicians have advocated infusion of 5% albumin 1 to 2 hours before the exchange transfusion in an attempt to facilitate bilirubin removal by promoting entry of extravascular bilirubin into the circulation. However, this intervention is unproven and could inadvertently result in hemodynamic overload in infants with increased intravascular volume (overload) or worsening hydrops. We avoid use of 25% albumin in view of its cardiopulmonary and circulatory side effects in infants.

7. Escalated phototherapy should be resumed after the exchange transfusion, and TSB should be monitored at 2, 4, and 6 hours after the procedure and then at least every 12 to 24 hours until TB declines sufficiently to discontinue phototherapy. Exchange transfusion may need to be repeated for increasing TSB or recurrent neurologic signs.

8. Clinical monitoring. Infants should be monitored for complications that are related to the procedure and use of blood products. Common complications include circulatory imbalance, thrombocytopenia, and coagulation abnormalities; hypoglycemia, hyperkalemia, and hypocalcemia; and acid–base abnormalities. Less frequent complications include necrotizing enterocolitis (see Chapter 27), portal vein thrombosis (probably due to umbilical catheter placement), air embolism, thromboembolism, cardiac arrhythmias, and both bacterial and viral infections.

IX. BILIRUBIN NEUROTOXICITY. Long-term sequelae occur following entry and deposit of bilirubin in the brain that may result in lifelong neurologic neurotoxicity that is structural or could be subtle. Extreme hyperbilirubinemia (TSB >25 mg/dL) is associated with increased risk in term or late-preterm infants; the level of risk in preterm infants is uncertain but presumed to be at lower thresholds. Exchange transfusion minimizes severity of injury and, if timely, may be preventive. Unconjugated bilirubin that is not bound to albumin is a potential toxin that can enter the brain and cause apoptosis and/or necrosis.

FFAs and certain drugs (e.g., ceftriaxone) may displace bilirubin from albumin and promote entry into the brain. If the blood–brain barrier is vulnerable due to conditions such as prematurity or disrupted by factors including hyperosmolarity, asphyxia, and hypercarbia, bilirubin can also enter the brain bound to albumin. Acidosis affects bilirubin solubility and promotes its deposition into brain tissue. The brain regions typically affected by bilirubin toxicity include the basal ganglia, cerebellum, white matter, and the brainstem nuclei for oculomotor and auditory function. Neurologic manifestations of bilirubin toxicity reflect the areas of the brain that are most often affected and are often called bilirubin-induced neurologic disorders or kernicterus spectrum disorders. These are sometimes reversible but mostly permanent.

A. ABE is the clinical manifestation of acute bilirubin toxicity seen in the neonatal period. ABE consists of three phases:

1. **Early phase.** Signs are subtle and may include lethargy, hypotonia, high-pitched cry, and poor suck. These may be reversible with timely intervention.
2. **Intermediate phase** is characterized by hypertonia of extensor muscles (rigidity, opisthotonus, and retrocollis), oculogyric crisis, irritability, fever, and seizures and may result in death. Infants who survive this phase typically develop chronic bilirubin encephalopathy (kernicterus). Timely exchange transfusion and phototherapy may minimize the severity of damage.
3. **Advanced phase.** Signs include pronounced opisthotonus and retrocollis, cry that can be weak or shrill, apnea, seizures, and coma. Affected infants die from intractable seizures or respiratory failure. Escalated phototherapy and exchange transfusion can be lifesaving.

B. Kernicterus, chronic bilirubin encephalopathy, is the chronic and permanent sequelae of bilirubin toxicity that develop during the first year after injury. Most infants who develop kernicterus have had signs of ABE in the neonatal period, although some have a history of high TSB level with few or unrecognized signs of ABE. The classic signs of kernicterus are the following:

1. Choreoathetoid hypertonic or hypotonic cerebral palsy with neuromotor impairments
2. Sensorineural hearing loss, characterized by abnormal brainstem **auditory evoked response with normal otoacoustic emission testing**
3. Limitation of upward gaze
4. Dental enamel dysplasia
5. Increased signal intensity of globus pallidus on magnetic resonance imaging

C. Subtle syndrome of bilirubin-induced neurologic dysfunction has been proposed as a spectrum of neurologic manifestations among vulnerable infants who have experienced a less extreme exposure to bilirubin. Clinical neuromotor manifestations include a range of subtle processing disorders as well as objective disturbances of visual-motor, auditory (sometimes isolated), speech, cognition, and language.

X. NEONATAL CHOLESTASIS.

Neonatal cholestasis or conjugated hyperbilirubinemia is due to failure to excrete bile. This may be caused by defects in intrahepatic bile production, defects in transmembrane transport of bile, or mechanical obstruction to flow. Conjugated hyperbilirubinemia is defined as a direct or conjugated bilirubin level >1 mg/dL bilirubin. Conjugated or direct bilirubin more than 10% of total serum/plasma bilirubin (and TSB <5 mg/dL) is also considered the 95th percentile threshold for healthy newborns. Higher levels are often associated with hepatomegaly, splenomegaly, pale stools, and dark urine. An infant with jaundice at 2 weeks of age should be evaluated for cholestasis by measuring total and direct (or conjugated) bilirubin level. Rapid diagnosis is important so that therapy for treatable disorders can be started promptly.

A. Disorders associated with neonatal cholestasis include the following, as well as others not listed.

1. **Obstructive bile duct disorders.** Biliary atresia is a frequent cause and must be identified promptly so that intervention (hepatoportoenterostomy) can be performed before 2 months of age. This condition may be associated with situs inversus, polysplenia or asplenia, and cardiac anomalies. Another cause of cholestasis is Alagille syndrome, which is characterized by unusual facial appearance, ocular abnormality (posterior embryotoxon), cardiac abnormalities (pulmonic stenosis), and vertebral anomalies (butterfly vertebrae). Choledochal duct cysts are uncommon but surgically treatable.
2. **Infectious causes** include sepsis and urinary tract infections as well as infections caused by numerous viral, bacterial, spirochetal, and other organisms.
3. **Metabolic disorders** include α1-antitrypsin deficiency, cystic fibrosis, galactosemia, tyrosinemia, galactosemia, storage diseases (Gaucher, Niemann-Pick), Zellweger syndrome, mitochondrial disorders, and congenital disorders of glycosylation.
4. **Immunologic disorders** include gestational alloimmune liver disease (formerly neonatal hemochromatosis) and neonatal lupus erythematosus.
5. **Endocrine disorders** include hypothyroidism and panhypopituitarism.
6. **Toxic disorders.** A frequent cause of cholestasis in the NICU occurs in infants unable to take enteral feeding who have prolonged courses of parenteral nutrition (PN) including lipid. This condition typically resolves with introduction of enteral feedings.
7. **Isoimmune hemolysis.** Conjugated hyperbilirubinemia occurs in a small proportion of infants with excessive hemolysis such as ABO/Rh incompatibility and may persist for 2 to 6 weeks.

B. Diagnosis

1. History and findings on physical examination may support a specific diagnosis and urgent evaluation. Acholic stools suggest obstruction.
2. Laboratory studies to evaluate LFT include total and direct or conjugated bilirubin, serum alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transpeptidase, alkaline phosphatase, and coagulation studies.

Specific laboratory studies should be performed based on findings from the history and physical examination. These include tests for infections and metabolic, genetic, or endocrine disorders.

3. Abdominal ultrasonography may suggest biliary atresia by failure to visualize the gallbladder or presence of the triangular cord sign. Choledochal duct cyst, gallstones, or vascular malformations may be identified.
4. Hepatobiliary scintigraphy with technetium-labeled iminodiacetic acid analogues may distinguish biliary atresia from other causes of cholestasis such as neonatal hepatitis. Bilirubin concentration measured in a duodenal aspirate and compared to serum concentration is an alternative to scintigraphy to assess bile excretion.
5. Percutaneous liver biopsy may be needed to evaluate cholestatic jaundice.
6. If studies support a diagnosis of biliary atresia, intraoperative cholangiography is performed. If biliary obstruction is demonstrated, a hepatoportoenterostomy (Kasai procedure) is performed.

C. Management of PN-associated cholestasis. Most cholestasis in the NICU is due to prolonged exposure to PN (see Chapter 21).

1. Enteral feedings, even at minimal volumes of 10 mL/kg/day, are initiated as soon as possible. If enteral feedings can be established, infants with persistent cholestasis and abnormal LFTs are supplemented with fat-soluble vitamin supplements (vitamins A, D, E, and K). If cholestasis persists as enteral feedings are increased, we consider use of ursodiol.
2. In infants unable to take enteral feedings and who continue on PN, LFTs are checked weekly. Copper and manganese, trace metals that are excreted in bile, are reduced or eliminated. We discontinue intralipid administration and substitute parenteral fish oil (Omegaven 10% fish oil emulsion, 1 g/kg/day—Fresenius Kabi, Homburg, Germany) on an investigational protocol in infants with PN-associated liver disease.

Suggested Readings

Bhutani VK, Konecny CM, Wong RJ. Mechanistic aspects of phototherapy for neonatal hyperbilirubinemia. In: Polin RA, Abman SH, Rowitch DH, et al, eds. *Fetal and Neonatal Physiology*. 6th ed. Philadelphia, PA: Elsevier Saunders; 2022:930–940.

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Götze T, Blessing H, Grillhösl C, et al. Neonatal cholestasis—differential diagnoses, current diagnostic procedures, and treatment. *Front Pediatr* 2015;3:43.

Kemper AR, Newman TB, Slaughter JL, et al. Clinical practice guideline revision: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics* 2022:e2022058859.

27 Necrotizing Enterocolitis

Cicely W. Fadel and Misty Good

KEY POINTS

- Necrotizing enterocolitis (NEC) remains the most common and most devastating surgical emergency in the neonatal intensive care unit (NICU).
- The etiology is multifactorial and different for preterm and term infants. Immature intestinal barrier function, formula feeding, bacterial dysbiosis, and a dysregulated host response are key factors in typical NEC of the preterm infant.
- The diagnosis is made by a combination of clinical and radiographical signs and can be confirmed by histopathology.
- Treatment includes gastric decompression, bowel rest, and broad-spectrum antimicrobial therapy. Transfer to a surgical center may be indicated.
- Current best evidence for reducing NEC risk exists for antenatal steroid use, standardized enteral feeding guidelines, use of human milk, avoidance of acid blockade, and minimization of empiric antibiotic exposure.
- The standard use of probiotics is an active area of study that remains controversial due to the lack of U.S. Food and Drug Administration (FDA)-approved pharmaceutical-grade products.

I. BACKGROUND.

Necrotizing enterocolitis (NEC) is the most common and most serious gastrointestinal (GI) emergency of the neonate. Its pathogenesis is complex and multifactorial, and the etiology remains unclear. In spite of the advances in neonatology over the last several decades, the mortality and morbidity secondary to NEC remains high. Current clinical practice is directed mainly toward prompt, early diagnosis and institution of proper intensive care management.

A. Definition.

NEC is characterized by inflammation and cell death of the distal small and often proximal large intestine. Surgical pathology reveals segmental coagulative necrosis of the mucosa with focal hemorrhage as evidence for ischemia. Other features include intramural gas (pneumatosis intestinalis) and sloughing of mucosa, submucosa, and muscularis mucosa,

which is in contrast to the preserved mucosal integrity in spontaneous intestinal perforation (SIP). Universally accepted risk factors include prematurity, bacterial dysbiosis, and formula feeding.

B. Epidemiology. Despite decades of research, NEC remains the most common serious surgical disorder among infants in a neonatal intensive care unit (NICU) and is a significant cause of neonatal morbidity and mortality.

1. The **incidence** of NEC varies from center to center and from year to year within centers. There are endemic and epidemic occurrences. An estimated 0.3 to 2.4 cases occur in every 1,000 live births. In most centers, NEC occurs between 1% and 5% of all NICU admissions and 5% and 10% of very low birth weight (VLBW) infants. Mortality ranges from 20% to 40% but can approach 100% in cases of NEC totalis. Overall, NEC is responsible for 12% of deaths in extremely premature infants <27 weeks of gestational age.

   Up to 30% of NEC cases result in surgical resection of affected tissue. However, the timing for surgical intervention and the type of surgery remain controversial. Severe NEC requiring surgical intervention increases the average length of stay by 43 days and is associated with increased morbidity (e.g., short bowel syndrome) and mortality.

2. **Prematurity** is the single greatest risk factor. Decreasing gestational age is associated with an increased risk of NEC. The postnatal age at onset is inversely related to birth weight and gestational age, with a mean age at onset of 12 days. The mean postmenstrual age of infants with NEC is between 30 and 32 weeks.

3. Approximately 10% of infants with NEC are **term**. Risk factors for this population include congenital heart disease with presumed decreased intestinal perfusion (e.g., hypoplastic left heart syndrome, coarctation of the aorta), polycythemia, intrauterine cocaine exposure, and intestinal anomalies, such as gastroschisis. The colon appears to be the most commonly affected site in these infants.

4. NEC pathogenesis is **multifactorial**. Additional risk factors for the disease include histologic plus clinical chorioamnionitis, intrauterine growth restriction (IUGR), maternal smoking, polycythemia, and other maternal or neonatal conditions. Antenatal steroids improve the maturity of the GI tract and have been shown to reduce the incidence of NEC.

5. Prolonged empiric antimicrobial use has been associated with increased NEC occurrence and matches other studies that documented decreased microbial diversity and overgrowth of potentially pathogenic bacteria (dysbiosis) prior to NEC onset.

6. Although bacteria are involved in the pathogenesis of the disease, no single infectious organism has been routinely isolated except in relatively rare outbreak situations. NEC should be differentiated from infectious (viral) or allergic (milk intolerance) colitis.

7. Transfusion-associated NEC (TANEC) has been described in numerous reports; however, anemia has been shown to likely be the risk factor for NEC in several studies.

8. A rare, more benign form of NEC has been described: *pneumatosis coli*. Neonates without the typical risk factors for NEC present with grossly bloody stools, minimal or absent abdominal and systemic signs, and isolated colonic pneumatosis without small bowel involvement.
9. Most infants with NEC have received enteral feedings prior to disease onset. Formula feeding increases the risk of NEC (relative risk is 2.8). However, up to 6% of infants <1,250 g birth weight still develop the disease despite receiving breast milk exclusively.

C. Pathogenesis

1. The pathogenesis of NEC remains a conundrum. NEC is a multifactorial disease resulting from complex interactions between immaturity, mucosal injury, and bacterial dysbiosis. Because these factors affect most preterm infants, infants who develop NEC must also exhibit an abnormal or dysregulated host response to intestinal antigens.
2. Genetic polymorphisms have been described in patients at higher risk for severe NEC, such as in genes encoding toll-like receptor 4 (TLR4) or interleukin 18 (IL-18) signaling. A maternal polymorphism in the secretor gene fucosyltransferase 2 (FUT2) leads to a low concentration of the human milk oligosaccharide 2′-fucosyllactose and has been associated with earlier and more severe NEC.
3. Intestinal immaturity plays an important role in the pathogenesis of NEC: increased permeability of the intestinal epithelium, decreased gut motility, a thinner mucus layer, low or absent levels of secretory immunoglobulin A (IgA), and lack of regulatory adaptation of the intestinal mucosal immune system.
4. Experiments in germ-free animals and TLR4 knockout mice strongly suggest that bacterial antigen is critical for the initiation of intestinal inflammation and NEC development. Previous studies used sequencing the 16S small subunit bacterial ribosomal RNA (16S rRNA) gene or the entire bacterial genome of the stool and discovered a reduction in the diversity of microbial communities with a shift toward an increased abundance of potentially pathogenic subgroups. Although not representative of the vast majority of sporadic NEC cases, the literature contains numerous reports of NEC "outbreaks" with detection of various specific bacteria or viruses.
5. An imbalanced intestinal inflammatory response appears to be a key inciting event that leads to NEC. Although specific antigenic triggers may vary, failure to downregulate the innate immune receptor TLR4 on intestinal epithelial cells and lower ratios of forkhead box protein P3 $(FOXP3)^+$ T regulatory cells in the mucosa are examples that can explain why the poorly adapted premature intestine is prone to inflammatory injury and dysregulated immune responses.
6. Evidence supports a critical role for inflammatory mediators in NEC pathogenesis. **Platelet-activating factor (PAF)**, **bacterial endotoxin**, lipopolysaccharide (LPS), tumor necrosis factor (TNF), proinflammatory interleukins, and nitric oxide are some of the inflammatory mediators that have been studied in the pathophysiology of NEC.

Both animal studies and samples from human infants demonstrate the association of elevated levels of PAF in infants with NEC compared with those without NEC. Various other proinflammatory mediators, such as cyclooxygenase 2 (COX-2), reactive oxygen species, TNF alpha (TNF-α), IL-8, IL-17, and IL-18, have been implicated in NEC pathogenesis in mice and humans. These data also point to the multifactorial etiology of the disease and underline the importance that not one, but several strategies are necessary for the prevention of NEC.

7. A large number of other factors such as low Apgar scores, timing and volumes of feeding, umbilical catheterization, hypoxic-ischemic insults, presence of a patent ductus arteriosus (PDA), or treatment with indomethacin or vasopressors have not been uniformly confirmed as independent pathophysiologic contributors.

II. DIAGNOSIS. Early diagnosis of NEC may be an important factor in determining the outcome. This is accomplished by a high index of suspicion and careful clinical observation for nonspecific signs in infants at risk.

A. Clinical characteristics. There is a broad spectrum of disease manifestations. The clinical features of NEC can be divided into systemic and abdominal signs. Most infants have a combination of both, although abdominal signs usually predominate.

1. **Systemic signs.** Respiratory distress, apnea and/or bradycardia, lethargy, temperature instability, irritability, poor feeding, hypotension (shock), decreased peripheral perfusion, acidosis, oliguria, or bleeding diathesis

2. **Abdominal (enteric) signs.** Abdominal distension or tenderness, vomiting (of bile, blood, or both), ileus (decreased or absent bowel sounds), hematochezia (grossly bloody stools), abdominal wall erythema or induration, persistent localized abdominal mass, or ascites

3. The **course of the disease** varies among infants. Most frequently, it will appear (i) as a fulminant, rapidly progressive presentation of signs consistent with intestinal necrosis and sepsis or (ii) as a slow, paroxysmal presentation of abdominal distension, ileus, and possible infection. Infants with NEC require consistent monitoring for worsening in clinical status.

B. Laboratory features. The diagnosis is suspected from clinical presentation but must be confirmed by diagnostic radiographs, surgery, or autopsy. No available laboratory tests are specific for NEC; nevertheless, some tests are valuable in confirming diagnostic impressions.

1. **Imaging studies.** The abdominal **radiograph** will often reveal an abnormal gas pattern suggestive of ileus. Both anteroposterior (AP) and cross-table lateral or left lateral decubitus views should be included. These films may reveal bowel wall edema, a fixed-position loop on serial studies, the appearance of a mass, pneumatosis intestinalis (the radiologic hallmark used to confirm the diagnosis), gasless abdomen indicating ascites, portal or hepatic venous air, pneumobilia, or pneumoperitoneum with the appearance of gas under the diaphragm. Of note, extremely low birth weight (ELBW) infants often present with abdominal distension and ileus. Intramural gas and/or pneumoperitoneum are more commonly

the presenting features after 30 weeks postmenstrual age. SIP may present with pneumoperitoneum without other clinical signs. Abdominal **ultrasound** can be a more sensitive method to detect intramural air and portal venous gas in experienced hands. Doppler studies can confirm bowel necrosis by absent blood flow. These techniques are particularly helpful to confirm radiographic appearance of pneumatosis intestinalis in well-appearing infants with feeding intolerance.

2. **Blood and serum studies.** Thrombocytopenia, persistent metabolic acidosis, and severe refractory hyponatremia constitute the most common triad of signs and help to confirm the diagnosis. Serial measurements of C-reactive protein (CRP) may also be helpful in the diagnosis and assessment of response to therapy of severe NEC. Blood cultures are positive in ~40% of cases.
3. **Analysis of stool** for blood has been used to detect infants with NEC based on changes in intestinal integrity. Although grossly bloody stools may be an indication of NEC, routine testing of stool for occult blood has no value for NEC diagnosis. Approximately 60% of infants will have Hemoccult-positive stools at any given time during hospitalization without any evidence for NEC.

C. Bell staging criteria with the Walsh and Kliegman modification allow for uniformity of diagnosis across centers. Bell staging is not a continuum; babies may present with advanced NEC without earlier signs or symptoms.

1. **Stages IA and IB** (suspected NEC) includes clinical signs and symptoms, including abdominal signs (bloody stools, abdominal distension) and nondiagnostic radiographs.
2. **Stages IIA and IIB** (definite NEC) includes clinical and laboratory signs and pneumatosis intestinalis (stage IIA) and/or portal venous gas (stage IIB) on radiographs.
   a. Mildly ill
   b. Moderately ill with systemic toxicity
3. **Stages IIIA and IIIB** (advanced NEC) includes more severe clinical signs and laboratory abnormalities, pneumatosis intestinalis, and/or portal venous gas on radiographs.
   a. Critically ill (e.g., disseminated intravascular coagulation [DIC], shock) and impending intestinal perforation
   b. Critically ill as in section II.C.3.a but with pneumoperitoneum

D. Differential diagnosis

1. **Pneumonia and sepsis** are common and frequently associated with intestinal ileus. The abdominal distension, discoloration, and tenderness characteristic of NEC should be absent in infants with ileus not due to NEC.
2. **Surgical abdominal catastrophes** include malrotation with obstruction (complete or intermittent), malrotation with midgut volvulus, intussusception, ulcer, gastric perforation, and mesenteric vessel thrombosis. The clinical presentation of these disorders may overlap with that of NEC. Occasionally, the diagnosis is made only at the time of exploratory laparotomy.

3. **SIP** is a distinct clinical entity occurring in approximately 2% of ELBW infants. It often presents as a gasless abdomen or as an asymptomatic pneumoperitoneum, although other clinical and laboratory abnormalities may be present. SIP tends to occur at an earlier postnatal age than NEC (younger than 10 days of age), has significantly lower morbidity and mortality, and is not associated with feeding. The risk of SIP is increased with early postnatal glucocorticoid exposure and indomethacin treatment for PDA. Concurrent treatment with glucocorticoids and indomethacin increases the risk of SIP.
4. **Infectious enterocolitis** is rare in this population but must be considered if diarrhea is present. Etiologies can be viral (e.g., cytomegalovirus [CMV] colitis) or bacterial (e.g., *Campylobacter* sp.). These infants typically lack any other systemic or enteric signs of NEC.
5. Severe forms of **inherited metabolic disease** (e.g., galactosemia with *Escherichia coli* sepsis) may lead to profound acidosis, shock, and vomiting and may initially overlap with some signs of NEC.
6. Severe **allergic colitis** can present with abdominal distension and bloody stools. Usually, these infants are well appearing and have normal abdominal radiographs and laboratory studies.
7. **Feeding intolerance** is a common but ill-defined problem in premature infants. Despite adequate GI function *in utero*, some premature infants will have periods of gastric residuals and abdominal distension associated with advancing feedings. The differentiation of this problem from NEC can be difficult. Cautious evaluation by withholding enteral feedings and administering parenteral nutrition (PN) and antibiotics for 48 to 72 hours may be indicated until this benign disorder can be distinguished from NEC. Serial monitoring of CRP, platelet counts, and kidney-ureter-bladder (KUB) x-rays can sometimes help distinguish feeding intolerance from NEC.

E. Additional diagnostic considerations

1. Because the early abdominal signs may be nonspecific, at present, **a high index of suspicion** is the most reliable approach to early diagnosis. The goal has been to prevent the initiation of a cascade that results in tissue injury, necrosis, and inflammatory sequelae characteristic of NEC. Several biomarkers have been suggested, such as inflammatory cytokines, intestinal or liver fatty acid–binding protein (I-FABP or L-FABP), heart rate characteristics, proteomics, microbiome changes, and machine learning algorithms have been studied with this endpoint in mind, but these have not been very specific for NEC. Traditionally, persistent or worsening abnormalities in white blood cells (WBCs), platelet counts, CRPs, and/or lactate levels have been used to indicate a relative indication for surgical intervention; newer biomarkers and algorithms may help with risk stratification to identify infants with a high likelihood for surgical disease more precisely and earlier.
2. **Radiographic findings** can often be subtle and confusing. For example, intestinal perforation in ELBW infants can present as ileus or gasless abdomen, and conversely, pneumoperitoneum does not necessarily indicate abdominal perforation from NEC. Serial review of the radiographs

with a pediatric radiologist is indicated to assist in the interpretation and to plan for further appropriate studies, which may include abdominal ultrasound with Doppler.

III. MANAGEMENT

A. Immediate medical management (Table 27.1). Treatment must begin promptly when a diagnosis of NEC is suspected. Therapy is based on intensive care support; bowel rest; antibiotics; and close clinical, laboratory, and radiologic monitoring.

1. **Respiratory function.** Rapid assessment of ventilatory status (physical examination, arterial blood gases) should be made with the provision of supplemental oxygen and mechanical ventilatory support as needed.
2. **Cardiovascular function.** Assessment of circulatory status (physical examination, blood pressure) should be made and circulatory support provided as needed. Volume in the form of normal saline, fresh frozen plasma, or packed red blood cells (PRBCs) may be used if circulatory volume is compromised. Pharmacologic support may be needed to ensure adequate blood pressure and tissue perfusion. Impending circulatory collapse will often be reflected by poor perfusion and oxygenation, although arterial blood pressure may be maintained. Intra-arterial blood pressure monitoring is often necessary. Further monitoring of central venous pressure (CVP) may become necessary if additional pharmacologic support of the circulation or failing myocardium is needed (see Chapter 40).
3. **Metabolic function.** Metabolic acidosis will generally respond to volume expansion. The use of sodium bicarbonate is controversial and should be reserved for severe metabolic acidosis with concerns for cardiac dysfunction (dose 1 to 2 mEq/kg). The blood pH and lactate level should be monitored; in addition, serum electrolyte levels, blood glucose, and cardiac and liver function should be measured.
4. **Nutrition.** All GI feedings are discontinued, and the bowel is decompressed by suctioning through a double-lumen nasogastric or orogastric tube. Length of withholding enteral nutrition generally coincides with duration of antibiotic treatment and varies between 5 and 14 days for medical NEC and 10 to 14 days for surgical disease. Guidance from randomized controlled trials is not available, but one study suggested safe refeeding once CRP levels have normalized. PN is given through peripheral or central access as soon as possible, with the aim of providing 90 to 110 kcal/kg/day once amino acid solutions and intralipid are both tolerated. A central venous catheter is almost always necessary to provide adequate calories in the VLBW infant. We wait to place a central catheter for this purpose until the blood cultures are negative, during which time peripheral PN can be given (see Chapter 21).
5. **Infectious disease.** Blood and sometimes urine cultures are obtained and sent for culture and sensitivities. Traditional culture and 16S rRNA gene sequencing from blood and peritoneal fluid of patients with NEC have identified a variety of aerobic and anaerobic gram-positive

Table 27.1. Management of Necrotizing Enterocolitis

Bell Staging Criteria	Diagnosis	Management (Usual Attention to Respiratory, Cardiovascular, and Hematologic Resuscitation Presumed)
Stage I (suspected)	Clinical signs, nondiagnostic radiograph	NPO with IV fluids Gastric decompression CBC, electrolytes Blood culture Ampicillin and gentamicin × 48 hours KUB q8–12h × 48 hours Abdominal ultrasound with Doppler
Stage II (definite)	Clinical signs, pneumatosis intestinalis and/or portal venous gas on radiograph	NPO with parenteral nutrition Gastric decompression CBC, electrolytes KUB (AP and lateral) q6–8h × 24–48 hours and then PRN Abdominal ultrasound with Doppler CBC, electrolytes Blood culture Ampicillin, gentamicin, and metronidazole × 10–14 days Surgical consultation
Stage III (advanced)	Clinical signs	NPO with parenteral nutrition
	Critically ill	Nasogastric drainage
	Pneumatosis intestinalis or pneumoperitoneum on radiograph	Gastric decompression CBC, electrolytes KUB (AP and lateral) q6–8h × 24–48 hours and then PRN Abdominal ultrasound with Doppler Ampicillin, gentamicin, and metronidazole Surgical consultation

NPO, nothing by mouth; IV, intravenous; CBC, complete blood count; KUB, kidney-urethra-bladder x-ray; AP, anteroposterior; PRN, as needed.

and gram-negative bacteria including *Klebsiella pneumoniae*, *E. coli*, *Pseudomonas* sp., *Clostridium* sp., *Bacteroides* sp., and *Staphylococcus* sp. Therefore, typical combination therapy is indicated, such as ampicillin, gentamicin, and metronidazole. Alternatively, treatment regimens include clindamycin, piperacillin-tazobactam, or meropenem, sometimes in combination with vancomycin. *Candida* spp. are early colonizers of the premature intestine and can be identified in preterm infants with NEC, especially in case of intestinal perforation and lack of antifungal prophylaxis. Safety and efficacy of a particular antibiotic regimen have not been established in infants with NEC, and therefore, none of these drugs or combinations are FDA labeled for this population. With changing antibiotic sensitivities, providers must be aware of the predominant local NICU flora, the organisms associated with NEC, and their resistance patterns and adjust antibiotic coverage accordingly. Antibiotic therapy is adjusted on the basis of culture results, but only 10% to 40% of blood cultures will be positive, necessitating continued broad-spectrum coverage in most cases. In infants requiring surgery, peritoneal fluid cultures may also help target appropriate antibiotic treatment. Treatment is generally maintained for 10 to 14 days in cases of definite NEC (Bell stage II or higher). There is no evidence to support the use of enteral antibiotics.

6. **Hematologic aspects.** Analysis of the complete blood count and differential is mostly helpful to detect clinically significant anemia and/or thrombocytopenia. PRBCs are often transfused to maintain the hematocrit >35%. The prothrombin time, partial thromboplastin time, fibrinogen, and platelet count should be evaluated for evidence of DIC. Fresh frozen plasma is often used to treat coagulation problems.
7. **Renal function.** Oliguria often accompanies the initial hypotension and hypoperfusion of NEC; measurement of urine output is indicated. In addition, serum blood urea nitrogen (BUN), creatinine, and serum electrolyte levels should be monitored. Impending renal failure from acute tubular necrosis, coagulative necrosis, or vascular accident must be anticipated, and fluid therapy adjusted accordingly (see Chapter 28).
8. **Neurologic function.** Evaluation of the infant's condition may be difficult given the degree of illness, but one must be alert to the problems of associated meningitis and intraventricular hemorrhage (IVH). Seizures are rare but may occur secondary to either meningitis, IVH, or from the metabolic perturbations associated with NEC. These complications must be anticipated and promptly recognized and treated.
9. **GI function.** Physical examination and serial (every 6 to 8 hours during the first 2 to 3 days) radiographs are used to assess the progression of disease. Unless perforation occurs or full-thickness necrosis precipitates severe peritonitis, management remains medical. The evaluation for surgical intervention, however, is controversial and complex (see section III.B).
10. **Family support.** Any family of an infant in the NICU may be overwhelmed by the crisis. Infants with NEC present a particular challenge because the disease often causes sudden deterioration for "no

apparent reason." Furthermore, the impending possibility of surgical intervention and the high mortality and uncertain prognosis make this situation most difficult for parents. Careful anticipatory sharing of information supports a trusting alliance with the family.

B. Surgical intervention

1. **Prompt early consultation** should be obtained with a pediatric surgeon. This allows the surgeon to become familiar with the infant and provides an additional evaluation by another skilled individual. If a pediatric surgeon is not available and advancement to more severe disease is likely, the infant should be transferred to a high-level center with pediatric surgery service.
2. **GI perforation** is the only absolute indication for surgical intervention. Unfortunately, there is no reliable or absolute indicator of imminent perforation; therefore, frequent monitoring is necessary. Perforation occurs in 20% to 30% of patients, usually 12 to 48 hours after the onset of NEC, although it can occur later. In some cases, the absence of pneumoperitoneum on the abdominal radiograph can delay the diagnosis, and paracentesis may aid in establishing the diagnosis. In general, an infant with increasing abdominal distension, an abdominal mass, a worsening clinical picture despite medical management, or a persistent fixed loop on serial radiographs may have a perforation and require operative intervention.
3. **Full-thickness necrosis of the GI tract** may require surgical intervention, although this diagnosis is difficult to establish in the absence of perforation. In most cases, the infant with bowel necrosis will have signs of peritonitis, such as ascites, abdominal mass, abdominal wall erythema, induration, persistent thrombocytopenia, progressive shock from third-space losses, or refractory metabolic acidosis. A paracentesis may help to identify these patients before perforation occurs.
4. The specific type of **surgical treatment** varies by center and extent of disease. It includes peritoneal drainage, laparotomy with diverting ostomy alone, laparotomy with intestinal resection and primary anastomosis, "clip and drop," or stoma creation, with or without second-look procedure. In very unstable infants, surgery in the NICU rather than transfer to the operating room is a commonly used option, especially in single-room NICUs. Mortality in these cases is high, likely due to the critical status of patients before surgery. The goal is to completely excise necrotic bowel while preserving as much bowel length as possible. If large areas are resected, the length and position of the remaining bowel are noted because this will affect the long-term outcome. In case of "NEC totalis" (bowel necrosis from duodenum to rectum), mortality is almost certain, and resection may not be attempted.
5. Recent clinical trials have been designed to inform the decision to perform **peritoneal drainage** under local anesthesia rather than **laparotomy**. Early data suggested that outcomes were equivalent; however, approximately half of patients with peritoneal drainage eventually receive laparotomy (35% to 74%), potentially limiting the validity of the intention-to-treat analyses. Peritoneal drainage can be particularly

useful for ELBW infants (<1,000 g) and extremely unstable infants. These infants are often overrepresented in peritoneal drainage study groups further confounding interpretation. Preliminary data from a recent multicenter, randomized clinical trial with 310 ELBW infants demonstrated that death or neurodevelopmental impairment (NDI) at 18 to 22 months were equivalent when NEC and isolated intestinal perforation were grouped together. However, for infants with a preoperative diagnosis of NEC, there was likely a benefit with laparotomy (Bayesian posterior probability of benefit with laparotomy of 97%).

C. Long-term management. Once the infant has been stabilized and effectively treated, feedings can be reintroduced. This process typically starts after 7 to 14 days of treatment by stopping gastric decompression. If infants can tolerate having the gastric tube to gravity, feedings are begun very slowly while parenteral alimentation is gradually tapered. No conclusive data are available on the best method or type of feeding, but breast milk may be tolerated best and is preferred. The incidence of recurrent NEC is 4%, and the occurrence of strictures may also complicate feeding plans. Recurrent disease should be treated as before and will generally respond similarly. If surgical intervention was required and an ileostomy or colostomy has been created, intestinal reanastomosis can be electively undertaken after an adequate period of healing. If an infant tolerates enteral feedings, reanastomosis may be performed after a period of growth at home. Earlier surgical intervention may be indicated in infants who cannot be advanced to full volume or strength feedings because of malabsorption and intestinal dumping. Before reanastomosis, a contrast study of the distal bowel is frequently obtained to establish the presence of a stricture that can be resected at the time of ostomy closure.

IV. PROGNOSIS.

Few detailed and accurate studies are available on prognosis. In uncomplicated cases of NEC, the long-term prognosis may be comparable with that of other low birth weight infants; however, those with stage IIB and stage III NEC have a higher incidence of mortality (more than 50%), growth delay (lagging head circumference is of most concern), and poor neurodevelopmental outcomes. NEC requiring surgical intervention may have more serious sequelae, including mortality secondary to infection, respiratory failure, PN-associated hepatic disease, rickets, and significant developmental delay.

A. Sequelae of NEC can be directly related to the severity of disease or to the long-term NICU management often necessary to treat it. GI sequelae include dysmotility, strictures, enteric fistulas, short bowel syndrome, malabsorption and chronic diarrhea, dumping syndromes related to loss of terminal ileum and ileocecal valve, fluid and electrolyte losses with rapid dehydration, and hepatitis or cholestasis related to long-term PN. Strictures occur in 25% to 35% of patients with or without surgery and are most common in the large bowel. However, not all strictures are clinically significant and may not preclude advancement to full feeding volumes. Short bowel syndrome occurs in approximately 10% to 20% following surgical treatment. **Metabolic sequelae** include failure to thrive, metabolic bone disease, and problems related to central nervous system (CNS) function in the VLBW infant. NEC is a significant predictor of lasting

neurodevelopmental morbidity independent of other factors. Survivors of NEC have significantly impaired motor and cognitive outcomes with on average 11 IQ points lower intelligence than matched control children. A recent systematic review suggests that although NEC still carries a high mortality and morbidity burden, outcomes may have improved over the last decade; however, data interpretation is complicated by variations in diagnosis criteria and outcome reporting.

B. Prevention of NEC is the ultimate goal. Unfortunately, this can best be accomplished only by preventing premature birth. If prematurity cannot be avoided, several preventive strategies may be of benefit.

1. **Induction of GI maturation.** The incidence of NEC is significantly reduced after antenatal steroid therapy.
2. **Exclusive feeding of human milk–based diet.** Premature infants who are fed expressed human milk compared to formula are at decreased risk for developing NEC. Mothers should be strongly encouraged to provide expressed milk for their premature babies when able. **Mother's own milk and donor breast milk reduces the risk of NEC compared to formula.** Formula-fed infants had greater increases in weight, length, and head circumference in several studies, but no difference was found on growth rates or neurodevelopmental outcomes after discharge. VLBW infants fed nutrient-fortified donor breast milk have comparable long-term growth and body composition when compared to those fed preterm formula during initial hospitalization.
3. **Optimization of enteral feedings** (see Chapter 21). Because of the lack of adequately sized randomized trials in ELBWs, currently, there is not enough evidence to support either early versus delayed feedings or an optimum rate of advancement of feedings. Of note, early feeds with prudent, steady advances have not been associated with an increase in NEC. From the available evidence, it is clear that adoption and strict adherence to a particular standardized feeding regimen reduces the risk of NEC; therefore, individual NICUs should agree on a feeding regimen and monitor adherence.
4. **Enterally fed probiotics** are a potentially promising new approach to the prevention of NEC. Probiotics fed to preterm infants may help to normalize intestinal microflora colonization. A Cochrane meta-analysis has shown that probiotics may reduce the incidence of NEC by up to 50% in infants fed probiotics (e.g., *Lactobacillus GG*, *Bifidobacterium breve*, *Saccharomyces boulardii*, *Lactobacillus acidophilus*) compared with controls. However, the studies included were quite disparate in the type of probiotics and in their use. Neither the large Probiotics in Preterm babies Study (PiPS) trial in the United Kingdom nor the ProPrems trial in Australia (together more than 2,500 babies) demonstrated any reduction in death, sepsis, or NEC in infants *<28 weeks'* gestational age. In addition, fatal infectious complications, including probiotic-induced bacteremia and mucormycosis secondary to contamination, have been reported in association with unregulated use of live probiotic supplementation. Given this, the American Academy of Pediatrics Committee on Fetus and Newborn recommends against the routine, universal use

of probiotics in the prevention and treatment of NEC until an effective pharmaceutical-grade product is available with a determined optimum dosage and long- and short-term safety profile.

5. A number of nutritional **supplements** (e.g., polyunsaturated fatty acids [PUFAs], L-arginine); **growth factors**, such as transforming growth factor beta (TGF-β) and heparin-binding epidermal growth factor (HB-EGF); **immune modulators**, such as immunoglobulins, trefoil factors, lactoperoxidase, superoxide dismutase, PAF acetylhydrolase, alkaline phosphatase, and inhibitors of TLR4; and others have been explored in animal models and even clinical trials but are not ready for routine clinical use. **Lactoferrin**, a glycoprotein with broad-spectrum antimicrobial activity found in colostrum and milk, showed promise in early studies when given for NEC prophylaxis. However, the enteral lactoferrin in neonates (ELFIN) trial in the United Kingdom (>2,000 babies) failed to show either a reduction in incidence or severity of NEC as a secondary outcome. Currently, the best evidence for **NEC prevention** strategies exists for antenatal steroids, standardized enteral feeding guidelines, human milk, avoidance of acid blockade, and minimization of empiric antibiotic exposure.

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28 Neonatal Kidney Conditions

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KEY POINTS

- Glomerular filtration rate (GFR) at birth is lower in the most premature infants and rises after birth dependent on the degree of prematurity.
- In term babies, GFR rises quickly, doubling by 2 weeks of age and reaching adult levels by 2 years of age.
- Management of infants who develop acute kidney injury (AKI) should focus on treating the underlying etiology, avoiding further injury, and addressing consequences of decreased renal function.
- Congenital anomalies of the kidney and urinary tract (CAKUT) may become apparent with prenatal ultrasound, discovered at birth, or present later in life.

Kidney problems in the neonate may be the result of specific inherited, developmental abnormalities or the result of acquired events either in the prenatal or in the postnatal period. For this reason, evaluation includes a detailed review of the history (family history, gestational history, and the neonatal events) as well as a review of the presenting clinical features and relevant laboratory/radiologic findings. An understanding of the developmental processes and the differences in renal physiology in the neonatal period compared to that at later ages is necessary for evaluation.

I. RENAL EMBRYOGENESIS AND FUNCTIONAL DEVELOPMENT

A. Embryogenesis. The development of the human kidney is a self-regulating process in which kidney function directs multiple interdependent cellular processes of the developing nephrons and tubules. Nephrogenesis requires a fine balance of numerous factors that can be disturbed by various genetic and/or epigenetic prenatal events including nutritional deficiencies, toxic insults, hypertension, pharmacologic exposures, prematurity, and low birth weight resulting in low nephron number at birth. The pronephros, initial precursor of the mature human kidney, develops at approximately 3 weeks' gestation and leads to the formation of the mesonephros by the fourth week of gestation. The mesonephros, consisting of vascularized glomeruli as well as proximal and distal tubule elements, makes a small amount of urine in the second month of gestation. A portion of the mesonephric duct fuses with the cloaca, eventually forming the urinary bladder while the remainder is

vestigial in females but forms part of the male reproductive organs in males. The metanephros is the final developmental stage and can be identified around the fifth week of gestation. It has two components: the ureteric bud (UB) and the metanephric mesenchyme. Signals between these components induce a reiterative branching of the UB, which results in the components of the collecting system: collecting duct, renal calyces, and pelvis as well as the ureters and bladder trigone. These signals also induce the metanephric mesenchymal cells to migrate closer to each other and convert into epithelial cells, which will become mature nephrons (from the glomerulus to the distal convoluted tubule) at the tip of each UB branch. Some of these mesenchymal cells will form the interstitium of the mature kidney and part of the vasculature. During this process, the metanephros rises to progressively higher levels, reaching the lumbar position by 8 weeks of gestation.

There are four stages of nephron development: stage I, where the renal vesicle appears; stage II, transformation of renal vesicle to a comma-shaped body; stage III, capillary loop stage; and stage IV, maturing nephron stage including proximal tubules, the loop of Henle, distal tubules, and development of the juxtaglomerular complex and part of the afferent arterioles. During this final stage, the renal interstitium differentiates into the various components of cortex, medulla, etc. Disruption of any part of this sequence leads to reduced nephron numbers. Human nephrogenesis is complete by 36 weeks of gestation with the greatest increase between 18 and 32 weeks' gestation. Nephron number varies from 300,000 to 1,800,000 (average 900,000) nephrons per kidney. Nephron endowment at birth has profound implications for the future development of chronic kidney disease (CKD) especially in preterm infants because there is no regeneration and postnatal nephrogenesis, if it occurs as some autopsy studies suggest, is suboptimal. Once the nephron number has been determined, postnatal factors (such as acute kidney injury [AKI] or chronic illness) can only further decrease the nephron population.

Gene-targeting experiments have greatly improved our understanding, although incomplete, of kidney and urinary tract morphogenesis as well as the abnormalities that arise from mutations or altered epigenetic modulation of genes expressed during nephrogenesis. The GDNF/c-Ret/Wnt1 pathway, for example, is considered a major positive regulator of UB development, playing multiple crucial roles in cell movements and growth. In its absence, kidneys display severe branching abnormalities and can lead to renal hypoplasia, renal agenesis, abnormal ureter–bladder connections, and so on. Given the complex nature of nephrogenesis even subtle changes in the process can have severe consequences on the ultimate development of the human kidney. Figure 28.1 shows some of the genes involved in early kidney development.

B. Functional development. At birth, the kidneys replace the placenta as the major homeostatic organs, maintaining fluid and electrolyte balance and removing harmful waste products. This transition occurs with increases in renal blood flow (RBF), glomerular filtration rate (GFR), and tubular function. Because of this postnatal transition, the level of renal function relates more closely to the postnatal age than to the gestational age at birth.

1. **RBF** remains low during fetal development, accounting for only 2% to 3% of cardiac output. At birth, RBF rapidly increases to 15% to 18% of cardiac output by 6 weeks of age because of (i) a decrease in renal

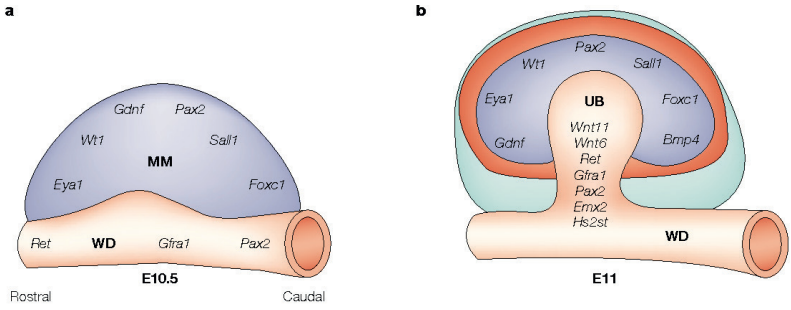


Figure 28.1. Some genes involved in early kidney development, mouse model. Kidney development starts with development of the ureteric bud (**A**) which moves into the metanephric mesenchyme (**B**); signals from each component induce continued development into the mature kidney and collecting system. MM, metanephric mesenchyme; WD, Wolffian duct (also known as mesonephric duct); E10.5, mouse embryonic day 10.5; UB, ureteric bud; E11, mouse embryonic day 11. (Reprinted by permission from Nature: Vainio S, Lin Y. Coordinating early kidney development: lessons from gene targeting. *Nat Rev Genet* 2002;3[7]:533–543.)

vascular resistance, which is proportionally greater in the fetal kidney compared to other organs; (ii) an increase in systemic blood pressure; and (iii) an increase in blood flow to the outer cortex of the kidney.

2. **Glomerular filtration** begins soon after the first nephrons are formed and GFR increases in parallel with gestational age and body and kidney growth (~1 mL/minute/kg of body weight). After all the glomeruli are formed, the GFR continues to increase until birth because of decreases in renal vascular resistance. In term neonates, GFR rises quickly, doubling by 2 weeks of age and reaching adult levels by the age of 2 years. Premature infants have a lower GFR at birth compared to term infants, in part due to lower nephron mass in the former group. However, their GFR also rises after birth although over a longer time interval (Table 28.1). GFR is less well autoregulated in the neonate than in older children. It is controlled by maintenance of glomerular capillary pressure by the greater vasoconstrictive effect of angiotensin II at the efferent than afferent arteriole where the effect is attenuated by concurrent prostaglandin-induced vasodilatation.

3. **Tubular function**

   a. Sodium (Na^+) handling. The ability of the kidneys to reabsorb Na^+ is developed by 24 weeks' gestation, although tubular resorption of Na^+ is low until after 34 weeks' gestation. This is important when evaluating a preterm infant because they will be unable to reabsorb sodium maximally and thus will have elevated fractional excretion of sodium (FENa; Table 28.2). Very premature infants cannot conserve Na^+ even when Na^+ balance is negative. Hence, premature infants below 34 weeks' gestation often develop hyponatremia when receiving formula or breast milk even in the absence of kidney injury or damage. Na^+ supplementation is warranted in those situations. After 34 weeks' gestation, Na^+ reabsorption becomes more efficient so that 99% of filtered Na^+ can

Table 28.1. Normal Serum Creatinine Values (mg/dL) in Term and Preterm Infants (Mean ± SD)

Age (Day)	<28 Weeks	28–32 Weeks	32–37 Weeks	>37 Weeks
3	1.05 ± 0.27	0.88 ± 0.25	0.78 ± 0.22	0.75 ± 0.2
7	0.95 ± 0.36	0.94 ± 0.37	0.77 ± 0.48	0.56 ± 0.4
14	0.81 ± 0.26	0.78 ± 0.36	0.62 ± 0.4	0.43 ± 0.25
28	0.66 ± 0.28	0.59 ± 0.38	0.40 ± 0.28	0.34 ± 0.2

SD, standard deviation.

Source: From Rudd PT, Hughes EA, Placzek MM, et al. Reference ranges for plasma creatinine during the first month of life. *Arch Dis Child* 1983;58:212–215; van den Anker JN, de Groot R, Broerse HM, et al. Assessment of glomerular filtration rate in preterm infants by serum creatinine: comparison with inulin clearance. *Pediatrics* 1995;96:1156–1158.

be reabsorbed, resulting in a FENa of <1% if challenged with renal hypoperfusion (prerenal state). Full-term neonates can retain Na^+ when in negative Na^+ balance but, like premature infants, are also limited in their ability to excrete an Na^+ load because of their low GFR. It is important to note that, under normal circumstances, there is a natriuresis that peaks at day 4 of life after which there is a shift to conserve sodium for growth.

Table 28.2. Commonly Used Equations and Formulas

eGFR = CrCl (mL/min/1.73 m^2) = $K \times$ length (cm)/P_{Cr}
eGFR = CrCl (mL/min/1.73 m^2) = $U_{Cr} \times U_{vol} \times 1.73/P_{Cr} \times$ BSA
FENa (%) = $100 \times (U_{Na^+} \times P_{Cr})/(P_{Na^+} \times U_{Cr})$
TRP = $100 \times [1 - (U_P \times P_{Cr})/(P_P \times U_{Cr})]$
TTKG = $(U_{K^+} \times P_{osm})/ P_{K}+ \times U_{osm})$
Calculated P_{osm} = 2 × plasma [Na^+] + (glucose/18) + (BUN/2.8)
Serum anion gap = [Na^+] − [Cl^-] − [HCO_3]

eGFR, estimated glomerular filtration rate; CrCl, creatinine clearance; *K*, 0.33 in premature infants and 0.45 in term infants; P_{Cr}, plasma creatinine; U_{Cr}, urinary creatinine; U_{vol}, urinary volume per minute; BSA, body surface area; FENa, fractional excretion of sodium; U_{Na^+}, urinary sodium; P_{Na^+}, plasma sodium; TRP, tubular reabsorption of phosphorus; U_P, urinary phosphorus; P_P, plasma phosphorus; TTKG, transtubular potassium gradient; U_{K^+}, urinary potassium; P_{osm}, plasma osmolarity; P_{K^+}, plasma potassium; U_{osm}, urine osmolality; BUN, blood urea nitrogen.

b. Potassium (K^+) handling. The limited ability of premature infants to excrete large K^+ loads is related to decreased distal tubular K^+ secretion, a result of decreased aldosterone sensitivity, low Na^+–K^+–ATPase activity, and their low GFR. Premature infants often have slightly higher serum K^+ levels than older infants and children. If there is a question of renal potassium handling and possible abnormal hyperkalemia, potassium should be accurately measured using a central blood draw (as opposed to a heel stick) and measurement of a whole blood potassium should be considered.

c. Acid and bicarbonate handling are limited by a low serum bicarbonate threshold in the proximal tubule (14 to 16 mEq/L in premature infants, 18 to 22 mEq/L in full-term infants), which improves as maturation of the Na^+–H exchanger, H+-ATPase and, to a smaller extent, the Na^+–K^+–ATPase occurs. Essentially, premature infants are born with a mild proximal RTA that improves with age. In addition to proximal tubular handling of bicarbonate, the production of ammonia in the distal tubule and proximal tubular glutamine synthesis are decreased. The lower rate of phosphate excretion limits the generation of titratable acid, further limiting infants' ability to eliminate an acid load. Very low birth weight infants can develop mild metabolic acidosis during the second to fourth week after birth that may require administration of additional base in the form of sodium bicarbonate or acetate.

d. Phosphorus handling in the neonate, when compared to older children and adults, is characterized by a pattern of increased phosphate retention to support growth. The intake and filtered load of phosphate, parathyroid hormone (PTH), and growth factors modulate renal phosphate transport. The higher phosphate level and higher rate of phosphate reabsorption in the neonate are not explained by the low GFR or tubular unresponsiveness to extrarenal factors (PTH, vitamin D). More likely, there is a developmental mechanism that favors renal conservation of phosphate in part due to growth and thyroid hormone effects, as well increase in Na^+-dependent phosphate transporter, so that a positive phosphate balance for growth is maintained. Tubular reabsorption of phosphate (TRP) is also altered by gestational age, increasing from 85% at 28 weeks to 93% at 34 weeks and 98% by 40 weeks.

e. Calcium handling. Calcium levels in the fetus and cord blood are higher than those in the neonate. Calcium levels fall in the first 24 hours, but low levels of PTH persist. This relative hypoparathyroidism in the first few days after birth may be the result of this physiologic response to hypercalcemia in the normal fetus. Although total plasma Ca^+ values <8 mg/dL in premature infants are common, they are usually asymptomatic because the ionized calcium level is usually normal. Factors that favor this normal ionized Ca^+ fraction include lower serum albumin and the relative metabolic acidosis in the neonate. Urinary calcium excretion is lower in premature infants and correlates with gestational age. At term, urinary calcium excretion rises and persists until approximately 96 months of age. The urine calcium excretion in premature infants varies directly with Na^+ intake, urinary Na^+ excretion, and inversely with plasma calcium. Neonatal stress and therapies such as aggressive fluid use or furosemide administration increase calcium excretion, aggravating the tendency toward hypocalcemia, hypercalciuria, or nephrocalcinosis (NC).

f. Water handling. The newborn infant has a limited ability to concentrate urine due to limited urea concentration within the renal interstitium (because of low protein intake and anabolic growth). The resulting decreased osmolality of the interstitium leads to a decreased concentrating ability and thus a diminished capacity to reabsorb water by the neonatal kidney. The maximal urine concentration (osmolality) is only 500 mOsm/L in premature infants and 800 mOsm/L in term infants (Table 28.3). Although this is of little consequence in infants receiving appropriate amounts of water with hypotonic feeding, it can become clinically relevant in infants receiving higher osmotic loads. In contrast, both premature and full-term infants can dilute their urine normally with a minimal urine osmolality of 35 to 50 mOsm/L. Their low GFR, however, limits their ability to handle water loads.

Table 28.3. Normal Urinary and Renal Values in Term and Preterm Infants

	Preterm Infants <34 Weeks	Term Infants at Birth	Term Infants 2 Weeks	Term Infants 8 Weeks
GFR (mL/minute/1.73 m^2)	13–58	15–60	63–80	—
Bicarbonate threshold (mEq/L)	14–18	21	21.5	—
TRP (%)	>85	>95	—	—
Maximal concentration ability (mOsmol/L)	500	800	900	1,200
Maximal diluting ability (mOsmol/L)	25–30	25–30	25–30	25–30
Specific gravity	1.002–1.015	1.002–1.020	1.002–1.025	1.002–1.030
Dipstick	—	—	—	—
pH	5.0–8.0	4.5–8.0	4.5–8.0	4.5–8.0
Proteins	Neg to 2+ (100mg/dl)	Neg to 1+ (30mg/dl)	Neg	Neg
Glucose	Neg to 2+ (100mg/dl)	Neg	Neg	Neg
Blood	Neg	Neg	Neg	Neg
Leukocytes	Neg	Neg	Neg	Neg

GFR, glomerular filtration rate; TRP, tubular reabsorption of phosphate; Neg, negative.

II. CLINICAL ASSESSMENT OF THE KIDNEYS AND URINARY TRACT.

Assessment of the kidneys and urinary tract involves a review of the patient's history, physical examination, and appropriate laboratory and radiologic tests.

A. History

1. **Prenatal history.** This includes review of any maternal illness, drug use, exposure to known and potential teratogens and antenatal imaging results.

   a. Maternal use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, or indomethacin decreases glomerular capillary pressure and GFR and has been associated with neonatal kidney failure.

   b. Fetal urine contribution to amniotic fluid volume is minimal in the first half of gestation (10 mL/hour) but increases significantly to an average of 50 mL/hour and is a necessary contribution to pulmonary development. Oligohydramnios may indicate a decrease in fetal urine production and can be associated with kidney agenesis, dysplasia, polycystic kidney disease (PKD), or severe obstruction of the urinary tract system. It is most often a sign of poor fetal perfusion due to placental insufficiency as seen in preeclampsia or maternal vascular disease (see Chapters 2 and 4). Conversely, polyhydramnios is seen in pregnancies complicated by maternal diabetes (see Chapter 2) and in fetal anomalies such as esophageal atresia (see Chapter 64) or anencephaly (see Chapter 57). It also may be a result of renal tubular dysfunction with inability to fully concentrate urine.

   c. Elevated serum/amniotic fluid α-fetoprotein and enlarged placenta are associated with congenital nephrotic syndrome.

2. **Family history.** The risk of renal disease increases if there is a family history of urinary tract anomalies, PKD, consanguinity, or inherited renal tubular disorders. Familial diseases (congenital nephrotic syndrome, autosomal recessive PKD [ARPKD], hydronephrosis, or dysplasia) may be recognized *in utero* or remain asymptomatic until later life.

3. **Delivery history.** Fetal distress, perinatal asphyxia, sepsis, and volume loss may lead to ischemic or anoxic injury. Although often multiorgan, the neonatal kidneys are at particular risk for ischemic injury due to their low GFR and relative hypoxia at baseline.

4. **Micturition.** Seventeen percent of newborns void in the delivery room, approximately 90% void by 24 hours, and 99% void by 48 hours. The rate of urine formation ranges from 0.5 to 5.0 mL/kg/hour at all gestational ages. The most common cause of delayed or decreased urine production is improper recording of initial void or inadequate perfusion of the kidneys. Delay in micturition may also be due to intrinsic kidney abnormalities or obstruction of the urinary tract.

B. Physical examination. Careful examination will detect abdominal masses in approximately 0.8% of neonates. Most of these masses are either renal in origin or related to the genitourinary (GU) system. It is important to consider in the differential diagnosis whether the mass is unilateral or bilateral (Table 28.4). Edema may be present in infants with congenital nephrotic syndrome (due to low oncotic pressure) or from fluid overload if input exceeds output. Tubular defects and use of diuretics can cause salt

Table 28.4. Abdominal Masses in the Neonate

Type of Mass	Total Percentage
Renal	55
Hydronephrosis	
Obstructive (e.g., secondary to PUV, UPJ, or UVJ obstruction)	
Nonobstructive	
Multicystic dysplastic kidney	
Polycystic kidney disease	
Simple renal cyst (large)	
Cystic dysplasia	
Mesoblastic nephroma	
Renal ectopia	
Renal vein thrombosis	
Nephroblastomatosis	
Wilms tumor	
Genital	15
Hydrometrocolpos	
Ovarian cyst	
Gastrointestinal	20

PUV, posterior urethral valves; UPJ, ureteropelvic junction; UVJ, ureterovesical junction.

Source: Modified from Pinto E, Guignard JP. Renal masses in the neonate. *Biol Neonate* 1995;68(3):175–184. Copyright © 1995 S. Karger AG, Basel.

and water losses, which can lead to dehydration. Many congenital syndromes may affect the kidneys; thus, a thorough evaluation is necessary in those presenting with congenital renal anomalies. Exam findings associated with congenital kidney anomalies are varied (Table 28.5). Spontaneous pneumothorax may occur in those who have pulmonary hypoplasia associated with renal abnormalities.

C. Laboratory evaluation. Kidney function tests must be interpreted in relation to gestational and postnatal age (see Tables 28.1 and 28.6).

1. Urinalysis reflects the developmental stages of renal physiology.
   a. Specific gravity. Full-term infants have a limited concentrating ability with a maximum specific gravity of 1.021 to 1.025.

Table 28.5. Congenital Syndromes with Renal Components

Dysmorphic Disorders, Sequences, and Associations	General Features	Renal Abnormalities
Oligohydramnios sequence (Potter syndrome)	Altered facies, pulmonary hypoplasia, abnormal limb and head position	Renal agenesis, severe bilateral obstruction, severe bilateral dysplasia, autosomal recessive polycystic kidney disease
VATER and VACTERL syndrome	Vertebral anomalies, anal atresia, tracheoesophageal fistula, radial dysplasia, cardiac and limb defects	Renal agenesis, renal dysplasia, renal ectopia
Mullerian, Renal, Cervicothoracic Somite association and Rokitansky sequence	Failure of paramesonephric ducts, vaginal and uterus hypoplasia/atresia, cervicothoracic somite dysplasia	Renal hypoplasia/agenesis, renal ectopia, double ureters
Prune belly	Hypoplasia of abdominal muscle, cryptorchidism	Megaureters, hydronephrosis, dysplastic kidneys, atonic bladder
Spina bifida	Meningomyelocele	Neurogenic bladder, vesicoureteral reflux, hydronephrosis, double ureter, horseshoe kidney
Caudal dysplasia sequence (caudal regression syndrome)	Sacral (and lumbar) hypoplasia, disruption of the distal spinal cord	Neurogenic bladder, vesicoureteral reflux, hydronephrosis, renal agenesis
Anal atresia (high imperforate anus)	Rectovaginal, rectovesical, or rectourethral fistula tethered to the spinal cord	Renal agenesis, renal dysplasia
Hemihypertrophy	Hemihypertrophy	Wilms tumor, hypospadias
Aniridia	Aniridia, cryptorchidism	Wilms tumor
Drash syndrome	Ambiguous genitalia	Mesangial sclerosis, Wilms tumor
Small deformed or low-set ears		Renal agenesis/dysplasia

(continued)

Table 28.5. Congenital Syndromes with Renal Components *(Continued)*

Dysmorphic Disorders, Sequences, and Associations	General Features	Renal Abnormalities
Autosomal Recessive		
Cerebrohepatorenal syndrome (Zellweger syndrome)	Hepatomegaly, glaucoma, brain anomalies, chondrodystrophy	Cortical renal cysts
Jeune syndrome (asphyxiating thoracic dystrophy)	Small thoracic cage, short ribs, abnormal costochondral junctions, pulmonary hypoplasia	Cystic tubular dysplasia, glomerulosclerosis, hydronephrosis, horseshoe kidneys
Meckel-Gruber syndrome (dysencephalia splanchnocystica)	Encephalocele, microcephaly, polydactyly, cryptorchidism, cardiac anomalies, liver disease	Polycystic/dysplastic kidneys
Johanson-Blizzard syndrome	Hypoplastic alae nasi, hypothyroidism, deafness, imperforate anus, cryptorchidism	Hydronephrosis, caliectasis
Schinzel-Giedion syndrome	Short limbs, abnormal facies, bone abnormalities, hypospadias	Hydronephrosis, megaureter
Short rib–polydactyly syndrome	Short horizontal ribs, pulmonary hypoplasia, polysyndactyly, bone and cardiac defects, ambiguous genitalia	Glomerular and tubular cysts
Bardet-Biedl syndrome	Obesity, retinal pigmentation, polydactyly	Interstitial nephritis
Autosomal Dominant		
Tuberous sclerosis	Fibrous-angiomatous lesions, hypopigmented macules, intracranial calcifications, seizures, bone lesions	Polycystic kidneys, renal angiomyolipoma
Melnick-Fraser syndrome (branchio-oto-renal [BOR] syndrome)	Preauricular pits, branchial clefts, deafness	Renal dysplasia, duplicated ureters

(continued)

Table 28.5. *(Continued)*

Dysmorphic Disorders, Sequences, and Associations	General Features	Renal Abnormalities
Nail-patella syndrome (hereditary osteo-onychodysplasia)	Hypoplastic nails, hypoplastic or absent patella, other bone anomalies	Proteinuria, nephrotic syndrome
Townes-Brocks syndrome	Thumb, auricular, and anal anomalies	Various renal abnormalities
X-Linked		
Oculocerebrorenal syndrome (Lowe syndrome)	Cataracts, rickets, mental retardation	Fanconi syndrome
Oral–facial–digital (OFD) syndrome type I	Oral clefts, hypoplastic alae nasi, digital asymmetry (X-linked, lethal in men)	Renal microcysts
Trisomy 21 (Down syndrome)	Abnormal facies, brachycephaly, congenital heart disease	Cystic dysplastic kidney and other renal abnormalities
X0 syndrome (Turner syndrome)	Small stature, congenital heart disease, amenorrhea	Horseshoe kidney, duplications and malrotations of the urinary collecting system
Trisomy 13 (Patau syndrome)	Abnormal facies, cleft lip and palate, congenital heart disease	Cystic dysplastic kidneys and other renal anomalies
Trisomy 18 (Edwards syndrome)	Abnormal facies, abnormal ears, overlapping digits, congenital heart disease	Cystic dysplastic kidneys, horseshoe kidney, or duplication
XXY, XXX syndrome (Triploidy syndrome)	Abnormal facies, cardiac defects, hypospadias and cryptorchidism in men, syndactyly	Various renal abnormalities
Partial trisomy 10q	Abnormal facies, microcephaly, limb and cardiac abnormalities	Various renal abnormalities

Table 28.6. Inulin Clearance Glomerular Filtration Rate in Healthy Premature Infants

Age	mL/minute/1.73 m^2
1–3 days	14.0 ± 5
1–7 days	18.7 ± 5.5
4–8 days	44.3 ± 9.3
3–13 days	47.8 ± 10.7
1.5–4 months	67.4 ± 16.6
8 years	103 ± 12

b. Protein excretion varies with gestational age. Urinary protein excretion is higher in premature infants and decreases progressively with postnatal age (see Table 28.3). In normal full-term infants, protein excretion is minimal after the second week of life.

c. Glycosuria is commonly present in premature infants of <34 weeks' gestation. The tubular resorption of glucose is <93% in infants born before 34 weeks' gestation compared with 99% in infants born after 34 weeks' gestation. Glucose excretion rates are highest in infants born before 28 weeks' gestation.

d. Hematuria is abnormal and rare in the term newborn. It is more frequent in premature infants and has a broad differential (see section III.F).

e. The urinary sediment examination will usually demonstrate multiple epithelial cells (thought to be urethral mucosal cells) for the first 24 to 48 hours. In infants with asphyxia, an increase in epithelial cells and transient microscopic hematuria with leukocytes is common. Further investigation is necessary if these sediment findings persist. Hyaline and fine granular casts are common in dehydration or hypotension. Uric acid crystals are common in dehydration states and concentrated urine samples. They may be seen as pink or reddish-brown diaper staining (particularly with modern absorptive diapers).

2. **Method of urine collection**

a. Suprapubic aspiration performed under ultrasound guidance is the most reliable (although impractical) method to obtain an uncontaminated sample collection for urine culture.

b. Bladder catheterization is used if an infant has failed to pass urine by 36 to 48 hours and is not apparently hypovolemic (see section III.B), if precise determination of urine volume is needed, or to optimize urine drainage if functional or anatomical obstruction is suspected.

c. Bag collections are adequate for most studies such as determinations of specific gravity, pH, electrolytes, protein, glucose, and sediment but should never be used for urine culture if urinary tract infection (UTI)

is suspected. Bladder catheterization can cause trauma of the urethral mucosa; therefore, bag collection is the preferred method if hematuria is suspected.

d. Diaper urine specimens are reliable for estimation of pH and qualitative determination of the presence of glucose, protein, and blood.

3. Evaluation of renal function

a. Serum creatinine at birth reflects maternal kidney function. In healthy term infants, serum creatinine levels fall quickly from the maternal value to a level of 0.2 to 0.4 mg/dL by 1 to 2 weeks of life. Premature infants' serum creatinine may rise transiently for the first few days and then will reduce slowly over weeks to months depending on the level of prematurity. The rate of decrease in serum creatinine in the first few weeks is slower in younger gestational age infants with lower GFR (see Table 28.1).

b. Blood urea nitrogen (BUN) is another potential indicator of kidney function. However, BUN can be elevated as a result of increased production of urea nitrogen in hypercatabolic states or increased protein intake, sequestered blood, tissue breakdown, or from hemoconcentration.

c. GFR can be measured directly by clearance studies of either exogenous substances (inulin, chromium ethylenediaminetetraacetic acid [Cr-EDTA], sodium iothalamate) or endogenous substances such as creatinine and cystatin C. Practical considerations such as frequent blood sampling, urine collection, or infusion of an exogenous substance limit their use and are used only for research purposes. GFR is most often estimated from serum creatinine and body length (see Table 28.2), although the equation must be used with caution because it is strictly an estimate with significant predictive variability in determining true GFR. Newer estimates using cystatin C (Table 28.7) are increasingly used in clinical practice.

d. Measurement of serum and urine electrolytes is used to guide fluid and electrolyte management and in assessing kidney tubular function. One must consider serum values and clinical context in order to interpret urine electrolyte measurements.

Table 28.7. Serum Cystatin Reference Range (mg/L) in Term and Preterm Infants (Mean ± 2 SD)

Age	Cystatin C
24–28 weeks	1.48 (0.65–3.37)
29–36 weeks	1.65 (0.62–4.42)
0–3 months	1.37 (0.81–2.32)
4–11 months	0.98 (0.65–1.49)

SD, standard deviation.

Source: Reproduced from Finney H, Newman DJ, Thakkar H, et al. Reference ranges for plasma cystatin C and creatinine measurements in premature infants, neonates, and older children. *Arch Dis Child* 2000;82(1):71–75. Copyright © 2000 Royal College of Paediatrics and Child Health, with permission from BMJ Publishing Group Ltd.

D. Radiologic studies

1. **Ultrasonography** is the initial imaging study to delineate kidney parenchymal architecture. This is a noninvasive, low-cost study that can be done at the bedside and is especially useful in unstable neonates. It can easily confirm the presence of gross renal abnormalities seen in an antenatal ultrasound, such as hydronephrosis or dysplastic kidney disease. As a general rule, the length of the kidneys in millimeters is approximately the gestational age in weeks. Normative data is presented in Table 28.8. Larger kidneys may suggest the presence of hydronephrosis, PKD, multicystic dysplastic kidney (MCDK), or rarely, congenital nephrotic syndrome or renal tumors. Smaller kidneys may suggest dysplasia or hypoplasia. The kidney cortex has echogenicity similar to that of the liver or spleen in the neonate, in contrast to the hypoechoic renal cortex seen in adults and older children. Hyperechoic kidneys can be seen in PKD, cystic dysplasia, glomerulocystic disease, or kidney injury. In addition, the medullary pyramids in the neonate are much more hypoechoic than the cortex and hence are more prominent in appearance. Color Doppler flow techniques have significant intraoperator variability but can visualize and measure RBF and renal artery resistive index (RI). Preterm infants tend to have higher RI compared to term infants; higher RI can suggest renal parenchymal disease and urinary tract obstruction.
2. **Voiding cystourethrography (VCUG)**, with fluoroscopy, is an excellent method to identify vesicoureteral reflux (VUR) and define bladder and lower tract anatomy such as in posterior urethral valves (PUV). Radionuclide cystography is often used to evaluate VUR because of its lower radiation dose. However, VCUG produces better static imaging for anatomical defects and is preferred for the initial evaluation of obstructive uropathy. Most radiologists perform VCUGs without sedation, the use of which has been associated with false-positive results.
3. **Radionuclide scintigraphy** is useful in demonstrating the position and relative function of the kidneys in infants who have sufficient GFR. Isotopes such as technetium-99m-diethylenetriaminepentacetic acid (DTPA) or mercaptoacetyltriglycine (MAG3) are handled by glomerular filtration and can be used to assess RBF and kidney function. In conjunction with intravenously administered furosemide, it can help differentiate obstructive from nonobstructive hydronephrosis. Isotopes that bind to the renal tubules, such as technetium-99m-dimercaptosuccinic acid (DMSA), produce static images of the renal cortex. This may be helpful for assessing acute pyelonephritis and renal scarring from renal artery emboli or renal vascular disorders and to quantify the amount of renal cortex in patients with renal dysplasia and hypoplasia. Most of these nuclear techniques rely on renal filtration and are thus of questionable use in very preterm infants.

Table 28.8. Longitudinal Dimensions (mm) of Right and Left Kidneys by Gestational Age and Gender

		Gestational age	Median	Minimum	Maximum	Percentile	
						5th	95th
Female	Right kidney Left kidney	≤24	28.6	23.7	33.1	23.7	33.1
		25–26	32.7	26.2	41.0	26.4	39.0
		27–28	33.0	27.8	42.4	28.1	41.0
		29–30	36.2	28.4	45.0	29.5	42.1
		31–32	38.4	30.5	45.8	30.8	44.0
		33–34	40.9	32.4	48.1	33.8	47.8
		35–36	42.8	35.3	49.3	35.6	48.4
		Full term*	41.0	31.0	50.0	37.0	48.0
		≤24	28.4	21.4	33.6	21.4	33.6
		25–26	31.8	27.7	37.7	27.7	37.6
		27–28	33.0	27.7	40.0	27.7	39.7
		29–30	36.5	27.4	46.8	29.4	42.6
		31–32	37.9	30.0	44.3	31.6	44.0
		33–34	40.4	34.2	50.0	34.6	49.1
		35–36	43.5	35.2	50.3	36.7	49.0
		Full term*	42.0	36.0	52.0	38.0	49.0
Male	Right kidney Left kidney	≤24	25.3	25.0	25.7	25.0	25.7
		25–26	33.3	27.9	36.6	27.9	36.6
		27–28	33.5	23.0	42.4	28.5	40.7
		29–30	36.7	25.4	50.2	30.7	48.4
		31–32	39.3	26.5	56.0	30.0	48.3
		33–34	42.3	34.6	50.6	34.8	50.2
		35–36	43.5	34.9	54.5	38.1	53.0
		Full term*	42.0	36.0	53.0	38.0	49.0

(continued)

Table 28.8. Longitudinal Dimensions (mm) of Right and Left Kidneys by Gestational Age and Gender *(Continued)*

		Gestational age	Median	Minimum	Maximum	Percentile	
						5th	95th
		≤24	25.4	24.1	26.8	24.1	26.8
		25–26	32.3	28.1	36.8	28.1	36.8
		27–28	34.0	26.1	40.7	27.5	40.4
		29–30	36.6	23.8	54.0	30.2	45.1
		31–32	39.7	28.3	52.2	30.8	47.1
		33–34	42.2	35.0	50.0	35.5	49.7
		35–36	43.5	36.2	52.4	37.5	50.3
		Full term*	44.0	38.0	55.0	39.0	51.0

*Mean gestational age 39.7 ± 0.7.

Source: Modified by permission from Springer: Erdemir A, Kahramaner Z, Cicek E, et al. Reference ranges for sonographic renal dimensions in preterm infants. *Pediatr Radiol* 2013;43(11):1475–1484.

III. COMMON CLINICAL KIDNEY PROBLEMS IN NEONATES

A. Conditions diagnosed by prenatal ultrasonography. Congenital anomalies of the kidney and urinary tract (CAKUT) comprise about 20% of fetal anomalies identified on routine maternal ultrasonographic screening.

1. Hydronephrosis is the most common abnormal finding, reported in >80% of the cases with a kidney abnormality. Approximately 75% of these are confirmed postnatally.

a. Initial management of a newborn with prenatally identified hydronephrosis depends on the clinical condition of the patient and the suspected nature of the lesion.

b. Unilateral hydronephrosis is more common and is not associated with systemic or pulmonary complications if the contralateral kidney is normal. Postnatal ultrasonographic confirmation may be carried out electively at approximately 2 to 4 weeks of life, depending on severity. Earlier ultrasonographic examination might miss abnormalities because hydronephrosis may not be detected because of physiologic dehydration. It is important to repeat the study if done in the first few days after birth.

c. Bilateral hydronephrosis is more worrisome, especially if oligohydramnios or pulmonary disease is present. In the male infant, postnatal evaluation (ultrasonography and VCUG) should be performed within

the first day to determine the etiology (PUV, ureteropelvic junction [UPJ] obstruction, ureterovesical junction [UVJ] obstruction, prune belly syndrome, or VUR). With postbladder obstruction such as PUV, ultrasonography will often demonstrate a trabeculated and thickened bladder wall. Concomitant tortuous ureters are an ominous finding for overall kidney function and development.

d. Antibiotic prophylaxis is recommended until VCUG rules out VUR. Nitrofurantoin (1 to 2 mg/kg/day) or trimethoprim-sulfamethoxazole (2 mg of trimethoprim plus 10 mg of sulfamethoxazole per kilogram per day) are used for UTI prophylaxis in older infants. In infants with postgestational age <48 weeks, nitrofurantoin can cause hemolytic anemia and sulfa displaces bilirubin from albumin and kernicterus can develop. Due to these reasons, amoxicillin (10 mg/kg/day) is the initial drug of choice in infants with postgestational age <48 weeks (see section III.G).

e. In the presence of VUR, long-term prophylactic antibiotics have been shown in one trial to reduce the number of symptomatic UTIs. Despite the improvement in clinical infections, there was no difference in the rate of renal scarring between children given prophylaxis or not. This finding might indicate the underlying renal dysplasia is often present during renal development even when early prophylaxis is initiated.

2. **MCDK** is being diagnosed more by routine prenatal ultrasonography, especially those with unilateral involvement. An MCDK is one composed of cysts of varying sizes resembling a "ball of grapes" and nonfunctional parenchyma. Infants with unilateral MCDK are usually asymptomatic, and functional imaging by definition, shows the affected kidney has no renal function. Although the affected kidney may initially grow (due to cyst growth) during infancy, the affected kidney usually involutes and is often no longer visible on imaging by age 5 years. Although surgical removal was previously been recommended to decrease the potential of malignant transformation, studies have shown that the incidence of malignant transformation is extremely low, and there is no evidence that surgical removal of asymptomatic MCDK improves long-term outcomes. There is general agreement that surgical removal is indicated only *rarely* in cases with recurrent infection or with respiratory compromise secondary to abdominal compression by the abnormal kidney. The contralateral kidney may have abnormalities such as VUR, and there is an increased risk of hypertension so ongoing follow-up is recommended.

3. Additional forms of CAKUT may be diagnosed with prenatal ultrasound or soon after birth. Common lesions include dysplastic kidneys (with or without cysts) and obstruction of the urinary system either at the level of the UPJ, UVJ, or by valves at the urethra (PUV). ARPKD, which is associated with liver fibrosis, can cause renal failure in neonates. Autosomal dominant PKD (ADPKD) is more common in the general population but does not generally present until later in life. Renal masses may also be diagnosed early (see Table 28.2). The severity of renal impairment in these diseases varies from extreme oligohydramnios and *in utero* compromise to late presentation in adulthood. Ultimately, the prognosis depends on the severity of the anomaly, whether the

Table 28.9. Acute Kidney Injury Criteria in Neonates

Stage	Serum Creatinine Criteria	Urinary Output Criteria
0	No change in SCr or rise <0.3 mg/dL	UOP >1 mL/kg/hour
1	SCr increase of ≥0.3 mg/dL within 48 hours or SCr increase to 150%–199% of baseline*	UOP >0.5 mL/kg/hour and ≤1 mL/kg/hour
2	SCr increase to 200%–299% of baseline	UOP >0.3 mL/kg/hour and ≤0.5 mL/kg/hour
3	SCr increase to ≥300% of baseline or SCr ≥2.5 mg/dL or receipt of dialysis	UOP ≤0.3 mL/kg/hour

*Baseline serum creatinine (SCr) will be defined as the lowest previous SCr value within 7 days.

UOP, urine output.

contralateral kidney is viable, and on extrarenal organ dysfunction. In the newborn course, the degree of pulmonary hypoplasia will dictate the likelihood of viability of the infant. Long term, CAKUT remains the most common cause of CKD and end-stage renal disease (ESRD) in childhood.

B. AKI, previously termed acute renal failure, is defined as an abrupt decrease in glomerular filtration, with or without underlying structural abnormalities. The condition often presents with diminished urinary output and/or elevation of serum creatinine (Table 28.9) and other electrolyte abnormalities. AKI correlates with mortality as in older pediatric and adult patients. It may be prerenal, intrinsic (tubular, glomerular, or interstitial disease), or postrenal (obstructive) in nature and is often multifactorial (Table 28.10).

1. **Prerenal AKI** occurs when the kidney becomes under perfused. The most common causes of prerenal azotemia are loss of effective blood volume, relative loss of intravascular volume from increased capillary leak, poor cardiac output, medications that decrease RBF, or intra-abdominal compartment syndrome. These conditions can lead to intrinsic renal tubular damage if not corrected expeditiously.
2. **Intrinsic AKI** implies direct damage to the glomeruli, interstitium, or tubules. In neonates, tubular injury is most commonly caused by prolonged or severe ischemia, nephrotoxins, or sepsis. Glomerular and primary interstitial injury is very rare in neonates.
3. **Postrenal AKI** results from obstruction to urinary flow in both kidneys. In boys, the most common lesion is PUV; however, acquired obstruction (from masses, stones, or fungal balls) can also occur. Renal function may be abnormal even after correction of the obstruction,

Table 28.10. Causes of Acute Kidney Injury in the Neonatal Period
1. Prerenal
a. Reduced effective circulatory volume
i. Hemorrhage/dehydration
ii. Sepsis
iii. Necrotizing enterocolitis
iv. Congenital heart disease
v. Hypoalbuminemia
b. Increased renal vascular resistance
i. Polycythemia
ii. Indomethacin
iii. Adrenergic drugs (e.g., tolazoline)
c. Hypoxia/asphyxia
2. Intrinsic or renal parenchymal
a. Sustained hypoperfusion leading to acute tubular necrosis
b. Congenital anomalies
i. Agenesis
ii. Hypoplasia/dysplasia
iii. Polycystic kidney disease
c. Thromboembolic disease
i. Bilateral renal vein thrombosis
ii. Bilateral renal arterial thrombosis
d. Nephrotoxins
i. Aminoglycosides
ii. Radiographic contrast media
iii. Maternal use of ACE inhibitors or indomethacin
3. Obstructive
a. Urethral obstruction
i. Posterior urethral valves
ii. Stricture
(continued)

Table 28.10. Causes of Acute Kidney Injury in the Neonatal Period *(Continued)*
b. Ureterocele
c. Ureteropelvic/ureterovesical obstruction
d. Extrinsic tumors
e. Neurogenic bladder
f. Megacystis or megaureter syndrome
ACE, angiotensin-converting enzyme.

and clinicians must anticipate and be prepared to manage excessive postobstructive diuresis and associated complications.

Evaluation to determine the underlying etiology of rising creatinine or decreased urine output is critical to AKI management.

4. Evaluate history for oligohydramnios, perinatal asphyxia, bleeding disorders, polycythemia, thrombocytosis, thrombocytopenia, sepsis, or maternal drug use. Evaluate for the presence of nephrotoxic medication. Aminoglycoside drugs such as gentamicin for sepsis rule out, nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen or indomethacin for patent ductus arteriosus (PDA) closure, and ACE inhibitors such as captopril or enalapril commonly used in infants with congenital heart defects can cause AKI.
5. Place an indwelling urinary catheter for accurate output measurement.
6. Evaluate for signs and symptoms of intravascular depletion (tachycardia, sunken fontanelle, poor skin turgor, dry mucous membranes).
7. If edema is present, evaluation to determine whether intravascular volume is depleted (e.g., in hypoalbuminemia) or elevated is helpful in determining the etiology and plan of action.
8. A fluid challenge with normal saline 10 to 20 mL/kg can not only replete intravascular volume but also help to determine if intravascular depletion is present. Evaluation for cardiac failure is imperative prior to aggressive fluid resuscitation for renal failure.
9. Renal ultrasonogram should be performed to rule out bladder obstruction and to assess for CAKUT.
10. Laboratory evaluation can help determine the underlying etiology. Table 28.11 lists laboratory tests that are helpful in differentiating prerenal azotemia from intrinsic and obstructive causes. Test samples should be obtained before fluid challenge if possible.

Management of those who develop AKI should focus on treating the underlying etiology, avoiding further injury, and addressing consequences of decreased renal function.

11. As mentioned, response to fluid challenge not only provides information about the underlying cause of AKI but also serves as the beginning

Table 28.11. Renal Failure Indices in the Oliguric Neonate

Indices	Prerenal Failure	Intrinsic Renal Failure
Urine sodium (mEq/L)	10–50	30–90
Urine/plasma creatinine	29.2 ± 1.6	9.7 ± 3.6
FENa*	0.9 ± 0.6	4.3 ± 2.2

*Fractional excretion of sodium (FENa) defined in Chapter 9.

Source: Modified with permission from Mathew OP, Jones AS, James E, et al. Neonatal renal failure: usefulness of diagnostic indices. *Pediatrics* 1980;65(1):57–60. Copyright © 1980 by the American Academy of Pediatrics.

of the management plan. Close evaluation of the cause of the intravascular volume depletion should be sought and appropriate fluid management should be given. Intravenous albumin should be considered for those with low serum albumin.

12. Avoidance of nephrotoxic medications to prevent further insult and dose adjustment of concurrent medications based on estimated renal function are critical to early recovery. Remember that rising creatinine is a late (and slow) manifestation of diminished GFR. Avoidance of further injury to damaged kidneys might prevent further complications.
13. Furosemide may be given to correct fluid overload but has not been shown to prevent or diminish AKI. Adequate urine output does not signify adequate or recovered GFR. If patient has response to diuresis, careful monitoring of electrolytes and fluid status should be followed as hypokalemia, metabolic alkalosis, or hypovolemia can result after several days of treatment in ongoing AKI. Low-dose or "renal dose" (2 μg/kg/day) dopamine has *not* been shown to prevent AKI, although it may also increase urine output.
14. If blood pressure is low in relation to vascular congestion and/or abdominal pressures, consider increasing blood pressure with inotropes to increase glomerular filtration (see Chapter 40).
15. **Management of complications**
    a. Discontinue or minimize potassium (K^+) intake. Low-K^+ formula such as Similac PM 60/40 or K^+-free IV solution are used. Treatment of hyperkalemia (K^+ >6 mEq/L) is as follows:
        i. **Calcium** is given as 1 to 2 mL/kg of calcium gluconate 10% over 2 to 4 minutes for cardioprotection. The electrocardiogram (ECG) is monitored.
        ii. **Sodium bicarbonate will shift potassium into the cells and can temporarily lower serum K^+.** A dose of 1 mEq/kg given intravenously over 5 to 10 minutes will decrease serum potassium by 1 mEq/L.
        iii. **Glucose and insulin will also shift K^+ into cells to temporarily lower serum K^+ levels.** Begin with a bolus of regular human

insulin (0.05 units/kg) and dextrose 10% in water (2 mL/kg) followed by a continuous infusion of dextrose 10% in water at 2 to 4 mL/kg/hour and human regular insulin (10 units per 100 mL) at 1 mL/kg/hour. Monitor blood glucose level frequently. Maintain a ratio of 1 or 2 units of insulin to 4 g glucose.

iv. **Furosemide** can be given for kaliuresis as well as natriuresis. A trial of 1 mg/kg intermittently is given. Avoid volume depletion due to over diuresis.

v. **Sodium polystyrene sulfonate (Kayexalate)** is often used in **older** children as needed (PRN) to decrease serum K levels. However, given the risk of intestinal necrosis and other serious gastrointestinal (GI) events such as bowel perforation, Kayexalate is no longer routinely used in neonates.

vi. **Dialysis** is considered when hyperkalemia cannot be controlled with the above medical therapy. Although hemodialysis (HD) is the most rapid way to remove K^+, peritoneal dialysis (PD) or continuous renal replacement therapy (CRRT) can be used (see section III.B.15.i later).

b. Fluid management is based on the patient's fluid status and determination of ongoing losses. Unless dehydration or polyuric states are present, volume should be limited to replacement of insensible losses and urine output (see Chapter 23). The inability to adequately prescribe nutrition due to fluid restriction and/or significant fluid overload is an indication for dialysis.

c. Sodium (Na^+) concentration is monitored, accounting for fluid balance. Hyponatremia is usually secondary to excess free water and the inability of the injured kidneys to appropriately reabsorb filtered Na^+. Close monitoring of electrolytes, especially sodium, is needed during diuretic therapy or with dialysis.

d. Phosphorus is restricted in AKI, if needed, by using a low-phosphorus formula (e.g., Similac PM 60/40). Oral calcium carbonate can be used as a phosphate-binding agent when administered with feeds.

e. Calcium supplementation is given if ionized calcium is decreased or the patient is symptomatic. In infants with CKD, 1,25-dihydroxyvitamin D or its analog is given to maximize intestinal Ca^{2+} absorption and prevent renal osteodystrophy (see Chapter 25).

f. Metabolic acidosis is usually mild unless there is (i) significant tubular dysfunction with decreased ability to reabsorb bicarbonate or (ii) increased lactate production due to decreased perfusion from heart failure or hemorrhagic volume loss (see section III.B). Use sodium bicarbonate or sodium citrate to correct severe metabolic acidosis.

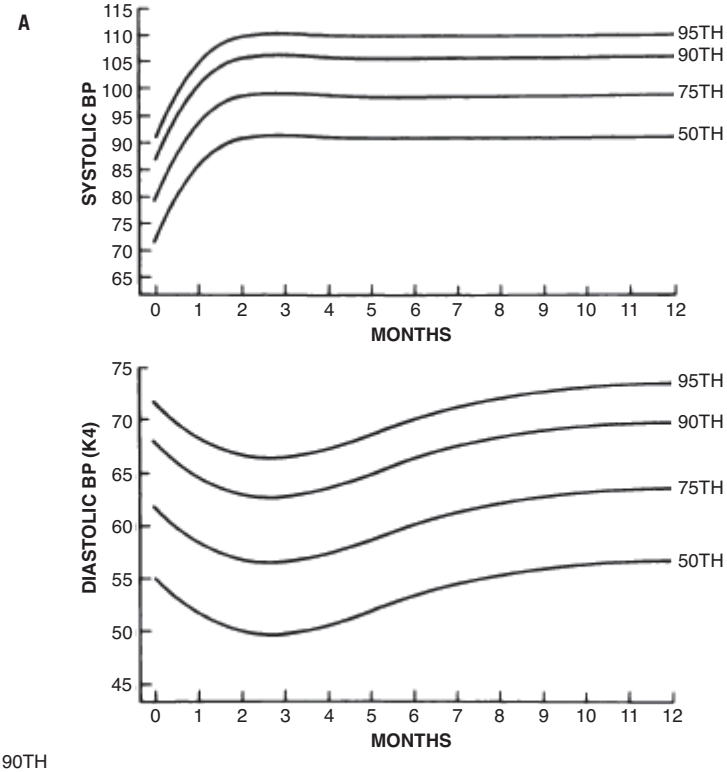
g. Nutrition is critical to the growing newborn. Infants who can take oral feeds are given a low-phosphate and low-potassium formula with a low renal solute load (e.g., Similac PM 60/40). Caloric density can be progressively increased while monitoring for signs of intolerance because the increased solute load is often not well tolerated. Adequate protein for neonates with otherwise normal renal function should be provided unless they are on CRRT or PD. Because these therapies can cause protein losses of 1.0 to 1.5 g/kg/day, additional protein supplementation is necessary.

h. Hypertension (see section III.C).

i. Dialysis is indicated when conservative management has been unsuccessful in correcting severe fluid overload, hyperkalemia, acidosis, and uremia. Inadequate nutrition because of severe fluid restriction in the anuric or oliguric infant is a relative indication for dialysis. Because the technical aspects and the supportive care are specialized and demanding, this procedure must be performed in centers where the staff has experience with acute dialysis in infants and neonates. PD is the preferred dialysis modality in neonates and makes use of the peritoneum as the dialyzer membrane. Clearance and fluid removal occur with repeated instillations of dextrose containing dialysate into the peritoneal cavity through a PD catheter. PD in neonates must be performed manually with individual exchanges due to the small volumes initially used (manual PD). Automated PD can be performed once larger exchange volumes are tolerated by the patient. In HD or CRRT, the small blood volume of neonates results in a relatively large extracorporeal blood volume during the procedure due to the size of available tubing and dialyzers. A blood prime is typically required for each treatment, and the infant may experience temperature instability and rapid fluid shifts. To address this, newer machines that require smaller extracorporeal blood circuit volumes are being used around the world. These include Aquadex (adapted for neonatal care in the United States), CARPEDIEM, and the Newcastle infant dialysis and ultrafiltration system (Nidus). Appropriate vascular access must be established for these modalities and anticoagulation is needed in most cases. Indications for specific dialysis modality will vary depending on the patient, clinical situation, and medical institution and are not discussed here. Despite recent advances in dialysis devices and more broadly based expertise, dialysis-dependent AKI in a neonate is still a disease with high morbidity and mortality.

C. Blood pressure in the newborn is much lower than in older children and adults. Specific values are related to weight and gestational age. Blood pressure rises with postnatal age, 1 to 2 mm Hg/day during the first week and 1 mm Hg/week during the next 6 weeks in both the preterm and full-term infant (Fig. 28.2).

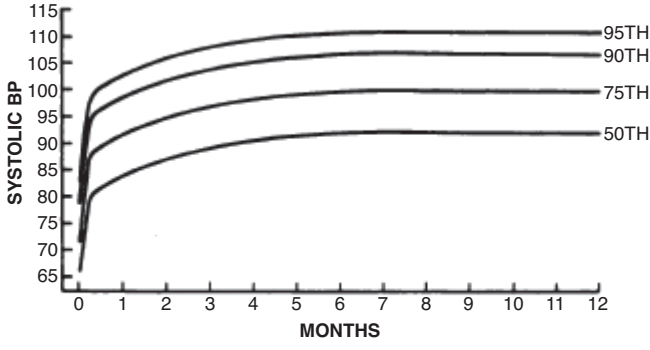
1. Normative values of blood pressure are shown for full-term infants and premature infants in Tables 28.12, 28.13, and 28.14. All normative values for blood pressure are based on pressures measured in the arm of calm infants. Leg pressures are often higher than arm pressures, as are measurements taken during crying or times of distress.
2. **Hypertension** is defined as persistent blood pressure >95th percentile (2 standard deviations above the mean) for postmenstrual age. The clinical signs and symptoms, which are all nonspecific and may even be absent, include cardiorespiratory abnormalities such as tachypnea, cardiomegaly, or heart failure; neurologic findings such as irritability, lethargy, or seizure; failure to thrive; or GI difficulties. All infants in the neonatal intensive care unit (NICU) should have their blood pressures measured, preferably in the arm when calm with an appropriate size cuff. Persistently elevated blood pressures should lead to a more thorough evaluation of etiology.

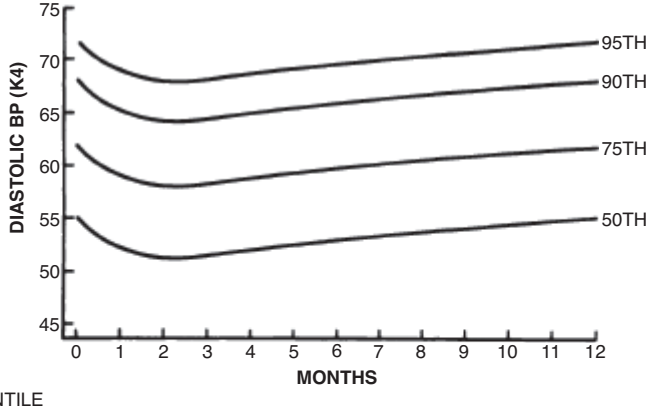


90TH PERCENTILE													
SYSTOLIC BP	87	101	106	108	106	105	106	105	106	106	105	105	105
DIASTOLIC BP	68	66	63	63	63	66	66	67	68	68	69	69	69
HEIGHT CM	51	59	63	66	68	70	72	73	74	76	77	78	80
WEIGHT KG	4	4	5	5	6	7	8	9	9	10	10	11	11

Figure 28.2. Age-specific percentiles for blood pressure (BP). **A:** Age-specific percentiles of BP measurements in boys—birth to 12 months of age; Korotkoff phase IV (K4) used for diastolic BP. **B:** Age-specific percentiles of BP measurements in girls—birth to 12 months of age; Korotkoff phase IV (K4) used for diastolic BP. (Reproduced with permission from Task Force on Blood Pressure Control in Children. Report of the Second Task Force on Blood Pressure Control in Children—1987. *Pediatrics* 1987;79[1]:1–25. Copyright © 1987 by the American Academy of Pediatrics.)

3. Neonatal hypertension has many causes (Table 28.15). The three most common causes of hypertension in newborns are secondary to umbilical artery thrombi, bronchopulmonary dysplasia, and renal parenchymal disease. Evaluation includes history and physical examination, a review of fluid status, medications, history of umbilical or arterial line placement, and four extremity blood pressure measurements. Renin-mediated hypertension and fluid overload may both contribute to renal causes of hypertension. Urinalysis, renal function studies, serum electrolyte levels, and renal ultrasonographic examination should also be obtained. Color Doppler flow studies may detect aortic or renal vascular





90TH PERCENTILE													
SYSTOLIC BP	76	88	101	104	105	106	106	106	106	106	106	106	106
DIASTOLIC BP	68	65	64	64	65	65	66	66	68	67	67	67	67
HEIGHT CM	54	55	56	58	61	63	66	66	70	72	74	75	77
WEIGHT KG	4	4	4	5	5	6	7	8	9	9	10	10	11

Figure 28.2. (*Continued*)

thrombosis, although this test is not reliable in neonates and carries the possibility of both false positives and false negatives. A DMSA renal scan may detect segmental renal arterial infarctions. Plasma renin levels are difficult to interpret in neonates. Echocardiogram is indicated if coarctation is suspected and can also be useful to determine if left ventricular hypertrophy has occurred from sustained hypertension.

4. Management is directed at correcting the underlying cause whenever possible. Antihypertensive therapy (Table 28.16) is administered for sustained hypertension that is not related to volume overload or concomitant medications. Hydralazine is most commonly used acutely or as a PRN medication. A calcium channel blocker such as amlodipine is a reasonable first choice for persistent hypertension. ACE inhibitor such as captopril also work well, but close monitoring for side effects (e.g., hyperkalemia) is necessary. Regardless of the need for antihypertensive medications, most neonatally acquired hypertension resolves within a few years. Because of their early course, NICU graduates are at increased

Table 28.12. Systolic and Diastolic Blood Pressure Ranges in Infants of 500–2,000 g Birth Weight at 3–6 Hours of Life

Birth Weight (g)	Systolic (mm Hg)	Diastolic (mm Hg)
501–750	50–62	26–36
751–1,000	48–59	23–36
1,001–1,250	49–61	26–35
1,251–1,500	46–56	23–33
1,501–1,750	46–58	23–33
1,751–2,000	48–61	24–35

Source: Reprinted from Hegyi T, Carbone MT, Anwar M, et al. Blood pressure ranges in premature infants. I. The first hours of life. *J Pediatr* 1994;124(4):627–633. Copyright © 1994 Elsevier. With permission.

risk for developing hypertension during adolescence, especially those who require treatment with antihypertensive medications.

D. Renal vascular thrombosis

1. **Renal artery thrombosis (RAT)** is often related to the use of indwelling umbilical artery catheters which can obstruct or emit an embolus into the renal artery. Other rare causes include congenital hypercoagulable states and severe hypotension. Although the management is controversial, potential options include surgical thrombectomy, thrombolytic agents, and conservative medical care including antihypertensive therapy. The surgical renal salvage rate is no better than medical management. As with other etiologies of neonatal hypertension, patients with unilateral RAT who receive conservative medical treatment are usually normotensive by 2 years of age, no longer requiring antihypertensive medications, and have normal creatinine clearance, although some have unilateral renal atrophy with compensatory contralateral hypertrophy. There have been reports of long-term complications with hypertension and/or proteinuria and progression to CKD in adolescence (see Chapter 44).
2. **Renal vein thrombosis (RVT)** has the predisposing conditions of hyperosmolarity, polycythemia, hypovolemia, and hypercoagulable states and is, therefore, often associated with infant of diabetic mothers, inherited thrombophilia, or use of umbilical venous catheters. Intrauterine RVT may occur and presents with calcified thrombus in the inferior vena cava (IVC). The classic clinical findings of RVT include gross hematuria, enlarged kidneys that may be palpable on exam, hypertension, and thrombocytopenia. The diagnosis of RVT is confirmed by ultrasonography, which typically shows an enlarged kidney with diffuse homogenous hyperechogenicity. Doppler flow studies may detect thrombi in the IVC or renal vein leading to absent renal flow. Initial therapy of RVT should focus on the maintenance of circulation, fluid,

Table 28.13. Estimated Blood Pressure Values after 2 Weeks of Age in Infants from 26 to 44 Weeks Postconceptional Age

Postconceptional Age	50th Percentile	95th Percentile	99th Percentile
44 weeks			
SBP	88	105	110
DBP	50	68	73
MAP	63	80	85
42 weeks			
SBP	85	98	102
DBP	50	65	70
MAP	62	76	81
40 weeks			
SBP	80	95	100
DBP	50	65	70
MAP	60	75	80
38 weeks			
SBP	77	92	97
DBP	50	65	70
MAP	59	74	79
36 weeks			
SBP	72	87	92
DBP	50	65	70
MAP	59	72	77
34 weeks			
SBP	70	85	90
DBP	40	55	60
MAP	50	65	70
32 weeks			
SBP	68	83	88
DBP	40	55	60
MAP	49	64	69

(continued)

Table 28.13. Estimated Blood Pressure Values after 2 Weeks of Age in Infants from 26 to 44 Weeks Postconceptional Age *(Continued)*

Postconceptual Age	50th Percentile	95th Percentile	99th Percentile
30 weeks			
SBP	65	80	85
DBP	40	55	60
MAP	48	63	68
28 weeks			
SBP	60	75	80
DBP	38	50	54
MAP	45	58	63
26 weeks			
SBP	55	72	77
DBP	30	50	56
MAP	38	57	63

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

Source: Reprinted by permission from Springer: Dionne JM, Abitbol CL, Flynn JT. Hypertension in infancy: diagnosis, management and outcome. *Pediatr Nephrol* 2012;27(1):17–32.

Table 28.14. Normal Longitudinal Blood Pressure in Full-Term Infants (mm Hg)

	Boys		Girls	
Age	Systolic	Diastolic	Systolic	Diastolic
First day	67 ± 7	37 ± 7	68 ± 8	38 ± 7
Fourth day	76 ± 8	44 ± 9	75 ± 8	45 ± 8
1 month	84 ± 10	46 ± 9	82 ± 9	46 ± 10
3 months	92 ± 11	55 ± 10	89 ± 11	54 ± 10
6 months	96 ± 9	58 ± 10	92 ± 10	56 ± 10

Source: Reprinted by permission from Springer: Gemeilli M, Manganaro R, Mamì C, et al. Longitudinal study of blood pressure during the 1st year of life. *Eur J Pediatr* 1990;149(5):318–320.

Table 28.15. Causes of Hypertension in the Neonate
1. Vascular
a. Renal artery thrombosis
b. Renal vein thrombosis
c. Coarctation of the aorta
d. Renal artery stenosis
e. Idiopathic arterial calcification
2. Renal
a. Obstructive uropathy
b. Polycystic kidney disease
c. Acute kidney injury
d. Chronic kidney disease
e. Renal tumor
f. Wilms tumor
g. Glomerulonephritis
h. Pyelonephritis
3. Endocrine
a. Congenital adrenal hypoplasia
b. Primary hyperaldosteronism
c. Hyperthyroidism
4. Neurologic
a. Increased intracranial pressure
b. Cushing disease
c. Neural crest tumor
d. Cerebral angioma
e. Drug withdrawal
5. Pulmonary
a. Bronchopulmonary dysplasia
(continued)

Table 28.15. Causes of Hypertension in the Neonate *(Continued)*
6. Drugs
a. Corticosteroids
b. Caffeine
c. Theophylline
d. Adrenergic agents
e. Phenylephrine
7. Other
a. Fluid/electrolyte overload
b. Abdominal surgery
c. Associated with extracorporeal membrane oxygenation (ECMO)

and electrolyte balance while examining for underlying predisposing clinical conditions. Assessment of the coagulation status, including platelet count, prothrombin time (PT), and partial thromboplastin time (PTT), is warranted to help assess safety of anticoagulation. The American Society of Hematology recommends anticoagulation for RVT, typically with low molecular weight heparin, for the potential benefit of preventing hypertension or further renal damage. Thrombolytic therapy is recommended only for patients with bilateral renal thromboses, in attempt to preserve renal function. In these cases, recombinant tissue plasminogen activator (r-TPA) may be used with very close monitoring because it confers a high bleeding risk. Neonates with RVT should be followed long term as Ouellette et al. have shown that they are at a 15.7-fold increased risk of developing hypertension and 12.3-fold increased risk of developing CKD or death when compared to healthy children and adolescents.

E. Proteinuria in small quantities during the first weeks of life is frequently noted. After the first week, persistent proteinuria >250 mg/m^2/day should be investigated (see Table 28.3).

1. In general, **mild proteinuria** reflects a vascular or tubular injury to the kidney or the inability of the immature tubules to reabsorb protein. Administration of large amounts of colloid can exceed the reabsorptive capacity of the neonatal renal tubules and may result in mild proteinuria. Glomerular disease is rare and usually associated with congenital nephrotic syndrome if presenting in the nursery. No specific treatment is required for mild proteinuria. Treat the underlying disease and monitor the proteinuria until resolved.
2. **Massive proteinuria** (>1.5 g/m^2/day), hypoalbuminemia with serum albumin levels <2.5 g/dL, and edema are all components of congenital

Table 28.16. Antihypertensive Agents for the Newborn

	Dose	Comment
Diuretics		
Furosemide	0.5–1.0 mg/kg/dose IV, IM, PO	May cause hyponatremia, hypokalemia, hypercalciuria
Chlorothiazide	5–15 mg/kg/dose PO; q12h	
Hydrochlorothiazide	1–3 mg/kg/dose; QD	
Vasodilators		
Hydralazine	0.25–1.0 mg/kg/dose PO; q6–8h	May cause tachycardia
	Max 7.5 mg/kg/day	
	0.15–0.6 mg/kg/dose IV; q4h	
Calcium Channel Blockers		
Amlodipine	0.05–0.3 mg/kg/dose PO; q12–24h	Slower onset of action, less likely to cause sudden hypotension; may cause tachycardia
	Max 0.6 mg/kg/day	
Nifedipine	0.1–0.25 mg/kg/dose PO; q4–6h	May cause sudden hypotension; tachycardia
Nicardipine	Titrated, 1–4 μg/kg/minute continuous infusion	May cause tachycardia
Isradipine	0.05–0.15 mg/kg/dose PO; q6h	May cause sudden hypotension; tachycardia
	Max 0.8 mg/kg/day	
β-Receptor Antagonist		
Propranolol	0.5–1.0 mg/kg/dose PO; q8h	May cause bronchospasm
	Max 8–10 mg/kg/day	
α- or β-Receptor Antagonist		
Labetalol	0.5–1.0 mg/kg/dose PO; q8–12h	Caution with heart failure and chronic lung disease
	Max 10 mg/kg/day	
	0.20–1.0 mg/kg/dose IV; q4–6h	

(continued)

Table 28.16. Antihypertensive Agents for the Newborn *(Continued)*

	Dose	Comment
ACE Inhibitor		
Lisinopril	0.07–0.6 mg/kg/day PO; q24h	May cause oliguria, hyperkalemia, renal failure
Captopril	<3 months: 0.01–0.5 mg/kg/dose PO; q8h	
	>3 months: 0.15–0.3 mg/kg/dose PO; q8h	
Enalapril	0.08–0.6 mg/kg/day PO; 12–24 hours	

IV, intravenous; IM, intramuscular; PO, by mouth; max, maximum; QD, every day; ACE, angiotensin-converting enzyme.

Source: Modified by permission from Springer: Starr MC, Flynn JT. Neonatal hypertension: cases, causes, and clinical approach. *Pediatr Nephrol* 2019;34(5):787–799. doi:10.1007/s00467-018-3977-4. Erratum in: Neonatal hypertension: cases, causes, and clinical approach. *Pediatr Nephrol* 2019;34(9):1637.

nephrotic syndrome. Prenatal clues to the diagnosis include elevated maternal/amniotic α-fetoprotein levels and enlarged placenta. Children with severe forms of congenital nephrotic syndrome require frequent intravenous albumin and Lasix for fluid removal, high caloric diets, replacement of thyroid hormone, iron and vitamins due to excess losses of binding proteins, and ultimately, require bilateral nephrectomies and renal transplantation. They are at high risk for infections and thrombosis due to immunoglobulin losses and loss of anticoagulant proteins.

F. Hematuria is defined as >5 red blood cells (RBCs) per high-power field. It is uncommon in newborns and should always be investigated.

1. Hematuria has many causes (Table 28.17) including hemorrhagic disease of the newborn if vitamin K supplementation has not been given. The differential diagnosis for hematuria includes urate staining of the diaper, myoglobinuria, or hemoglobinuria. A negative dipstick with benign sediment suggests urates, whereas a positive dipstick with negative sediment for RBCs indicates the presence of globin pigments. Vaginal bleeding ("pseudomenses") in girls or a severe diaper rash is also a possible cause of blood in the diaper or positive dipstick for heme.
2. Evaluation of neonatal hematuria depends on the clinical situation. Depending on the clinical situation, one may consider performing the following tests: urinalysis with examination of the sediment, urine culture, ultrasonography of the upper and lower urinary tract, evaluation of renal function (serum creatinine and BUN), and coagulation studies.

Table 28.17. Etiology of Hematuria in the Newborn
1. Acute tubular necrosis
2. Cortical necrosis
3. Vascular disease
a. Renal vein thrombosis
b. Renal artery thrombosis
4. Bleeding and clotting disorders
a. Disseminated intravascular coagulation
b. Severe thrombocytopenia
c. Clotting factors deficiency
5. Urologic anomalies
6. Glomerular disease
7. Tumors
a. Wilms tumor
b. Neuroblastoma
c. Angiomas
8. Nephrocalcinosis
9. Trauma
a. Suprapubic bladder aspiration
b. Urethral catheterization

G. Urinary tract infection

1. Infections of the urinary tract in newborns can present with a spectrum of findings from asymptomatic bacteriuria to pyelonephritis and/or sepsis. A urine culture should be obtained from every infant with fever, poor weight gain, poor feeding, unexplained prolonged jaundice, or any clinical signs of sepsis. A UTI is uncommon in the first 48 hours of life.
2. The diagnosis is confirmed by positive urine culture obtained by suprapubic bladder aspiration or a catheterized specimen with a colony count exceeding 1,000 colonies per millimeter. A blood culture should also be obtained prior to antibiotic administration, even from asymptomatic infants with UTI. Although most newborns with UTIs have leukocytes in the urine, an infection can be present in the absence of leukocyturia.
3. *Escherichia coli* accounts for approximately 75% of the infections. The remainder are caused by other gram-negative bacilli (*Klebsiella*, *Enterobacter*,

Proteus) and by gram-positive cocci (enterococci, *Staphylococcus epidermidis*, *Staphylococcus aureus*).

4. Evaluation of the urinary tract by ultrasonography is required to rule out hydronephrosis, obstructive uropathy, severe VUR, or neurogenic bladder with inability to empty the bladder. Adequate drainage or relief of obstruction is necessary for effective antibiotic control of the infection. Although controversial in older children, a VCUG is needed in neonates following a UTI to define lower tract abnormalities and to detect reflux. VUR occurs in 40% of neonates with UTIs and predominates slightly in boys. Inadequate therapy, particularly in the presence of urologic abnormalities, could lead to renal scarring with potential development of hypertension and loss of renal function.
5. The initial treatment is antibiotics, usually a combination of ampicillin and gentamicin (to be used with caution in the setting of AKI), given parenterally. The final choice of antibiotic is based on the sensitivity of the cultured organism. Treatment is continued for 10 to 14 days, and amoxicillin prophylaxis (10 mg/kg/day) is administered until a VCUG is performed. If VUR is present, prophylactic treatment should be continued. For later onset infections (>7 days) in hospitalized infants, some experts would suggest using vancomycin rather than ampicillin to cover the possibility of hospital-acquired organisms until definitive culture results are available.

   The decision for circumcision is based primarily on parental preference. Data on risk of UTIs, penile cancer, and protection from sexually transmitted diseases in circumcised and uncircumcised men are insufficient to recommend routine circumcisions. Medical indications for circumcision include urinary retention due to adhesions of the foreskin or too tight phimosis. Circumcision should be avoided in cases of hypospadias, ambiguous genitalia, and bleeding disorders (see Chapter 9).

H. Tubular disorders

1. **Fanconi syndrome** is a group of disorders with generalized dysfunction of the proximal tubule resulting in excessive urinary losses of amino acids, glucose, phosphate, and bicarbonate. The glomerular function is usually normal.
   a. **Clinical and laboratory findings** include the following:
      i. Hypophosphatemia due to the excessive urinary loss of phosphate. In these patients, the TRP is abnormally low. Rickets and osteoporosis are secondary to hypophosphatemia and can appear in the neonatal period.
      ii. Metabolic acidosis is secondary to bicarbonate wasting (proximal renal tubular acidosis [RTA]).
      iii. Aminoaciduria and glycosuria do not result in significant clinical signs or symptoms.
      iv. These infants are often polyuric and, therefore, at risk for dehydration.
      v. Hypokalemia, due to increased excretion by the distal tubule to compensate for the increased sodium reabsorption, is also frequent and sometimes profound.

b. Etiology. The primary form of Fanconi syndrome is rare in the neonatal period and is a diagnosis of exclusion. Although familial cases (mainly autosomal dominant) have been reported, it is generally sporadic. Most secondary forms of the syndrome in the neonatal period are related to inborn errors of metabolism, including cystinosis, hereditary tyrosinemia, hereditary fructose intolerance, galactosemia, glycogenosis, Lowe syndrome (oculocerebrorenal syndrome), and mitochondrial disorders. Cases associated with heavy metal toxicity have also been described.

2. **RTA** is defined as metabolic acidosis resulting from the inability of the kidney to excrete hydrogen ions or to reabsorb bicarbonate. Poor growth may result from RTA. RTA cannot be diagnosed in a patient with diarrhea or other GI sources of bicarbonate losses.
   a. Distal RTA (type I) is caused by a defect in the secretion of hydrogen ions by the distal tubule. The urine cannot be acidified below a pH of 6. It is frequently associated with hypercalciuria, and NC is common later in life. In the neonatal period, distal RTA may be primary, due to a genetic defect, or secondary to several disorders.
   b. Proximal RTA (type II) is a defect in the proximal tubule with reduced bicarbonate reabsorption leading to bicarbonate wasting. Serum bicarbonate concentration falls until the abnormally low threshold for bicarbonate reabsorption is reached in the proximal tubule (generally $<$16 mEq/L). Once this threshold has been reached, no significant amount of bicarbonate reaches the distal tubule, and the urine can be acidified at that level. Proximal RTA can occur as an isolated defect or in association with Fanconi syndrome (see section III.H.1).
   c. Hyperkalemic RTA (type IV; remember, there is no type III) is a result of a combined impaired ability of the distal tubule to excrete hydrogen ions and potassium. In the neonatal period, this disorder is seen in infants with aldosterone deficiency, adrenogenital syndrome, reduced tubular responsiveness to aldosterone, or associated obstructive uropathies such as in older patients.
   d. The treatment of RTA is based on correction of the acidosis with alkaline therapy. Bicitra or sodium bicarbonate, 2 to 3 mEq/kg/day in divided doses, is usually sufficient to treat type I and type IV RTA. The treatment of proximal RTA requires larger doses, sometimes as high as 10 mEq/kg/day bicarbonate. In secondary forms of RTA, the treatment of the primary cause often results in the resolution of the RTA.

I. **NC** is detected by ultrasound examinations.

1. NC is generally associated with a hypercalciuric state. Drugs that are associated with NC and increased urinary calcium excretion include loop diuretics such as furosemide, methylxanthines, glucocorticoids, and vitamin D in pharmacologic doses. In addition, hyperoxaluria, often associated with parenteral nutrition, and hyperphosphaturia facilitate the deposition of calcium crystals in the kidney.
2. Kidney stones and NC secondary to primary hyperoxaluria/oxalosis, RTA, or UTIs are rare in newborns, although these conditions might present within a few months of birth.
3. Few follow-up studies of NC in premature infants are available. In general, kidney function is not significantly impaired and 75% of cases

resolve spontaneously often within the first year of life as demonstrated by ultrasonography. Resolution may take up to 5 to 7 years, however, and significant tubular dysfunction at 1 to 2 years of age has been reported.

It is unclear whether NC requires a specific treatment. If possible, drugs such as furosemide that cause hypercalciuria should be discontinued. Change to or addition of thiazide diuretics and supplemental magnesium in patients with bronchopulmonary dysplasia with a need for long-term diuretic therapy may be helpful. Monitoring of urinary calcium excretion (urine calcium:creatinine ratio) helps in determining response to therapy. Genetic testing should be considered in neonates with kidney stones and no history of inciting medications.

J. Cystic disease of the kidney may result from abnormalities in development, such as cystic dysplasia, or from genetic conditions. The principal differential diagnosis of bilateral cystic kidney disease in the newborn includes ARPKD, ADPKD, and glomerulocystic kidney disease.

1. In ARPKD, the genetic defect has been mapped to chromosome 6p21, which encodes a novel protein product named fibrocystin or polyductin. In infants with ARPKD, the kidneys appear markedly enlarged and hyperechogenic by ultrasonography, with a typical "snowstorm" appearance with concurrent liver fibrosis and/or dilated bile ducts. In contrast, macroscopic cysts are usually detected in cases of ADPKD and glomerulocystic disease and the liver is spared. The clinical findings of ARPKD are variable and include bilateral smooth enlarged kidneys, varying degrees of renal insufficiency, which usually progresses to ESRD over time, and severe renin-mediated hypertension. Infants with more severe involvement may have oligohydramnios with pulmonary hypoplasia and Potter syndrome, but those patients who survive the neonatal period can be carried to renal transplantation in later childhood or adolescence. ARPKD is always associated with liver involvement, which may progress to liver failure requiring transplantation in adolescence. In general, one-third of patients will have primarily renal manifestations, one-third will have primarily liver manifestations, and one-third will have significant involvement in both kidneys and liver.
2. In ADPKD, an abnormal gene (PKD1) has been identified and located on the short arm of chromosome 16, and a second gene (PKD2) located on the long arm of chromosome 4. These two genes account for most of the ADPKD patients. Clinical manifestations may include bilateral renal masses that are usually less symmetrical than in ARPKD. Because of its dominant genetics, ADPKD is much more common than ARPKD, even in neonates.
3. Other hereditary syndromes that can manifest as renal cystic disease include tuberous sclerosis; von Hippel-Lindau disease; Jeune asphyxiating thoracic dysplasia; oral–facial–digital syndrome type 1; brachymesomelia-renal syndrome; and trisomy 9, 13, and 18.

K. Kidney tumors are rare in the neonatal period. These include mesoblastic nephroma and nephroblastomatosis. The differential diagnosis includes other causes of renal masses (see Table 28.4).

Suggested Readings

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29 Mechanical Ventilation

Eric C. Eichenwald and L. Dupree Hatch

KEY POINTS

- Use of noninvasive respiratory support often avoids the need for mechanical ventilation in preterm infants with respiratory distress.
- Volume-targeted, patient-triggered ventilation reduces the duration of mechanical ventilation and the risk of bronchopulmonary dysplasia (BPD) in preterm infants.
- Ventilatory support strategy should target the pathophysiology of the pulmonary condition causing respiratory failure.

I. GENERAL PRINCIPLES. Mechanical ventilation is an invasive life support procedure with many effects on the cardiopulmonary system. The goal is to optimize both gas exchange and clinical status while protecting the lungs and other organs from the harmful effects of mechanical ventilation. This is often accomplished by using the minimum amount of fractional concentration of inspired oxygen (FiO_2) and ventilator pressures/tidal volume (V_T) to ensure physiologic stability. The ventilator strategy used to accomplish these goals depends, in part, on the infant's pulmonary disease process. Recent advances in ventilator technology have brought more options for newborn respiratory therapy. Throughout this chapter, oxygen requirement indicates the FiO_2 needed to maintain the desired oxygen saturation level.

II. NONINVASIVE VENTILATORY SUPPORT

A. Continuous positive airway pressure (CPAP)

1. CPAP is the most commonly used respiratory therapy in newborns.

CPAP is usually administered by means of a ventilator, stand-alone CPAP delivery system, or "bubble" CPAP systems. Any system used to deliver CPAP should allow continuous monitoring of the delivered pressure and be equipped with safety alarms to indicate when the pressure is above or below the desired level. Alternatively, CPAP may be delivered by a simplified system providing blended oxygen flowing past the infant's airway, with the end of the tubing submerged in 0.25% acetic acid in sterile water solution to the desired depth to generate pressure ("bubble CPAP"). Stand-alone variable flow CPAP devices, in

which expiratory resistance is decreased via a "fluidic flip" of flow at the nosepiece during expiration, are also available.

2. **General characteristics.** A continuous flow of heated, humidified gas is circulated past the infant's airway, typically at a set pressure of 3 to 8 cm H_2O, maintaining an elevated end-expiratory lung volume while the infant breathes spontaneously. The air–oxygen mixture and airway pressure can be adjusted. Variable flow CPAP systems may decrease the work of breathing and improve lung recruitment in infants on CPAP but have not been shown to be clearly superior to conventional means of delivery. CPAP is usually delivered by means of nasal prongs or nasal mask. Endotracheal CPAP should not be used because the high resistance of the endotracheal tube increases the work of breathing, especially in small infants.

3. **Advantages**

   a. CPAP is less invasive than mechanical ventilation and causes less lung injury.

   b. When used early in infants with respiratory distress syndrome (RDS), CPAP can help prevent alveolar and airway collapse and thereby reduce the need for mechanical ventilation.

   c. Use of first-intention CPAP in the delivery room for spontaneously breathing immature infants ≥24 weeks' gestation decreases the need for mechanical ventilation and administration of surfactant. Although individual trials comparing early CPAP versus mechanical ventilation and early surfactant treatment show similar rates of bronchopulmonary dysplasia (BPD), meta-analyses of these prospective randomized trials of early CPAP show that initial CPAP use is associated with a decreased risk of death or BPD. Success of this strategy is higher in infants delivered at >27 weeks' gestation but can be attempted even at the lowest gestational ages.

   d. CPAP decreases the frequency of obstructive and mixed apneic spells in some infants.

   e. Limited data suggest that extended use of CPAP until 34 weeks' postmenstrual age may increase functional residual capacity (FRC) in preterm infants at time of neonatal intensive care unit (NICU) discharge, although the clinical significance is uncertain.

4. **Disadvantages**

   a. CPAP is not effective in patients with frequent central apnea or inadequate respiratory drive.

   b. CPAP provides inadequate respiratory support in infants with severely abnormal pulmonary compliance and resistance.

   c. Maintaining nasal or nasopharyngeal CPAP in large, active infants may be technically difficult.

   d. CPAP therapy can result in gastric/intestinal distension and elevation of the diaphragm, necessitating decompression by a gastric tube.

5. **Indications** (see section III.A)

B. Nasal intermittent positive pressure ventilation (NIPPV). NIPPV provides noninvasive respiratory support to preterm infants who otherwise might require endotracheal intubation and ventilation. It is often used as a

supplement to CPAP. During NIPPV, positive pressure breaths are delivered through nasal prongs or mask and the user sets the rate, peak inspiratory pressure (PIP), inspiratory time, and positive end expiratory pressure. Some devices attempt to synchronize positive pressure breaths with the infant's spontaneous inspirations (synchronized NIPPV [sNIPPV]).

1. **Advantages**
   a. Given the similarities to CPAP, NIPPV has advantages listed earlier for CPAP therapy.
   b. Following extubation from mechanical ventilation, NIPPV compared with nasal CPAP has been shown to reduce extubation failure and decrease the risk of reintubation in infants with RDS. These benefits have been more consistently noted in studies of sNIPPV.
   c. NIPPV may be attempted in infants with inadequate respiratory drive or apnea of prematurity where CPAP fails.
2. **Disadvantages**
   a. NIPPV requires a mechanical ventilator or similar device to administer.
   b. Similar to CPAP, NIPPV can result in gastric/intestinal distention and the need for gastric decompression.

C. High-flow nasal cannula (HFNC)

1. Many units use HFNC as an alternative to conventional CPAP or NIPPV devices. HFNC allows delivery of distending pressure to the infant's airway with a simpler patient interface. Instead of setting the target pressure as in CPAP or NIPPV, the flow is set in HFNC and pressure varies based on a number of variables.
2. **General characteristics.** HFNC usually refers to the delivery of blended, heated, and humidified oxygen at flows ≥2 L/minute via small binasal prongs. Two commercial devices for delivery of HFNC are available for use in newborns.
3. **Advantages**
   a. Reported advantages to HFNC include ease of use, a simpler patient interface, and a lower incidence of nasal breakdown compared to conventional CPAP.
4. **Disadvantages**
   a. Potential disadvantages include more variable distending pressure delivery (both low and high) and a tendency for a longer duration of respiratory support compared to CPAP.
   b. Recent evidence suggests that HFNC is inferior to CPAP in preventing respiratory failure and intubation in preterm infants when used as the primary respiratory modality.

D. Noninvasive high-frequency ventilation (NIHFV)

1. During NIHFV, high-frequency oscillatory waveforms are superimposed on a background of constant positive airway pressure through a noninvasive interface such as a mask, nasal prongs, or pharyngeal tube. This modality is similar in concept to NIPPV (see earlier).
2. Data regarding the safety and efficacy of NIHFV are currently limited, and NIHFV is used in a minority of units.

III. INVASIVE MECHANICAL VENTILATORY SUPPORT

A. Despite many different ventilator manufacturers, designs, and terminologies, most frequently used conventional ventilator modes in newborns can be understood by the following variables:

1. Method for breath initiation

a. Unsynchronized ventilation. Breaths are initiated at a defined time interval determined by the set respiratory rate and are independent of a patient's respiratory effort.

b. Synchronized or patient-triggered ventilation. Breaths are initiated in concert with the patient's respiratory effort. This occurs through use of a sensor that detects a patient's inspiratory effort by measuring either airway pressure, airflow, respiratory movement, or the electrical activity of the diaphragm (Edi). These sensors are most commonly found in the ventilator, at the proximal end of the endotracheal tube, or, in the case of the Edi sensor, on a nasogastric tube with the sensors placed at the level of the diaphragm.

2. Method for gas handling during the inspiration

a. Pressure-limited ventilation. Delivers a constant or preset PIP during each breath and VT varies based on respiratory compliance and resistance

b. Volume-controlled ventilation. Delivers a constant or preset VT during each breath and PIP varies based on respiratory compliance and resistance

3. Method for breath termination

a. Time-cycled ventilation. Expiration begins after a set time (inspiratory time) has elapsed.

b. Flow-cycled ventilation. Expiration begins when the inspiratory flow declines to a set percentage of the peak inspiratory flow (usually 15% to 20%).

c. Volume-cycled ventilation. Expiration begins after a set volume is infused into the ventilator circuit; rarely used in neonatal ventilation

B. Ventilators used in newborns with respiratory failure range from unsynchronized, pressure-limited, time-cycled, continuous-flow ventilators to patient-triggered, volume-targeted ventilators, which are associated with improved outcomes.

1. General characteristics of unsynchronized, pressure-limited ventilation modes. A continuous flow of heated and humidified gas is circulated past the infant's airway; the gas is a mixture of air, blended with oxygen to maintain the desired oxygen saturation level. PIP, positive end-expiratory pressure (PEEP), and respiratory timing (rate and duration of inspiration and expiration) are selected.

2. Advantages

a. The continuous flow of fresh gas allows the infant to make spontaneous respiratory efforts between ventilator breaths (intermittent mandatory ventilation [IMV]).

b. Good control is maintained over respiratory pressures.

c. Inspiratory (TI) and expiratory time (TE) can be independently controlled.

d. The system is relatively simple, inexpensive, and can be provided by nearly all ventilators.

3. Disadvantages

a. VT is poorly controlled. Because of this, lung injury due to excessive VTS (volutrauma) may be increased.

b. The ventilator does not respond to changes in respiratory compliance or resistance.

c. Spontaneously breathing infants, who breathe out of phase with the set respiratory rate ("bucking" or "fighting" the ventilator), may receive inadequate ventilation, may require higher rates of sedation/paralysis, and are at increased risk for air leak.

C. Synchronized and patient-triggered (assist/control [AC] or pressure support) ventilation modes are adaptations of conventional pressure-limited ventilators used for newborns.

1. General characteristics. These modes combine the features of pressure-limited, time-cycled, continuous-flow ventilators with an airway pressure, airflow, respiratory movement, or Edi sensor to sense patient respiratory effort. By measuring patient breath initiation, these ventilators can deliver breaths in synchrony with an infant's native respiratory efforts. Two main forms of synchronized ventilation modes exist:

a. Synchronized IMV (SIMV) delivers intermittent positive pressure breaths at a fixed rate but in synchrony with the baby's inspiratory efforts. During periods of apnea, SIMV modes continue to deliver the set IMV rate. The size of the IMV breath is determined by the clinician and can either be pressure limited, volume targeted (see following text), or volume controlled. Normally, SIMV is augmented with pressure-supported breaths (SIMV/PS). This allows infants to breathe faster than the set IMV rate with all breaths above the set IMV rate supported by a set amount of inspiratory pressure. As a result, the ventilator delivers more frequent positive pressure breaths, usually allowing a decrease in the PIP and average VT needed for adequate gas exchange.

b. Fully patient-triggered ventilation modes deliver a positive pressure breath using the same type of inflation pattern every time an inspiratory effort is detected by the ventilator. During apnea in these modes, the ventilator delivers an operator-selected IMV ("control" or "backup") rate similar to SIMV. Two types of patient-triggered ventilation are commonly used in neonatal ventilation:

i. In A/C ventilation, the ventilator delivers a **time-cycled** breath with each inspiratory effort. The clinician sets the inspiratory time and either the PIP (when paired with pressure-limited ventilation) or target VT (when paired with volume-targeted ventilation [VTV]). The clinician also sets the control or backup rate to maintain adequate minute ventilation during periods of apnea or hypoventilation.

ii. In pressure support ventilation (PSV), the ventilator delivers a **flow-cycled** breath with each inspiratory effort. The difference between A/C and PSV modes is that in PSV modes, each breath is terminated when inspiratory gas flow falls to a predetermined proportion of peak flow (usually 15% to 20%). As a result, the patient determines the inspiratory and expiratory times and inspiratory:expiratory (I:E) ratio. As in A/C, the clinician sets either the PIP (when paired with pressure-limited ventilation) or

target VT (when paired with VTV) and the control or backup rate to maintain adequate minute ventilation during periods of apnea or hypoventilation. During periods of apnea, the inspiratory time is determined by the inspiratory time constant of the respiratory system.

c. Both SIMV and fully patient-triggered ventilation modes can counteract the resistance imposed by the endotracheal tube and ventilator circuit by providing additional inspiratory flow that is either preset by the clinician or automatically provided by the ventilator (automatic tube compensation) based on the size and length of the endotracheal tube, tracheal pressures, and measurement of inspiratory flow. The inspiratory flow rate (rise time or slope) determines the time to reach maximal airway pressure or target VT, with higher flow rates (shorter rise times or slopes) translating into lower work of breathing.

2. **Advantages**

a. Synchronizing the delivery of positive pressure breaths with the infant's inspiratory effort reduces the phenomenon of breathing out of phase with IMV breaths ("fighting" the ventilator). This may decrease the need for sedative medications and aid in weaning mechanically ventilated infants.

b. Pronounced asynchrony with ventilator breaths during conventional IMV has been associated with the development of air leak and intraventricular hemorrhage. Whether the use of SIMV or A/C ventilation reduces these complications is not known.

3. **Disadvantages**

a. Under certain conditions, the ventilators may inappropriately trigger a breath (autocycling) because of signal artifacts or fail to trigger because of problems with the sensor.

b. Limited data are available comparing fully patient-triggered ventilation to other modes of ventilation in newborns. Small studies suggest that compared to SIMV, A/C modes may result in lower work of breathing. PSV may not be appropriate for small premature infants with irregular respiratory patterns and short inspiratory time constants due to the potential for ineffective, short inspiratory times, and dead space ventilation. However, some data suggest that use of patient-triggered modes of ventilation in premature infants may decrease markers of lung inflammation and facilitate earlier extubation, when used as the initial mode of mechanical ventilator support.

4. **Indications.** Although the absolute indications for SIMV, A/C, and PSV have not been established, approximately half of neonatologists in North America use SIMV as the initial mode in preterm infants and approximately half use fully patient-triggered modes (A/C and PSV). Large inter- and intraunit variation in the use of these modes exists. Evidence from small studies suggests that patient-triggered modes may result in lower work of breathing, but any potential benefit on long-term outcomes is not known.

D. VTV modes. Advances in technology for measuring delivered VTs have made these modes optimal first-line therapy for newborns with respiratory failure.

Only ventilators specifically designed to measure small VTs should be used to provide VTV in newborns.

1. **General characteristics.** VTV modes combine the benefits of pressure-limited ventilation modes with the benefits of closely regulating VT. In VTV modes, the operator selects the target VT to deliver rather than the PIP. With each delivered breath, the ventilator senses the VT delivered to the patient and adjusts the inspiratory flow (or pressure) of the subsequent breath to "target" the set VT. In this way, VTV modes offer a breath-to-breath adjustment or weaning of the PIP as respiratory mechanics such as compliance and resistance change. VTV modes, features, and terminology differ by ventilator manufacturers, but all follow the principles above of "autoweaning" of the PIP with changes in pulmonary mechanics. Examples of VTV include modes that use the "volume guarantee" feature on common neonatal ventilators and pressure-regulated volume control (PRVC) modes. In VTV modes, the operator selects the target VT and the maximal PIP. If an inflating pressure higher than the maximal PIP is needed to generate the target VT, only the maximal PIP will be delivered and the target VT will not be reached.

2. **Advantages**
   a. The inspiratory flow (and consequently the PIP) automatically varies with respiratory system compliance to deliver the selected VT, therefore minimizing variability in minute ventilation and avoiding wide swings in VT frequently seen with pressure-limited ventilators.
   b. In randomized trials, rates of death or BPD (combined outcome), hypocarbia, severe intraventricular hemorrhage, pneumothorax, and duration of mechanical ventilation are lower in VTV modes compared to pressure-limited modes in preterm infants.

3. **Disadvantages**
   a. VTV modes can be technically complex and require training and familiarity to operate.
   b. Ventilators designed primarily for adult patients may not be able to accurately measure and adjust for the small VTs required in very preterm newborns.
   c. To measure VT most accurately, a flow sensor at the proximal end of the endotracheal tube is needed.
   d. Given the use of uncuffed endotracheal tubes in newborns, large endotracheal tube leaks are common and potentially affect the ventilator's ability to sense the VT delivered to the infant. Many newer neonatal ventilators have leak compensation features that account for this when delivering VTV.

4. **Indications.** If available, VTV modes should be the first-line ventilator modes in most neonatal pathologies. VTV modes are particularly useful if lung compliance is rapidly changing, as in infants with RDS who are receiving surfactant therapy.

E. Miscellaneous conventional ventilation modes

1. **Proportional assist ventilation (PAV)** is a patient-triggered mode of conventional mechanical ventilation in which the ventilator delivers a

pressure support that is directly proportional to the patient's inspiratory effort as measured by pressure or airflow sensors. During PAV, higher patient inspiratory effort (higher negative pressure or higher inspiratory flow) leads to more ventilator assistance to "offload" or augment the patient's effort and allow for a normal transpulmonary pressure and thus lower respiratory effort. PAV is more technically complex than other commonly used ventilation modes as clinicians must set the gain or proportionality factors to determine the ventilator support that will be delivered based on the markers of inspiratory effort. A key disadvantage of PAV is that PAV assumes a mature respiratory drive. In preterm infants, especially those with recurrent apnea, hypopnea can result in poor support due to the positive feedback mechanism used in PAV. Small studies in limited populations in the NICU suggest that PAV is safe for short-term ventilation in infants with mature respiratory drives, but long-term data on safety and outcomes are not available. PAV is currently limited mainly to research settings.

2. **Neurally adjusted ventilatory assist (NAVA)** is a novel ventilator modality that uses the electrical activity of the diaphragm (measured by Edi sensor) to deliver pressure supported breaths with a positive feedback mechanism similar to PAV earlier. In NAVA, the ventilator interprets higher electrical activity of the diaphragm as increased patient inspiratory effort and the ventilator provides support for breaths that is directly proportional to this electrical activity. Clinicians set the gain or proportionality factor, known as the "NAVA level," to determine how much support the ventilator delivers for each breath relative to the diaphragmatic activity. Similar to PAV, NAVA assumes a mature respiratory drive that is often not present in preterm infants. At this time, NAVA is available on only one ventilator approved for use in the United States.

3. **Airway pressure release ventilation (APRV)** is a modality commonly used to improve oxygenation in adult patients with acute RDS. During APRV, a high CPAP (P_{HIGH}) is used to maintain alveolar recruitment with a brief "release" phase consisting of a lower positive airway pressure (P_{LOW}) for a short period of time (T_{LOW}) used to allow some ventilation. Patients are allowed to breathe over the set pressures to provide additional ventilation. APRV use in newborns is limited to small case series and the safety or efficacy of this mode of ventilation in not known. Thus, use of APRV should be limited to research settings.

F. High-frequency ventilation (HFV) is an important adjunct to conventional mechanical ventilation in newborns. Three types of high-frequency ventilators are approved for use in newborns in the United States: a high-frequency oscillator (HFO), a high-frequency flow interrupter (HFFI), and a high-frequency jet (HFJ) ventilator.

1. **General characteristics.** Available high-frequency ventilators are similar despite considerable differences in design. All are capable of delivering extremely rapid rates (300 to 1,500 breaths per minute, 5 to 25 Hz; 1 Hz = 60 breaths per minute), with V_Ts equal to or smaller than anatomic dead space. These ventilators apply continuous distending

pressure to maintain an elevated lung volume; small V_Ts are superimposed at a rapid rate. HFJ ventilators are paired with a conventional pressure-limited ventilator, which can be used to deliver intermittent "sigh" breaths to help prevent atelectasis. Sigh breaths are not used with HFO ventilation. Expiration is passive (i.e., dependent on chest wall and lung recoil) with HFFI and HFJ machines, whereas expiration is active with HFO. The mechanisms of gas exchange in HFV are incompletely understood.

2. **Advantages**
   a. HFV can achieve adequate ventilation and oxygenation while avoiding large swings in lung volume required by conventional ventilators and associated with lung injury. Because of this, HFV may be useful in pulmonary air leak syndromes (pulmonary interstitial emphysema [PIE], pneumothorax) or in infants failing conventional mechanical ventilation.
   b. HFV allows the use of a high mean airway pressure (MAP) for alveolar recruitment and resultant improvement in ventilation–perfusion ($\dot{\mathbf{V}}/\dot{\mathbf{Q}}$) matching. This may be advantageous in infants with severe respiratory failure, requiring high MAP to maintain adequate oxygenation on a conventional mechanical ventilator.
3. **Disadvantages.** Despite theoretical advantages of HFV, no significant benefit of this method has been demonstrated in routine clinical use over conventional ventilation. Only one rigorously controlled study found a small reduction in BPD in infants at high risk treated with HFO ventilation as the primary mode of ventilation. This experience is likely not generally applicable, however, because other studies have shown no difference. These ventilators are more complex and expensive. The initial studies with HFO suggested an increased risk of significant intraventricular hemorrhage, although this complication has not been observed in recent clinical trials. Studies comparing the different types of high-frequency ventilators are unavailable; therefore, the relative advantages or disadvantages of HFO, HFFI, and HFJ, if any, are not characterized.
4. **Indications.** HFV is primarily used as a rescue therapy for infants failing conventional ventilation. Both HFJ and HFO ventilators have been shown to be superior to conventional ventilation in infants with air leak syndromes, especially PIE. Because of the potential for complications and equivalence to conventional ventilation in the incidence of BPD, we do not use HFV as the primary mode of ventilatory support in infants.

IV. INDICATIONS FOR RESPIRATORY SUPPORT

A. Indications for CPAP in the preterm infant with RDS include the following:

1. Recently delivered preterm infant with minimal respiratory distress and low supplemental oxygen requirement (to prevent atelectasis)
2. Respiratory distress at any gestational age and requirement of $FiO_2 > 0.30$ by hood or nasal cannula
3. FiO_2 need > 0.40 by hood or nasal cannula

4. Initial stabilization in the delivery room for spontaneously breathing, extremely preterm infants (24 to 28 weeks' gestation)
5. Initial management of preterm infants with moderate respiratory distress
6. Clinically significant retractions and/or distress after recent extubation
7. In general, infants younger than 72 hours of age with RDS who require FiO_2 >0.30 to 0.40 on CPAP should receive surfactant replacement therapy (see Chapter 33).
8. After extubation to facilitate maintenance of lung volume and prevent extubation failure. Although HFNC may also be considered for post-extubation support, CPAP results in lower likelihood of reintubation than HFNC.

B. Relative indications for mechanical ventilation in any infant include the following:

1. Frequent intermittent apnea unresponsive to methylxanthine therapy
2. Early treatment when use of mechanical ventilation is anticipated because of deteriorating gas exchange
3. Relieving "increased work of breathing" in an infant with signs of moderate-to-severe respiratory distress on noninvasive ventilation
4. Administration of surfactant therapy in infants with RDS, although this may be transient

C. Absolute indications for mechanical ventilation

1. Prolonged apnea
2. Partial pressure of oxygen (PaO_2) <50 mm Hg, or FiO_2 >0.80. This indication may not apply to the infant with cyanotic congenital heart disease.
3. Partial pressure of carbon dioxide ($PaCO_2$) >65 mm Hg with persistent acidemia
4. General anesthesia
5. Upper airway obstruction causing increased work of breathing unresponsive to medical therapy or noninvasive ventilation

V. HOW VENTILATOR CHANGES AFFECT BLOOD GASES

A. Oxygenation (Table 29.1)

1. **FiO_2.** The goal is to maintain adequate tissue oxygen delivery. Generally, this can be accomplished by achieving a PaO_2 of 50 to 70 mm Hg and results in a hemoglobin saturation of 88% to 95% (Fig. 29.1). Increasing inspired oxygen is the simplest and most direct means to improve oxygenation. In preterm infants, the risk of retinopathy and pulmonary oxygen toxicity argue for minimizing PaO_2 and closely monitoring oxygen saturation. For infants with other conditions, the optimum PaO_2 may be higher. Direct pulmonary oxygen toxicity begins to occur at FiO_2 values >0.60 to 0.70.

Table 29.1. Ventilator Manipulations to Increase Oxygenation

Parameter	Advantage	Disadvantage
↑ FiO_2	Minimizes barotrauma	Fails to affect $\dot{V}/\dot{Q}$ matching
	Easily administered	Direct oxygen toxicity, especially >0.6
↑ PIP or V_T	Improves $\dot{V}/\dot{Q}$ matching	Lung injury: ↑ air leak, ↑ BPD
↑ PEEP	Maintains FRC/prevents collapse	Shifts to stiffer part of compliance curve
	Splints obstructed airways	May impede venous return and decrease cardiac output
		Increases expiratory work and CO_2
		Increases dead space
		Excessive levels may increase pulmonary vascular resistance and worsen pulmonary hypertension.
↑ T_I	Increases MAP	Decreases I:E ratio and may cause air trapping
	"Critical opening time"	Lower minute ventilation for given PIP–PEEP combination
		Increased risk for air leak with longer T_I
↑ Flow or ↓ rise time or slope	Square wave—maximizes MAP	Greater shear force, more lung injury
		Greater airway resistance at higher flows
↑ Rate	Increases MAP while using lower PIP	Inadvertent PEEP with high rates or long time constant

Increase in any setting (except fractional concentration of inspired oxygen [FiO_2]) results in higher mean airway pressure. ↑, increase; $\dot{V}/\dot{Q}$, ventilation–perfusion ratio; PIP, peak inspiratory pressure; V_T, tidal volume; BPD, bronchopulmonary dysplasia; PEEP, positive end-expiratory pressure; FRC, functional residual capacity; CO_2, carbon dioxide; T_I, inspiratory time; MAP, mean airway pressure; I:E, inspiratory:expiratory; ↓, decrease.

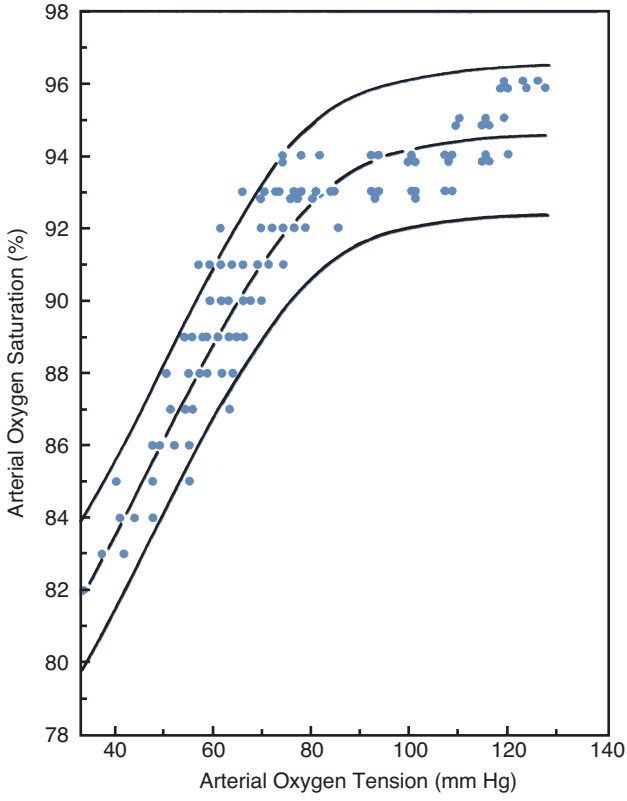

Figure 29.1. Comparison of paired measurements of oxygen saturation by pulse oximetry and of oxygen tension by indwelling umbilical artery oxygen electrode. The lines represent ±2 standard deviations. (Modified from Wasunna A, Whitelaw AG. Pulse oximetry in preterm infants. *Arch Dis Child* 1987;62[9]:957–958. Copyright © 1987 with permission from BMJ Publishing Group Ltd.)

2. MAP

a. MAP is the average area under the curve of the pressure waveform. Most ventilators now display MAP or can be equipped with a device to do so; it may also be calculated using the following equation: MAP = [(PIP − PEEP) (T_I) / T_I + T_E] + PEEP. MAP is increased by increases in PEEP, PIP, T_I, inspiratory flow rate (rise time or slope), and rate; all these changes lead to higher PaO_2, but each has different effects on $PaCO_2$. For a given rise in MAP, increasing PEEP gives the greatest improvement in PaO_2.

b. Optimum MAP results from a balance between optimizing PaO_2, minimizing direct oxygen toxicity, minimizing barotrauma and volutrauma, achieving adequate ventilation, and minimizing adverse

cardiopulmonary effects. Ventilator-induced lung injury is probably most closely related to peak-to-peak swings in lung volume, although changes in airway pressure are also implicated.

c. MAP as low as 5 cm H_2O may be sufficient in infants with normal lungs, whereas 15 cm H_2O or more may be necessary in severe RDS. Excessive MAP may impede venous return, increase pulmonary vascular resistance, and adversely affect cardiac output.

3. **Ventilation** (Table 29.2)

a. Carbon dioxide (CO_2) elimination depends on alveolar minute ventilation. Alveolar minute ventilation can be calculated as the product of the respiratory rate and the alveolar VT. Alveolar VT is the total VT minus the

Table 29.2. Ventilator Manipulations to Increase Ventilation and Decrease $PaCO_2$

Parameter	Advantage	Disadvantage
↑ Rate	Easy to titrate	Maintains same dead space/VT
	Minimizes lung injury	May lead to inadvertent PEEP
↑ PIP or VT	Better bulk flow (improved dead space/VT)	More volutrauma and/or barotrauma
		Shifts to stiffer compliance curve
↓ PEEP	Increases VT if on the upper part of compliance curve	Decreases MAP
	May decrease dead space	Decreases oxygenation; may result in alveolar collapse
	Shifts to steeper part of compliance curve	Decreases splinting of obstructed/closed airways
↑ Flow	Permits shorter TI, longer TE	More barotrauma
↑ TE	Allows longer time for passive expiration in face of prolonged time constant	Shortens TI
		Decreases MAP
		Decreases oxygenation

$PaCO_2$, partial pressure of carbon dioxide, arterial; ↑, increase; VT, tidal volume; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; ↓, decrease; MAP, mean airway pressure; TI, inspiratory time; TE, expiratory time.

volume of dead space. Because of these relationships, increasing either the respiratory rate or VT should improve ventilation under normal conditions. Increases in VT can be achieved by increasing the PIP in pressure-limited ventilation modes or by increasing target VT in volume-controlled or VTV modes. Because VT is a function of the difference between PIP and PEEP, a reduction in PEEP may also improve ventilation. At very low VTs, the volume of dead space becomes important and may lead to CO_2 retention.

b. Optimal $PaCO_2$ varies according to disease state. For very immature infants or infants with air leak, a $PaCO_2$ of 50 to 60 mm Hg may be tolerated to minimize ventilator-induced lung injury, provided pH can be maintained >7.20 to 7.25.

VI. DISEASE STATES

A. Effects of diseases. Respiratory failure can result from numerous illnesses through a variety of pathophysiologic mechanisms. Optimal ventilatory strategy must take into account the pathophysiology, expected time course, and particular vulnerabilities of the patient.

B. Pulmonary mechanics influence the ventilator strategy selected.

1. **Compliance is the stiffness** or distensibility of the lung and chest wall; that is, the change in volume (ΔV) produced by a change in pressure (ΔP), or $\Delta V/\Delta P$. It is decreased with surfactant deficiency, excess lung water, and lung fibrosis. It is also decreased when the lungs are hyperexpanded.
2. **Resistance is the impediment** to airflow due to friction between gas and airways (airway resistance) and between tissues of the lungs and chest wall (viscous tissue resistance); that is, the change in pressure (cm H_2O) divided by the change in flow (L/second). Almost half of airway resistance is in the upper airways, including the endotracheal tube when in use. Resistance is high in diseases characterized by airway obstruction, such as meconium aspiration and BPD. Resistance can increase rapidly if, for example, secretions partially occlude the endotracheal tube.
3. **Time constant** is the product of compliance (mL/cm H_2O) and resistance (cm H_2O/mL/second). This is a measure of the time it takes to equilibrate pressure between the proximal airway and the alveoli. Expiratory time constants are somewhat longer than inspiratory ones due to narrowed diameter and increased resistance of conducting airways during expiration. When time constants are long, as in meconium aspiration, care must be taken to set ventilator inspiratory times and rates that permit adequate inspiration to deliver the required VT and adequate expiration to avoid inadvertent PEEP.
4. **FRC** is a measure of the volume of the lungs at end expiration. FRC is decreased in diseases that permit alveolar collapse, particularly surfactant deficiency.
5. **$\dot{V}/\dot{Q}$ matching.** Diseases that reduce alveolar surface area (through atelectasis, inflammatory exudates, or obstruction) permit intrapulmonary shunting of desaturated blood. The opposite occurs in persistent pulmonary hypertension when extrapulmonary shunting diverts blood

flow away from the ventilated lung. Both mechanisms result in systemic recirculation of desaturated blood.

6. **Work of breathing** is especially important in the smallest infants and those with chronic lung disease whose high airway resistance, decreased lung compliance, compliant chest wall, and weak musculature may overwhelm their metabolic energy requirements and impede growth.

C. Specific disease states. Optimal ventilatory strategies for five common neonatal conditions are described next and in Table 29.3. Before initiating ventilatory support, clinicians must evaluate for mechanical causes of distress, including pneumothorax or airway obstruction.

1. **RDS** (see Chapter 33)

a. Pathophysiology. RDS is caused by surfactant deficiency, which results in increased alveolar surface tension and a severe decrease in compliance (stiff lung). This causes diffuse alveolar collapse with $\dot{V}/\dot{Q}$ mismatching and increased work of breathing.

b. Surfactant replacement. Early initiation of CPAP, usually starting in the delivery room, may avoid the need for mechanical ventilation and surfactant therapy in many infants, even at early gestational ages. Ventilatory strategies should anticipate the increased risk of pneumothorax due to increased compliance and lengthened time constants following surfactant administration. In all approaches, a $PaCO_2$ value higher than the physiologic value is acceptable to minimize ventilator-induced lung injury.

c. Ventilator strategy

i. CPAP. In mild to moderately affected infants who may not require intubation and surfactant administration, CPAP is used

Table 29.3. Neonatal Pulmonary Physiology by Disease State

Disease	Compliance (mL/cm H_2O)	Resistance (cm H_2O/mL/second)	Time Constant (seconds)	FRC (mL/kg)	$\dot{V}/\dot{Q}$ Matching	Work
Normal term	4–6	20–40	0.25	30	—	—
RDS	↓↓	—	↓↓	↓	↓/↓↓	↑
Meconium aspiration	—/↓	↑↑	↑	↑/↑↑	↓↓	↑
BPD	↑/↓	↑↑	↑	↑↑	↓↓/↓	↑↑
Air leak	↓↓	—/↑	—/↑	↑↑	↓/↓↓–	↑↑
VLBW apnea	↓	—	↓↓	—/↓	↓/—	—/↑

FRC, functional residual capacity; $\dot{V}/\dot{Q}$, ventilation–perfusion ratio; —, little or no change; RDS, respiratory distress syndrome; ↓, decrease; /, either/or; ↑, increase; BPD, bronchopulmonary dysplasia; VLBW, very low birth weight.

early in the disease course to prevent further atelectasis. CPAP is initiated at 5 to 6 cm H_2O and increased to a maximum of 7 to 8 cm H_2O. Higher levels of CPAP pressure may increase the risk of pneumothorax. CPAP is titrated by clinical assessment of retractions and respiratory rate and by observation of O_2 saturation and FiO_2 requirement. NIPPV may be used as an alternative to CPAP in this setting. In infants with more severe RDS, intubation for surfactant administration with prompt extubation followed by CPAP (INSURE technique) can be considered.

ii. **Mechanical ventilation** is used when $\dot{V}/\dot{Q}$ mismatching is so severe that increased FiO_2 and CPAP are inadequate to maintain gas exchange or in infants who tire from the increased work of breathing. Because a ventilator strategy that avoids large changes in V_T may reduce ventilator-induced lung injury, VTV modes are preferable. All strategies of assisted ventilation should aim to provide the lowest level of ventilatory support for the shortest time possible to support adequate oxygenation and ventilation while minimizing acute and chronic lung injury secondary to barotrauma/volutrauma and oxygen toxicity.

iii. **V_T** is usually initially set at 4 to 6 mL/kg depending on the infant's weight and adjusted for adequate minute ventilation. In general, infants who weigh <800 g have larger amounts of instrumental dead space and may need V_Ts of 5.5 to 6.0 mL/kg, whereas those with higher birth weight may be effectively ventilated with V_Ts closer to 4.0 to 4.5 mL/kg. With pressure-limited ventilation, PIP is initially estimated by visible chest excursion and is typically 20 to 25 cm H_2O.

iv. **PEEP.** PEEP is usually set at 4 to 6 cm H_2O. Higher PEEP may be needed but also risks interfering with cardiac output.

v. **Flow.** Flow rates of 7 to 12 L/minute provide a relatively square pressure waveform. At very high PIP (>35 cm H_2O), higher flows may be required. Most neonatal ventilators adjust flow rates automatically to meet the selected ventilator settings.

vi. **Rates** in IMV and SIMV modes are generally set initially at 20 to 40 breaths per minute and adjusted according to blood gas results. In fully patient-triggered modes, backup rates can also be set at 20 to 40 breath per minute; lower rates allow better patient-ventilator synchrony.

vii. **Weaning.** With improvement, FiO_2 and PIP or V_T are weaned first, alternating with rate, in response to assessment of chest excursion, oxygen saturation, and blood gas results. In VTV modes, the PIP will decrease automatically in response to improved compliance; weaning may be accomplished by decreasing the targeted level of V_T. In patient-triggered modes, the backup rate of the ventilator is usually not changed, and progressive decreases in PIP are used to wean the ventilator. Extubation is usually successful when ventilator rates are <20 to 25 breaths per minute in IMV or SIMV modes, or PIP is <16 to 18 cm H_2O to deliver the desired V_T. Prior to extubation,

caffeine citrate therapy should be started to facilitate spontaneous breathing in preterm infants and increase the likelihood of successful extubation.

viii. **Advantages and disadvantages.** This ventilatory strategy maximizes alveolar recruitment but may result in lung injury secondary to volutrauma due to higher VT.

ix. HFV may be initiated if conventional ventilation fails to maintain adequate gas exchange at acceptable settings. HFV should be used only by clinicians familiar with its use. We consider using HFV when the MAP required for adequate gas exchange exceeds 10 to 11 cm H_2O in small infants, and 12 cm H_2O in larger infants, or if air leak occurs. Strategies differ depending on whether HFJ, HFO, or HFFI is used. We prefer HFJ or HFO ventilation because of their ease of use and applicability in a wide range of pulmonary diseases and infant weights.

a) **HFJ ventilation.** HFJ requires a special adapter for a standard endotracheal tube to allow connection to the jet port of the ventilator.

1) **PIP and PEEP.** Peak pressures on the jet ventilator are initially set approximately 20% lower than those used with conventional ventilation and adjusted to provide adequate chest vibration assessed clinically and by blood gas determinations. PIP, PEEP, and FiO_2 are adjusted as needed to maintain oxygenation. CO_2 elimination is dependent on the pressure difference (PIP − PEEP). Because of the lower peak pressures required to ventilate, PEEP should be increased to 8 to 10 cm H_2O if needed to improve oxygenation.

2) **Rate.** The frequency is usually set at 360 to 420 breaths per minute, with an inspiratory jet valve on time of 0.02 second.

3) **Conventional ventilator settings.** Once the HFJ PEEP is properly adjusted, the conventional ventilator rate is either turned off or decreased to 2 to 10 breaths per minute to help maintain alveolar recruitment, with PIP set 2 to 3 cm H_2O lower than the jet PIP. In air leak syndromes, sigh breaths from the conventional ventilator are not used if PEEP is set high enough to maintain lung volume.

4) **Weaning** from HFJ ventilation is accomplished by decreasing the jet PIP in response to blood gas determinations and FiO_2 requirement. PEEP is weaned as tolerated if pressures higher than 10 to 12 cm H_2O are used. Frequency and jet valve on-time are generally not adjusted.

5) **Strategies** outlined for the HFJ also apply to HFFI.

b) **HFO ventilation.** With HFO, operator-selected parameters include MAP, frequency, and piston amplitude.

1) **MAP.** In RDS, the initial MAP selected is usually 2 to 5 cm H_2O higher than what was used on the conventional ventilator to enhance alveolar recruitment. MAP is then titrated to O_2 requirement and to provide adequate lung expansion on chest x-ray. Lung hyperinflation, which might adversely

affect oxygen delivery by reducing cardiac output, should be avoided.

2) **Frequency is usually set at 10 to 15 Hz** with inspiratory time set at 33%.
3) **Amplitude or power.** Changes in piston amplitude (power) primarily affect ventilation. It is set to provide adequate chest vibration, assessed clinically and by blood gas determinations.
4) **Flow rates** of 8 to 15 L/minute are usually adequate.
5) **Weaning.** FiO_2 is typically weaned first, followed by MAP in decrements of 1 to 2 cm H_2O once the FiO_2 falls <0.6. Piston amplitude is adjusted in response to assessment of chest vibration and blood gas determinations. Frequency is usually not adjusted unless adequate oxygenation or ventilation cannot otherwise be achieved. In contrast to conventional mechanical ventilation, decreasing the frequency of breaths in HFO ventilation improves ventilation by increasing delivered VT. In both HFJ and HFO, infants can be extubated directly from HFV or transitioned to conventional ventilation prior to extubation. Limited evidence suggests that pulmonary outcomes are better in infants extubated directly from HFO without a trial of conventional ventilation.

2. Meconium aspiration syndrome (MAS) (see Chapter 35)

a. Pathophysiology. Aspirated meconium causes acute airway obstruction, markedly increased airway resistance, scattered atelectasis with mismatching, and hyperexpansion due to obstructive ball-valve effects. The obstructive phase is followed by an inflammatory phase 12 to 24 hours later, which results in further alveolar involvement. Aspiration of other fluids (such as blood or amniotic fluid) has similar but milder effects.

b. Ventilator strategy. Because of the ball-valve effects, the application of positive pressure may result in pneumothorax or other air leak, so initiating mechanical ventilation requires careful consideration of the risks and benefits. Low levels of PEEP (4 to 5 cm H_2O) help splint open partially obstructed airways and equalize matching. Higher levels may lead to hyperinflation. If airway resistance is high and compliance is normal, a slow-rate, moderate-pressure/volume strategy is used. If pneumonitis is more prominent, more rapid rates can be used. Sedation or muscle relaxation may minimize the risks of air leak in severe MAS because these large infants can generate high transpulmonary pressures when "fighting" the ventilator and the ball-valve hyperexpansion caused by their disease. Patient-triggered ventilation may avoid the need for muscle relaxation and is preferred. Weaning may be rapid if the illness is primarily related to airway obstruction or prolonged if complicated by lung injury and severe inflammation.

HFV has been successfully used in infants with MAS who are failing conventional ventilation or who have air leak using strategies similar to those described earlier. During HFO, slower frequencies (8 to 10 Hz) may help improve oxygenation and ventilation in severe cases.

3. **BPD** (see Chapter 34)

a. Pathophysiology. BPD results from injury to the alveoli and airways. Bleb formation may lead to poor recoil. Fibrosis and excess lung water may cause stiffer compliance. Airways may be narrowed and fibrotic or hyperreactive. The upper airways may be overdistended and conduct airflow poorly. BPD is marked by shifting focal atelectasis, hyperinflation with mismatch, chronic and acute increases in airway resistance, and a significant increase in the work of breathing.

b. Ventilator strategy. In infants with severe BPD, the goal is to wean infants off the ventilator as soon as possible to prevent further mechanical injury and oxygen toxicity, although the best strategy is uncertain. If this is not feasible, ventilator settings should be optimized to permit tissue repair, long-term linear and pulmonary growth, and decreased work of breathing and caloric expenditure. Some centers use pressure-limited or volume-targeted SIMV combined with PSV to improve work of breathing and ventilation. Longer inspiratory times (0.5 to 1.0 seconds), lower SIMV rates, and resulting longer expiratory times are used as time constants are longer in infants with severe BPD. PEEP depends on the infant's phenotype; higher PEEP is needed when airway malacia is severe. Higher PIPs (30 to 50 cm H_2O) may be needed because lungs are stiff; the high resistance prevents transfer of most of this pressure to the alveoli. Oxygenation should be maintained (saturations of 90% to 92%), but hypercapnia ($PaCO_2$ 55 to 65 mm Hg) is permitted provided the pH is acceptable. Acute decompensations resulting from bronchospasm and interstitial fluid accumulation are treated with adjustment of PIP, bronchodilators, sedation, and diuretics. Acute BPD "spells" in which oxygenation and airway resistance worsen rapidly are usually due to larger airway collapse and may respond to higher PEEP (>7 to 8 cm H_2O). Frequent rapid desaturations secondary to acute decreases in FRC with crying or infant movement respond to changes in FiO_2 but may also respond to higher PEEP. Weaning is slow and difficult, decreasing SIMV rate by 1 to 2 breaths per minute or 1 cm H_2O decrements in PIP every day when tolerated. With improved medical and ventilatory care, infants with BPD rarely require tracheostomy for chronic ventilation.

4. **Air leak** (see Chapter 38)

a. Pathophysiology. Pneumothorax (air in the pleural space) and PIE are the most common air leak syndromes. In PIE, the interstitial air reduces both tissue compliance and recoil. In addition, peribronchial and perivascular air may cause "air block" by compressing the airways and vascular supply.

b. Ventilator strategy. Because the ventilatory cycle drives air into the interstitium, the primary goal is to reduce positive pressure breaths and provide oxygenation with increased FiO_2. If dropping MAP is not tolerated, other techniques are tried. Because the time constants for interstitial air are longer than those for the alveoli, HFV (the better choice) or rapid rate conventional ventilation is used. With HFJ and HFFI, PEEP is maintained at normal levels, PIP and rate are lowered, and few to no sigh breaths are provided. With HFO, the MAP initially used is the same as that being used on the conventional ventilator and the frequency

set at 15 Hz. While weaning, MAP is decreased progressively, tolerating higher FiO_2 in order to limit the MAP exposure and allow areas of lung injury to heal.

5. **Apnea** (see Chapter 31)

a. Pathophysiology. Occasionally, apnea is severe enough to warrant ventilator support, even in the absence of pulmonary disease. This may result from apnea of prematurity, infection, or during or following general anesthesia.

b. Ventilator strategy. For infants completely dependent on the ventilator, the goal should be to provide "physiologic" ventilation using moderate PEEP (3 to 4 cm H_2O), low gas flow, and normal rates (30 to 40 breaths per minute), with PIP or V_T adjusted to prevent hyperventilation (10 to 18 cm H_2O). Prolonged T_I is unnecessary. For infants requiring a ventilator because of intermittent but prolonged apnea, patient-triggered ventilator modes with low backup rates (20 to 30 breaths per minute) are preferred.

VII. ADJUNCTS TO MECHANICAL VENTILATION

A. Sedation (see Chapters 69 and 70) can be used when agitation or distress is associated with excessive lability of oxygenation and hypoxemia. As discussed, synchronized IMV or patient-triggered ventilation may also help diminish agitation and ventilatory lability.

B. Muscle relaxation with pancuronium bromide (0.1 mg/kg per dose, repeated as needed) or vecuronium (0.1 mg/kg per dose) is rarely used but may be indicated in some infants who continue to breathe out of phase with the ventilator after attempts at finding appropriate settings and sedation have failed; the need for muscle relaxation is reduced in patient-triggered ventilation as babies will breathe "in sync" with the delivered ventilator breaths. Although unequivocal data are not available, gas exchange may be improved in some infants following muscle relaxation. Prolonged muscle relaxation leads to fluid retention and may result in deterioration in compliance. Sedation should be routinely administered to infants receiving muscle relaxants.

C. Blood gas monitoring (see Chapter 30). All infants receiving mechanical ventilation require continuous monitoring of oxygen saturation and intermittent blood gas measurements. Transcutaneous CO_2 monitoring can also be used to decrease the frequency of blood gas measurements. Close monitoring of skin integrity should be performed at the site of transcutaneous CO_2 monitoring due to the increased risk of skin breakdown or thermal injury, especially in preterm infants.

VIII. COMPLICATIONS AND SEQUELAE.

As a complex and invasive technology, mechanical ventilation can result in numerous adverse outcomes, both iatrogenic and unavoidable.

A. Lung injury and oxygen toxicity

1. **BPD** is related to increased airway pressure and changes in lung volume, although oxygen toxicity, anatomic and physiologic immaturity, and

individual susceptibility also contribute. The duration of invasive mechanical ventilation is directly proportional to increasing risk for BPD.

2. **Air leak** is directly related to increased airway pressure. Risk is increased at MAPs in excess of 14 cm H_2O.

B. Mechanical

1. Obstruction of endotracheal tubes may result in hypoxemia and respiratory acidosis.
2. Equipment malfunction, particularly disconnection, is not uncommon and requires functioning alarm systems and vigilance.

C. Complications of invasive monitoring

1. Peripheral arterial occlusion with infarction (see Chapter 44)
2. Aortic thrombosis from umbilical arterial catheters, occasionally leading to renal impairment and hypertension
3. Emboli from flushed catheters, particularly to the lower extremities, the splanchnic bed, or even the brain

D. Anatomic

1. Subglottic stenosis from prolonged intubation; risk increases with multiple reintubations
2. Acquired tracheobronchomalacia from prolonged mechanical intubation
3. Palatal grooves from prolonged orotracheal intubation
4. Vocal cord damage

E. Neurodevelopmental impairment

1. Increasing evidence has shown that the duration of mechanical ventilation therapy is independently associated with altered hippocampal and brainstem development, abnormal white matter maturation, lower motor function scores at preschool age, and higher rates of cerebral palsy.

Suggested Reading

Goldsmith J, Karotkin E, Keszler M, et al. *Assisted Ventilation of the Neonate: An Evidence-Based Approach to Newborn Respiratory Care*. 6th ed. Philadelphia, PA: Elsevier; 2017.

30 Blood Gas and Pulmonary Function Monitoring

Jonathan C. Levin and Lawrence M. Rhein

KEY POINTS

- Assessment of oxygenation and ventilation is critical to assess respiratory function.
- Pulse oximetry is the primary tool for noninvasive oxygen monitoring in newborns.
- A neonatal intensive care unit (NICU) policy is essential to guide target saturation values and alarm limits in infants treated with supplemental oxygen.
- Monitoring of carbon dioxide (CO_2) levels can occur invasively or noninvasively, each with its advantages and disadvantages.
- Pulmonary function can be assessed using graphic visualization on ventilators as well as formal infant pulmonary function testing.

I. GENERAL PRINCIPLES. Both invasive and noninvasive techniques are used to monitor respiratory health in the clinical setting. Although both methods have limitations, monitoring of oxygenation and ventilation is critical to assess respiratory function. Invasive techniques, including blood gas monitoring, allow (i) assessment of pulmonary gas exchange; (ii) determination of hemoglobin oxygen saturation and arterial oxygen content; and (iii) evaluation, although limited, of adequacy of tissue oxygen delivery. Noninvasive techniques may be less specific but allow easier determination of serial measurements and identification of trends.

II. OXYGEN USE AND MONITORING. Causes of hypoxemia include hypoventilation, mismatch of ventilation and perfusion, diffusion impairment, and shunt. In situations of hypoxemia and/or respiratory distress, oxygen monitoring with pulse oximetry should be initiated as soon as possible, and the concentration of oxygen should be adjusted to maintain saturation values within a targeted range. Monitoring of oxygen use is necessary to reduce both hypoxic injury to tissues and to minimize oxidative injury to the lungs or the immature retina of the preterm infant.

A. Arterial blood gas (ABG) measurements. Arterial partial pressure of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) are direct indicators of efficiency of

pulmonary gas exchange in infants with acute lung disease. PaO_2 measured under steady-state conditions from an indwelling catheter is the "gold standard" for oxygen monitoring.

1. **Usual values.** Most sources consider 50 to 80 mm Hg to be an acceptable target range for newborn PaO_2. Preterm infants who require respiratory support may exhibit wide swings in PaO_2 values. In such circumstances, a single blood gas value may not accurately reflect the overall trend of oxygenation.
2. **Sampling.** To minimize sampling and dilutional artifacts, ABG samples should be collected in dry heparin syringes that are commercially available for this purpose. Most blood gas analyzers allow determination of blood gas values as well as other whole blood parameters on 0.2- to 0.3-mL samples. Samples should be analyzed within 15 minutes or preserved on ice if sent to a remote laboratory site. Blood gas sampling by percutaneous puncture is used when the need for measurement is infrequent or an indwelling catheter is not available. However, the discomfort of the puncture may result in agitation and a fall in PaO_2 so that the value obtained underestimates the true steady-state value. In addition, the presence of air bubbles within the sample may cause overestimation of PaO_2.

B. Noninvasive oxygen monitoring provides real-time trend data that is particularly useful in infants exhibiting frequent swings in PaO_2 and oxygen saturation. Noninvasive devices also may reduce the frequency of blood gas sampling in more stable patients.

1. **Pulse oximetry** is the primary tool for noninvasive oxygen monitoring in newborns and has become the standard for routine oxygen monitoring in the neonatal intensive care unit (NICU). Pulse oximeters provide continuous measurement of hemoglobin oxygen saturation (SpO_2) with a high level of accuracy ($\pm 3\%$) when compared to control values measured by co-oximetry, at least down to the range of 70%. SpO_2 levels reflect the approximately 98% of arterial oxygen content that is bound by hemoglobin. SpO_2 levels between 85% and 95% generally correlate to PaO_2 of 40 to 55 mm Hg, due to a "left-shifted" curve from the presence of fetal hemoglobin.

   a. General characteristics. Oximeters depend on different absorption characteristics of oxygenated versus reduced hemoglobin for various wavelengths of light. Differences in transmission of two (usually red and near-infrared [IR]) or more wavelengths through tissues with pulsatile blood flow are measured. Using the measured values, the proportion of oxygenated and reduced hemoglobin is calculated and displayed as percent saturation. Modern pulse oximeters can efficiently discriminate artifactual values from valid measurements. Sensitivity of detection of hypoxemia by pulse oximeters is dependent on the averaging time of the oximeters; shorter averaging times detect hypoxemia more sensitively compared to longer averaging times but can lead to excess alarms.

   b. Disadvantages. Pulse oximetry does not measure the PaO_2 and thus is insensitive in detecting hyperoxemia. Due to the shape of the oxyhemoglobin dissociation curve, if SpO_2 is $>95\%$, PaO_2 is unpredictable. Under such

conditions, PaO_2 may be >100 mm Hg. Patient movement and the low amplitude pulse wave of small preterm infants may introduce artifacts that result in false episodes of desaturation, although software modifications have reduced this problem. Poor peripheral perfusion may result in falsely low readings. Other potential sources of artifact include inappropriate sensor placement, presence of high-intensity light (some phototherapy devices), fetal hemoglobin values >50%, and presence of carboxyhemoglobin or methemoglobin.

c. Targeted saturation values. Mean SpO_2 in healthy, term infants is 97%. During neonatal transition, SpO_2 reaches 80% to 90% by 10 minutes of life. In preterm infants, multiple trials have been conducted to define the optimal range of oxygen saturation, balancing consequences of hypoxemia such as death and of hyperoxemia such as retinopathy of prematurity (ROP) and chronic lung disease. In older studies that targeted oxygen saturation values in preterm infants after the immediate newborn period (supplemental therapeutic oxygen for prethreshold ROP [STOP-ROP], benefits of oxygen saturation targeting [BOOST]), SpO_2 values >95% in preterm infants receiving supplemental oxygen was associated with increased need for prolonged supplemental oxygen. Subsequent meta-analysis of several well-designed multicenter randomized controlled trials (Canadian Oxygen Trial [COT], Surfactant, Positive Pressure, and Oxygen Randomized Trial [SUPPORT], and BOOST-II) concluded that targeting lower oxygen saturations (85% to 89%) is associated with an increased risk of mortality and necrotizing enterocolitis but a lower risk of ROP and oxygen requirement at 36 weeks' postmenstrual age (PMA) when compared to higher oxygen saturations (91% to 95%). However, due to significant overlap in actual oxygen saturation between the two groups, these results are interpreted with caution. In addition, post hoc analyses of trial data suggest that the differences in mortality may be most pronounced in small for gestational age infants; thus, too much uncertainty exists to make a clear recommendation. Determination of an optimal target saturation in preterm infants may be elusive because some babies may be more vulnerable to oxidative injury and others to hypoxia. These vulnerabilities may affect end organs (e.g., the eye, the brain, and the gut) differently and may vary over time with organ maturation.

Because the optimal oxygen target is not certain, a NICU policy is essential. One approach is as follows: For infants who require supplemental oxygen, we maintain SpO_2 in the 89% to 94% range for infants <32 weeks' PMA (monitor alarm limits 88% to 95%), 90% to 97% for infants 32 to 37 weeks' PMA (alarm limits 89% to 98%), and 92% to 97% (alarm limits 91% to 98%) for infants >37 weeks' PMA. For infants with persistent pulmonary hypertension of the newborn on supplemental oxygen, we target saturations 94% to 99%. If these targets are maintained, arterial PO_2 will rarely exceed 90 mm Hg. Other NICUs may target a slightly higher SpO_2 range and a wider set of alarm limits.

In the future, automated closed-loop feedback of monitoring and adjusting oxygen supplementation may improve adherence to accepted targets.

C. Transcutaneous oxygen monitoring uses a heated electrode applied to the skin to measure diffused oxygen. However, due to frequent need for calibration and concerns for skin injury, pulse oximetry has largely supplanted this technique in the NICU.

D. Regional tissue oxygenation monitoring using near-IR spectroscopy (NIRS) is becoming more commonplace in the NICU, particularly during states of volatile oxygen delivery such as initial stabilization, management of a patent ductus arteriosus, and during blood transfusion. NIRS measures hemoglobin oxygenation (similar to pulse oximetry) but does not subtract nonpulsatile sources and thus represents total oxygenated hemoglobin from arterial, capillary, and venous hemoglobin. As a result, NIRS is considered a surrogate of regional tissue oxygen utilization. Most studies have evaluated its use in measuring cerebral oxygen utilization, but NIRS monitoring of renal, splanchnic, and peripheral muscle oxygenation has been reported.

III. ASSESSMENT OF PULMONARY VENTILATION.

Alveolar ventilation is assessed by direct or noninvasive measurement of $PaCO_2$. In preterm infants, rapid fluctuations in $PaCO_2$ leading to hypocarbia or hypercarbia, particularly in the first few days of life, increases risk of intraventricular hemorrhage and periventricular leukomalacia. Permissive hypercapnia (target 50 to 55 mm Hg) may be used as a minimal ventilation strategy to avoid ventilator-associated trauma, facilitate extubation toward noninvasive ventilation, and prevent bronchopulmonary dysplasia (BPD).

A. Blood gas determination. As is the case with oxygen monitoring, a $PaCO_2$ value obtained at steady state from an indwelling arterial catheter provides the most accurate indicator of alveolar ventilation. Lack of a catheter, however, limits the availability of this sampling for many patients, especially infants with chronic lung disease. Blood obtained by percutaneous arterial puncture is an alternative but may not reflect steady-state values because of artifacts introduced by pain and agitation. In addition, frequent blood sampling may increase the need for blood transfusion.

1. **Venous blood** from a central catheter may be useful in certain circumstances. If alveolar ventilation and circulatory function are normal, venous $PaCO_2$ usually exceeds arterial values by 5 to 6 mm Hg. However, if significant hypoventilation or circulatory dysfunction is present, this relationship is unpredictable.
2. **Capillary blood gases.** $PaCO_2$ and pH values obtained from properly collected capillary blood samples can closely reflect arterial values. The extremity must be warmed, and a free-flowing blood sample collected under strictly anaerobic conditions without squeezing the extremity. In smaller premature infants, these conditions may be difficult to achieve.
3. **Acute versus chronic respiratory derangements** can be determined from analyzing the pH and $PaCO_2$ on blood gas assessments. In acute derangements of $PaCO_2$, pH will be affected due to buffering with bicarbonate and hydrogen ion. A rule of thumb is that in acute respiratory acidosis, for every 10 mm Hg increase in $PaCO_2$, pH will drop by approximately 0.08. In chronic respiratory acidosis, such as occurs

Acute, chronic, and mixed respiratory acidosis			
	$PaCO_2$	**pH**	**Bicarbonate**
Acute respiratory acidosis	>45 mm Hg	↓ by 0.08 for every ↑ 10 mm Hg in $PaCO_2$	Normal
Chronic respiratory acidosis	>45 mm Hg	↓ by 0.04 for every ↑ 10 mm Hg in $PaCO_2$	Elevated
Mixed respiratory acidosis/metabolic alkalosis	>45 mm Hg	Greater than expected for pure respiratory acidosis	Elevated
$PaCO_2$, arterial partial pressure of carbon dioxide.			

with BPD, increased renal excretion of hydrogen ion increases serum bicarbonate and results in compensation and normalization of pH; in these cases, for every 10 mm Hg increase in $PaCO_2$, pH will decrease by approximately 0.04. Medications such as diuretics may result in a mixed respiratory acidosis and metabolic alkalosis, with the pH and bicarbonate higher than would be expected if there were chronic respiratory acidosis alone.

B. Noninvasive CO_2 monitoring. Although measurement of $PaCO_2$ by ABG sampling and analysis is the gold standard for assessing ventilation, $PaCO_2$ can be a dynamic and rapidly changing value and may not be accurately reflected in a single invasive measurement. Noninvasive, continuous monitoring offers theoretical benefits over intermittent blood sampling, including sooner recognition of hypercarbia or hypercarbia, rapid identification of unplanned extubation, monitoring during neonatal transport, identifying trends in $PaCO_2$ after changes in ventilator settings or modes (particularly high-frequency modes), identifying changes based on infant positioning, and monitoring for stability of ventilation after extubation. Noninvasive monitoring can also decrease the need for percutaneous blood draws and indwelling catheters, potentially reducing painful stimuli, risk for infection, risk of anemia, and need for blood transfusion.

1. **Transcutaneous CO_2 monitoring** ($PtcCO_2$) estimates the $PaCO_2$ through electrochemical measurements of CO_2 gas diffusing through body tissue and skin. A sensor at the skin surface measures the pH of an electrolyte solution that is separated from the skin by a permeable membrane. The sensor is warmed to approximately 42° to 43°C to induce a local hyperemia, resulting in vasodilation of the dermal capillary bed below the sensor, increasing arterial blood flow. This vasodilation also facilitates diffusion of CO_2. $PtcCO_2$ is often slightly higher than the corresponding measured $PaCO_2$ value due to two main factors. First, the elevated skin temperature alters the solubility of CO_2. Second, the hyperemia increases the metabolism of the skin cells, which contributes to CO_2 levels. To align

$PtcCO_2$ monitor values more closely with the $PaCO_2$ may therefore require a corrective algorithm.

a. Although transcutaneous monitoring is generally considered safe, tissue injury may occur at the measuring site, including blisters, burns, and skin tears. Because of hyperemia where the probe is applied, the probe site must be changed (and often recalibrated) during continuous monitoring to avoid skin-related complications that primarily occur when the sensor is in place for long periods of time. Transcutaneous monitoring should be avoided in patients with poor skin integrity or adhesive allergy.

b. Clinical situations that may lead to an increased discrepancy between the $PtcCO_2$ and $PaCO_2$ include improper probe placement or application, increased distance from probe to capillaries (such as body wall edema or thickness of the patient's skin or subcutaneous tissue), metabolic acidosis (pH $<$ 7.3), poor perfusion of the site of probe placement, or hyperoxemia (PaO2 $>$100 torr).

c. In the normal range, $PtcCO_2$ exceeds that of $PaCO_2$ by a mean of 4 mm Hg, but this gradient may more than double in the presence of hypercapnia.

2. **Capnography** refers to the noninvasive measurement of the $PaCO_2$ in exhaled breaths, expressed as the CO_2 concentration over time. The relationship of CO_2 concentration to time can be represented graphically as a waveform or capnogram (Fig. 30.1) and can be used to determine the maximum CO_2 concentration at the end of each tidal breath, or end-tidal CO_2 ($EtCO_2$).

Capnography has been widely used in the United States since the 1980s; its clinical uses include assessment of disease severity, response to therapy, and the confirmation of proper endotracheal tube placement.

a. Capnography uses IR radiation and absorption to detect CO_2. Molecules of CO_2 absorb IR radiation at a specific wavelength (4.26 μm), and the amount of absorption is exponentially related to the CO_2 concentration.

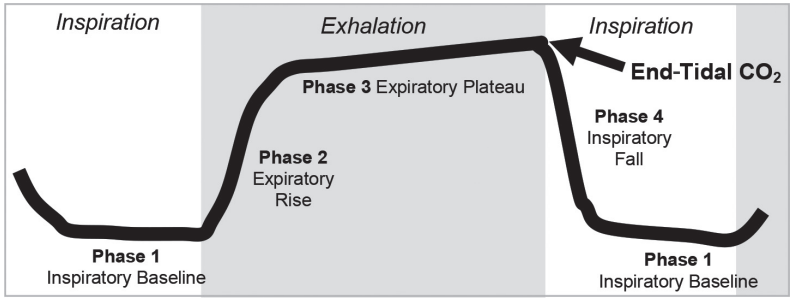

Figure 30.1. End-tidal capnograph. Representation of expired carbon dioxide (CO_2) detection using a capnograph, showing the four phases: inspiratory baseline, expiratory rise, expiratory plateau, and inspiratory fall. The end-tidal CO_2 is measured at the end of the expiratory plateau. Tachypneic newborns may not reach an expiratory plateau, potentially underestimating the end-tidal CO_2.

Capnometers use photodetectors to detect changes in IR levels at this wavelength to calculate the concentration of CO_2 in the sample; the more IR absorbed and less detected, the higher the CO_2 concentration in the sample. Oxygen and nitrogen do not absorb radiation at this wavelength, so during inspiration (when nitrogen and oxygen are passing through the detector), no IR radiation is absorbed, and therefore, no CO_2 signal is generated. During expiration, the first gas to pass through the detector will be from the dead space and contain little or no CO_2; this is followed by a rise in CO_2 concentration until a plateau signal is generated as alveolar CO_2 is exhaled and detected. The concentration of exhaled CO_2 may increase slightly in this phase. The peak CO_2 detected is the $EtCO_2$. As the patient inhales again, the signal quickly falls to zero

b. Capnography devices are categorized based on their location for sampling and therefore also on the types of patients for whom they are effective.

- **i. Mainstream** devices measure CO_2 directly from the airway, with the sensor located on the airway adapter at the hub of the endotracheal tube, between the breathing circuit and the endotracheal tube. The signals detected are amplified and transmitted via cable to a monitor where the $PaCO_2$ is calculated and displayed. Mainstream sensors are heated to slightly above body temperature to prevent condensation of water vapor because this can cause falsely high CO_2 readings. Potential disadvantages of mainstream capnography include relative fragility of adapters, increased mechanical dead space, additional weight on the airway, and use limited to intubated patients.
- **ii. Sidestream** devices can be used in both intubated and nonintubated patients by siphoning a small sample from the exhaled breath through the ventilator circuit or cannula tubing to a sensor located inside the CO_2 monitor. Gases can even be sampled from the nasal cavity during the administration of oxygen using nasal cannula. Sidestream systems used in infants usually use low flow rates of approximately 50 mL/minute. These devices may require additional safeguards, including a gas scavenging system to collect anesthetic gases in the sample if present, and a water trap to collect condensation from humidified sample gas or patient secretions. Disadvantages of sidestream capnography include variation in humidity and temperature between the sampling and measurement sites, pressure drops through the tubing that may affect CO_2 measurement, and a delay of up to several seconds to display the measurement.
- **iii.** Although not widely used, distal sidestream analysis using a double-lumen endotracheal tube to sample at the intratracheal end of the endotracheal tube has also been described.

c. Several factors limit the utility of $EtCO_2$ measurements in newborns.

- **i.** Mechanical ventilation typically uses relatively rapid rates compared to adult strategies, and most ventilator circuits deliver a continuous fresh flow of gas throughout the respiratory cycle. This limits the ability to obtain a true end-expiratory plateau.

ii. Air leak around an uncuffed endotracheal tube may depress $EtCO_2$ measurements in intubated neonates.

iii. Arterial–alveolar CO_2 gradients are elevated in babies with serious parenchymal lung disease because of maldistribution of ventilation (mean 6 to 10 mm Hg). As a result, end-tidal measurements may significantly underestimate $PaCO_2$ values. However, in babies with more uniform distribution of ventilation, end-tidal measurements may be useful to monitor trends.

d. Confirming endotracheal intubation placement. The Neonatal Resuscitation Program recommends use of an exhaled CO_2 detector (colorimetric device or capnograph) to confirm correct tube placement during endotracheal intubation.

e. Monitoring during anesthesia. The Standards for Basic Anesthetic Monitoring of the American Society of Anesthesiologists specifies the use of continuous $EtCO_2$ monitoring of all patients, including newborns, during general anesthesia with endotracheal tube or laryngeal mask airway.

IV. PULMONARY GRAPHICS MONITORING.

Several devices are marketed for bedside pulmonary function testing in infants and young children. In addition, most newer generation ventilators graphically display various measured or calculated parameters. Despite the added cost and increasing availability of these modalities, evidence of beneficial effect on neonatal outcomes is lacking. Several techniques have been advocated in limited studies.

A. Tidal volume measurements may be used to assist in manual adjustment of ventilator settings. Alternatively, such measurements may be used for software-automated ventilator adjustments designed to maintain a defined range of delivered tidal volume (volume guarantee) or consistent tidal volume delivery using minimal peak airway pressure (pressure-limited volume control). However, technical issues may limit efficacy of these modalities. Measured tidal volume varies markedly in devices from different manufacturers. These discrepancies result from differences in measurement sites, variations in tubing system compliance, and use of different strategies to compensate for endotracheal tube leaks. In addition, some software algorithms average adjustments in tidal volume over several breaths. Despite these shortcomings, tidal volume measurements using the same device consistently over time may provide clinically useful information during chronic mechanical ventilation and may be helpful with weaning following surfactant treatment when lung compliance changes rapidly.

B. Pressure–volume and flow–volume loops. Positive end-expiratory pressure (PEEP) is an important tool in management of infants with severe BPD. In limited case studies, real-time pressure–volume and flow–volume loop tracings have been used to guide determination of optimal PEEP to oppose airway collapse and achieve maximal compliance and minimize airway obstruction. However, indices that quantify the flow–volume relationship have not been validated in young infants. Because of rapid breathing, onset of inspiration often occurs before end-expiratory closure of the loop is achieved. As a result, "normal" tracings are difficult to obtain and clinical

application of this technique in small infants is limited. In addition, abnormally flattened flow–volume loops may suggest large airway disease such as tracheobronchomalacia.

C. Infant pulmonary function tests (iPFTs) remain limited to mostly research uses. These can be performed in intubated or spontaneously breathing infants. Most methods require sedation, often using chloral hydrate. Raised-volume rapid thoracic compression, which involves inflation to vital capacity followed by rapid exhalation using chest compression ("hug"), has been used to measure spirometry to evaluate forced expiratory volume over 0.5 seconds ($FEV_{0.5}$) and forced vital capacity. Body plethysmography, performed with a sealed facemask in a body box, can estimate total lung capacity (TLC) and functional residual capacity (FRC). These techniques have been used to classify infants with severe BPD as obstructive or restrictive phenotypes.

Suggested Readings

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31 Apnea

Ann R. Stark

KEY POINTS

- Apnea spells typically resolve by 36 to 37 weeks' postmenstrual age (PMA) in infants born at 28 weeks of gestation or more but may persist to or beyond 40 weeks' PMA in more preterm infants.
- Caffeine is a safe and effective treatment for apnea.
- Evidence does not support treatment of gastroesophageal reflux to reduce apnea frequency.
- Prior to discharge, a 5- to 7-day period after discontinuation of caffeine therapy without recorded apnea events predicts a low likelihood of recurrent symptomatic apnea.

I. BACKGROUND

A. Definition. Apnea is defined as the cessation of airflow. Apnea is pathologic (an apneic spell) when absent airflow is prolonged (usually 20 seconds or more) or accompanied by bradycardia (heart rate <100 beats per minute [bpm]) or hypoxemia that is detected clinically (cyanosis) or by oxygen saturation monitoring. Bradycardia and desaturation are usually present after 20 seconds of apnea, although they typically occur more rapidly in the small preterm infant. If the spell continues, pallor and hypotonia may be seen, and infants may be unresponsive to tactile stimulation. The level or duration of bradycardia or desaturation that may increase the risk of neurodevelopmental impairment is not known.

B. Classification of apnea is based on whether absent airflow is accompanied by continued inspiratory efforts and upper airway obstruction. Most spells in preterm infants are mixed.

1. Central apnea occurs when inspiratory efforts are absent.
2. Obstructive apnea occurs when inspiratory efforts persist in the presence of airway obstruction, usually at the pharyngeal level.
3. Mixed apnea occurs when airway obstruction with inspiratory efforts precedes or follows central apnea.

C. Incidence. Apneic spells occur frequently in premature infants. The incidence of apnea increases with decreasing gestational age. Essentially, all infants <28 weeks' gestational age have apnea. As many as 25% of all premature

infants who weigh <1,800 g (~34 weeks' gestational age) have at least one apneic episode.

1. **Onset.** In infants not receiving ventilatory support, apneic spells generally begin at 1 or 2 days after birth; if they do not occur during the first 7 days, they are unlikely to occur later. Apnea spells may become apparent for the first time when assisted ventilation is discontinued.
2. **Duration.** Apneic spells persist for variable periods postnatally and usually cease by 36 to 37 weeks' postmenstrual age (PMA) in infants born at 28 weeks' gestation or more. In infants born before 28 weeks' gestation, however, spells often persist beyond term PMA. After resolution of apnea, preterm infants may also have intermittent hypoxemic events that are not clinically apparent or detected by routine monitoring. Furthermore, in a study in which infants were monitored at home, significant apnea and/or bradycardia were recorded up to 43 weeks' PMA in 20% of preterm infants who were free of spells for at least 5 days before discharge and in 33% of those who had spells observed during that period (Collaborative Home Infant Monitoring Evaluation [CHIME] study). The clinical significance of these events is uncertain.
3. **Term infants.** Apneic spells occurring in infants at or near term are always abnormal and are nearly always associated with serious, identifiable causes, such as birth asphyxia, intracranial hemorrhage, seizures, or depression from medication. Failure to breathe at birth in the absence of drug depression or asphyxia is generally caused by irreversible structural abnormalities of the central nervous system.

II. PATHOGENESIS.

Several mechanisms have been proposed to explain apnea in premature infants, although those responsible for this disorder are unknown. Many clinical conditions have also been associated with apneic spells, and some may be causative.

A. Developmental immaturity of central respiratory drive

is a likely contributing factor because apneic spells occur more frequently in immature infants.

1. The occurrence of apnea may correlate with brainstem neural function. The frequency of apnea decreases over a period in which brainstem conduction time of the auditory-evoked response shortens as gestational age increases.
2. Breathing in infants is strongly influenced by sleep state. Active or rapid eye movement (REM) sleep is marked by irregularity of tidal volume and respiratory frequency. REM sleep predominates in preterm infants, and apneic spells occur more frequently in this state than in quiet sleep.

B. Chemoreceptor response

1. In preterm infants, hypoxia results in transient hyperventilation, followed by hypoventilation and sometimes apnea, in contrast to the response in adults. In addition, hypoxia makes the premature infant less responsive to increased levels of carbon dioxide. This suggests that immaturity of peripheral chemoreceptors may be involved in the pathogenesis of apnea. Although most infants do not appear to be hypoxemic before the onset of apnea, hypoxemia might play a role in prolonging the spell.

2. The ventilatory response to increased carbon dioxide is decreased in preterm infants with apnea compared with a matched group without apnea and is also decreased compared to term infants or adults. This suggests the possible contribution of immature central chemoreceptors to the pathogenesis of apnea.

C. Reflexes. Active reflexes invoked by stimulation of the posterior pharynx, lung inflation, fluid in the larynx, or chest wall distortion can precipitate apnea in infants. These reflexes may be involved in the apnea that is sometimes associated, for example, with vigorous use of suction catheters in the pharynx or with fluid in the upper airway during feeding.

D. Respiratory muscles. Ineffective ventilation may result from impaired coordination of the inspiratory muscles (diaphragm and intercostal muscles) and the muscles of the upper airway (larynx and pharynx).

1. Airway obstruction contributes to mixed and obstructive apneic spells. The site of this obstruction is usually the upper pharynx, which is vulnerable because of poor muscle tone, especially in REM sleep. Passive neck flexion, pressure on the lower rim of a face mask, and submental pressure (all encountered during nursery procedures) can obstruct the airway in infants and lead to apnea, especially in a small premature infant. Spontaneously occurring airway obstruction is seen more frequently when preterm infants assume a position of neck flexion.
2. Nasal obstruction can lead to apnea, especially in preterm infants who usually do not switch to oral breathing after nasal occlusion.

E. Gastroesophageal reflux is common in preterm infants. However, no association has been demonstrated between apnea of prematurity and gastroesophageal reflux.

F. Many inhibitory neurotransmitters are thought to play a role in the pathogenesis of apnea.

III. MONITORING AND EVALUATION

A. All infants <35 weeks' gestational age should be monitored for apneic spells for at least the first week after birth because of the risk of apneic spells in this group. Monitoring should continue until no significant apneic episode has been detected for at least 5 days. Because impedance apnea monitors may not distinguish respiratory efforts during airway obstruction from normal breaths, heart rate should be monitored in addition to, or instead of, respiration. Pulse oximetry should be monitored to detect episodes of desaturation. Even with careful monitoring, some prolonged spells of apnea and bradycardia may not be recognized.

B. When a monitor alarm sounds, one should respond to the infant, not the monitor, checking for bradycardia, cyanosis, and airway obstruction.

C. Most apneic spells in preterm infants respond to tactile stimulation. Infants who fail to respond to stimulation should be ventilated during the spell with bag and mask, generally starting with a fractional concentration of inspired oxygen (FiO_2) equal to the FiO_2 used before the spell to avoid marked elevations in arterial oxygen tension.

Table 31.1. Evaluation of an Infant with Apnea

Potential Cause	Associated History or Signs	Evaluation
Infection	Feeding intolerance, lethargy, temperature instability	Complete blood count, cultures, if appropriate
Impaired oxygenation	Desaturation, tachypnea, respiratory distress	Continuous oxygen saturation monitoring, arterial blood gas measurement, chest x-ray examination
Metabolic disorders	Jitteriness, poor feeding, lethargy, CNS depression, irritability	Glucose, calcium, electrolytes, newborn screen
Drugs	CNS depression, hypotonia, maternal history	Magnesium; screen for toxic substances in urine.
Temperature instability	Lethargy	Monitor temperature of patient and environment.
Intracranial pathology	Abnormal neurologic examination, seizures	Cranial ultrasonographic examination

CNS, central nervous system.

D. After the first apneic spell, the infant should be evaluated for a possible underlying cause (Table 31.1); if a cause is identified, specific treatment can then be initiated. One should be particularly alert to the possibility of a precipitating cause in infants who are >34 weeks' gestational age. Evaluation should include a history and physical examination and may include arterial blood gas measurement; complete blood count; and measurement of blood glucose, calcium, and electrolyte levels.

E. Although sudden infant death syndrome (SIDS) occurs more frequently in preterm infants, a history of apnea of prematurity does not increase this risk.

IV. TREATMENT

A. General measures

1. **Specific therapy** should be directed at an underlying cause, if one is identified.
2. The optimal range of oxygen saturation for preterm infants is not certain. However, supplemental oxygen should be provided if needed to maintain values in the targeted range (see Chapter 30).
3. **Care should be taken** to avoid reflexes that may trigger apnea. Suctioning of the pharynx should be done carefully, and tolerance of oral feedings when appropriate should be closely monitored.

4. **Positions of extreme flexion** or extension of the neck should be avoided to reduce the likelihood of airway obstruction. Prone positioning stabilizes the chest wall and may reduce apnea.

B. Caffeine. Treatment with caffeine, a methylxanthine, markedly reduces the number of apneic spells and the need for mechanical ventilation. The primary mechanism by which methylxanthines may decrease apnea is antagonism of adenosine, a neurotransmitter that can cause respiratory depression by blocking both its inhibitory A_1 receptor and its excitatory A_{2A} receptors. Respiratory effects include increased carbon dioxide sensitivity, decreased hypoxic depression of breathing, and decreased periodic breathing.

In the Caffeine for Apnea of Prematurity (CAP) study, survival without neurodevelopmental disability at 18 to 21 months of age, the primary outcome, was improved in infants 500 to 1,250 g birth weight treated early with caffeine compared to placebo. Caffeine treatment also reduced the rate of bronchopulmonary dysplasia. We therefore begin caffeine citrate treatment in all infants <1,250 g birth weight soon after birth and continue until it is deemed no longer necessary to treat apnea. In preterm infants >1,250 g birth weight who require mechanical ventilation, we begin caffeine treatment prior to extubation. In other infants with apnea of prematurity, we begin caffeine to treat frequent and/or severe apnea.

1. We use a loading dose of 20 mg/kg of caffeine citrate (10 mg/kg caffeine base) orally or intravenously >30 minutes, followed by maintenance doses of 5 to 10 mg/kg in one daily dose beginning 24 hours after the loading dose.
   a. If apnea continues at the lower range of maintenance doses, we give an additional dose of 10 mg/kg caffeine citrate and increase the maintenance dose by 20%.
   b. Caffeine serum levels of 5 to 20 μg/mL are considered therapeutic. We do not routinely measure serum drug concentration because of the wide therapeutic index and the lack of an established dose–response relationship.
   c. Caffeine is generally discontinued at 33 to 34 weeks' PMA if no apneic spells have occurred for 5 to 7 days. As noted previously, apnea in infants born at <28 weeks' gestation frequently persists beyond this PMA, and caffeine is continued until the spells resolve. The effect of caffeine likely remains for up to 1 week after it has been discontinued. We continue monitoring until no apnea has been detected for at least 5 days after that period.
2. Additional long-term benefits or risks of caffeine therapy are uncertain. In the CAP trial, weight gain was less during the first 3 weeks after randomization in infants treated with caffeine but not at 4 and 6 weeks, and head circumference was similar in the two groups during the 6-week observation period. Mean percentiles for growth parameters were similar at 18 to 21 months corrected age.
3. Most reports of side effects of methylxanthines in newborns are based on experience with theophylline. Caffeine appears to be less toxic than theophylline and is well tolerated.

C. Nasal continuous positive airway pressure (CPAP) at moderate levels (4 to 6 cm H_2O) can reduce the number of mixed and obstructive apneic spells. By helping to maintain a higher end-expiratory volume, CPAP may limit the depth and duration of desaturation that occurs during central apnea spells. Humidified high-flow nasal cannula can be used to provide increased end-expiratory volume, although its effect on reduction of apnea frequency has not been specifically evaluated. Nasal intermittent positive pressure ventilation (NIPPV) may reduce extubation failure due to apnea following mechanical ventilation (see Chapter 29).

D. Whether blood transfusion reduces the frequency of apneic spells in some infants remains controversial because results of studies are conflicting and do not demonstrate sustained reduction following transfusion. We consider a transfusion of packed red blood cells (PRBCs) if the hematocrit is <25% to 30% and the infant has episodes of apnea and bradycardia that are frequent or severe while continuing treatment with caffeine (see Chapter 45).

E. Gastroesophageal reflex (GER) frequently occurs in preterm infants who are having apnea, although these events are rarely precede a spell. Pharmacologic treatment of GER with agents that increase motility or decrease gastric acidity have not been shown to reduce apnea frequency and may be harmful.

F. Mechanical ventilation may be required if the other interventions are unsuccessful.

V. DISCHARGE CONSIDERATIONS

A. We typically require that preterm infants have no apnea spells recorded for 5 to 7 days prior to discharge, although this may be extended for extremely low gestation infants or those with severe events. Because of the long half-life of caffeine (50 to 100 hours) and even longer effects in some infants, we typically start this "countdown" period several days after caffeine is stopped. Feeding-associated events are generally not included, although severe events during feeding may suggest lack of discharge readiness. However, a monitored apnea-free period does not preclude later apnea, as shown by the CHIME study (see section I.C.2 earlier), and apnea may take longer to resolve in infants born at lower gestational ages.

B. Intercurrent viral illness, anesthesia, and ophthalmologic examinations may precipitate recurrent apnea in preterm infants. These infants should be monitored closely at least until 44 weeks' PMA. Immunizations (primarily 2 months and rarely 4 months) may also exacerbate apnea in very preterm infants who remain in the neonatal intensive care unit.

Suggested Reading

Eichenwald EC; and the American Academy of Pediatrics Committee on Fetus and Newborn. Apnea of prematurity. *Pediatrics* 2016;137(1):1–7.

32 Transient Tachypnea of the Newborn

Kristen T. Leeman

KEY POINTS

- Transient tachypnea of the newborn (TTN) is a common cause of newborn respiratory distress in the immediate newborn period caused by retained fetal lung fluid.
- TTN is usually benign and self-limited.
- Management is supportive with oxygen or continuous positive airway pressure (CPAP), and symptoms generally resolve in 12 to 72 hours.
- Clinicians should exclude other respiratory, infectious, cardiac, or neurologic etiologies.

I. DEFINITION. Transient tachypnea of the newborn (TTN), first described by Avery and colleagues in 1966, is a parenchymal lung disease with pulmonary edema resulting from delayed clearance of fetal lung fluid. As the name implies, it is usually a benign, self-limited process. TTN occurs in the immediate period after birth and generally affects infants born at late preterm or term gestation. The disorder is characterized by tachypnea with signs of mild respiratory distress including retractions and cyanosis.

II. PATHOPHYSIOLOGY. In the process of transition from the fetal to newborn life, the lung epithelium must switch from a secretory mode that provides the fetal lung fluid required for normal lung growth and development *in utero*, to an absorptive mode. This transition is facilitated by changes in the maternal–fetal hormonal milieu, including a surge in glucocorticoids and catecholamines, associated with physiologic events near the end of pregnancy and during spontaneous labor. Amiloride-sensitive epithelial sodium channels (ENaC) expressed in the apical membrane of the alveolar epithelium play an important role in lung fluid clearance. Adrenergic stimulation and other changes near birth lead to passive transport of sodium through the ENaC, followed by active transport of sodium into the interstitium via the basolateral Na^+/K^+-ATPase pump. This creates an osmotic gradient and allows for passive movement of chloride and water through paracellular and intracellular pathways out of the airspace into the pulmonary interstitium. Interstitial lung fluid pools in perivascular cuffs of tissue and in the interlobar fissures and then is cleared through absorption into pulmonary capillaries and lymphatics. Disruption or delay in

clearance and resorption of fetal lung fluid results in the transient pulmonary edema that characterizes TTN. This pulmonary edema leads to tachypnea to compensate for reduced pulmonary compliance. Compression of the compliant airways by fluid accumulated in the interstitium can lead to airway obstruction, air trapping, and ventilation–perfusion mismatch. Functional residual capacity may be reduced due to obstruction, whereas thoracic gas volume may increase secondary to air trapping.

III. EPIDEMIOLOGY. The incidence of TTN is 0.3% to 0.6% of term deliveries. Risk factors for TTN include cesarean delivery without labor, delivery before 39 weeks' gestational age, prematurity, maternal diabetes, and birth asphyxia. The absence of the hormonal changes that accompany spontaneous labor can result in delayed or abnormal fetal lung fluid clearance. Diagnosis at preterm gestations is often complicated by the presence of comorbidities such as respiratory distress syndrome (RDS). Other risk factors include male sex and maternal history of asthma. The mechanism underlying the sex- and asthma-associated risks is unclear, but it may be related to altered sensitivity to catecholamines that play a role in lung fluid clearance. Genetic polymorphisms in β-adrenergic receptors in alveolar type II cells have been associated with TTN and may influence lung fluid clearance by regulating ENaC expression as well as explain the correlation between TTN and wheezing in the first years of life. Small and large for gestational age infants are also at increased risk for TTN. The associations between TTN and other obstetric factors such as excessive maternal sedation, prolonged labor, and volume of maternal intravenous fluids have been less consistent. Administration of antenatal corticosteroids may reduce rates of TTN in late preterm infants, although risk versus benefits must be considered given the transient nature of TTN.

IV. CLINICAL PRESENTATION. Affected term or late preterm infants usually present within the first 6 hours after birth with tachypnea (respiratory rates typically 60 to 120 breaths per minute). The tachypnea may be associated with mild to moderate respiratory distress with retractions, grunting, nasal flaring, and/or mild cyanosis that usually responds to supplemental oxygen at <0.40 fraction of inspired oxygen (FiO_2). Respiratory failure and need for mechanical ventilation are rare. Infants may have an increased anteroposterior diameter of the chest (barrel shaped) due to hyperinflation, which may also push down the liver and spleen, making them palpable. Auscultation usually reveals good air entry, and crackles may or may not be appreciated. Signs of TTN usually persist for 12 to 24 hours in cases of mild disease but can last up to 72 hours in more severe cases.

V. DIFFERENTIAL DIAGNOSIS. The diagnosis of TTN requires the exclusion of other potential etiologies for mild to moderate respiratory distress presenting in the first 6 hours of age. The differential diagnosis includes but is not limited to pneumonia, sepsis, RDS, persistent pulmonary hypertension of the newborn, meconium aspiration, cyanotic congenital heart disease, congenital malformations (e.g., congenital diaphragmatic hernia, congenital pulmonary airway malformation), central nervous system injury

(subarachnoid hemorrhage, hypoxic-ischemic encephalopathy) causing central hyperventilation, pneumothorax, polycythemia, and metabolic acidosis/inborn error of metabolism.

VI. EVALUATION

A. History and physical examination. A careful history identifies elements such as prematurity, infectious risk factors, meconium, or perinatal depression that may aid in directing the evaluation. Similarly, findings on physical examination such as cardiac or neurologic abnormalities may lead to a more targeted investigation.

B. Radiographic evaluation. The chest radiograph of an infant with TTN is consistent with retained fetal lung fluid, with characteristic prominent perihilar streaking (sunburst pattern) due to engorgement of periarterial lymphatics that participate in the clearance of alveolar fluid. Coarse, fluffy densities may reflect alveolar edema. Hyperaeration with widening of intercostal spaces, mild cardiomegaly, widened and fluid-filled interlobar fissure, and mild pleural effusions may also be observed. The radiographic findings in TTN usually improve by 12 to 18 hours and resolve by 48 to 72 hours. This rapid resolution helps distinguish the process from pneumonia and meconium aspiration. The chest radiograph can also be used to exclude other diagnoses such as pneumothorax, RDS, and congenital malformations. Lung ultrasound can differentiate TTN from RDS with good specificity but is not in common clinical use. Of note, the presence of increased pulmonary vascularity in the absence of cardiomegaly may represent total anomalous pulmonary venous return.

C. Laboratory evaluation. A complete blood count (CBC) and appropriate cultures can provide information concerning possible pneumonia or sepsis. If risk factors or laboratory data suggest infection, or if respiratory distress does not improve, broad-spectrum antibiotics should be initiated. An arterial blood gas may be used to determine the extent of hypoxemia and adequacy of ventilation. Infants with TTN may have mild hypoxemia and mild respiratory acidosis that typically resolves over 24 hours. With persistent or severe hypoxemia or differential preductal and postductal oxygen saturations, a cardiac evaluation including an echocardiogram should be considered. Respiratory alkalosis may reflect central hyperventilation due to CNS pathology or metabolic disorder. If the infant is lethargic and has a metabolic acidosis, an ammonia level should be obtained to rule out inborn error of metabolism.

VII. MANAGEMENT.

Management is mainly supportive with provision of supplemental oxygen as needed. More severe cases may respond to continuous positive airway pressure (CPAP) to improve lung recruitment. Infants often undergo an evaluation for infection and are treated with antibiotics for 48 hours until blood cultures are negative, although evidence is increasing that empiric antibiotic exposure may not be necessary if the infant is closely observed and there are no risk factors for infection. If tachypnea persists and is associated with increased work of breathing, gavage feedings or intravenous fluids may be needed to provide nutrition and hydration. Relatively restricted

fluid intake has been shown to decrease duration of respiratory support in severe cases of TTN.

Strategies aimed to facilitate lung fluid absorption have not shown clinical efficacy. Oral furosemide has not been shown to decrease the duration of tachypnea or length of hospitalization. In a trial based on the hypothesis that infants with TTN have relatively low levels of catecholamines that facilitate fetal lung fluid absorption, treatment with racemic epinephrine did not change the rate of resolution of tachypnea compared to placebo.

VIII. COMPLICATIONS. Although TTN is a self-limited process, supportive therapy may be accompanied by complications. CPAP is associated with increased risk of air leak. Delayed initiation of oral feeds may interfere with parental bonding and establishment of breastfeeding and may prolong hospitalization.

IX. PROGNOSIS. TTN is a self-limited process with no risk of recurrence, and the prognosis is excellent. Generally, there are no significant long-term residual effects. However, observational studies suggest a possible link between TTN and reactive airway disease in childhood.

Suggested Readings

Alhassen Z, Vali P, Guglani L, et al. Recent advances in pathophysiology and management of transient tachypnea of newborn. *J Perinatol* 2021;41(1):6–16.

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33 Respiratory Distress Syndrome

Susan Guttentag

KEY POINTS

- Respiratory distress syndrome (RDS), a disease affecting preterm infants, is caused by insufficient pulmonary surfactant.
- Antenatal corticosteroids (ANC) given to a pregnant woman in anticipation of preterm and late-preterm birth prevents RDS.
- Treatment entails establishment and maintenance of functional residual capacity by application of continuous positive airway pressure (CPAP) and surfactant administration.

I. INTRODUCTION. Respiratory distress syndrome (RDS), formerly known as hyaline membrane disease (HMD), describes a disease typical of preterm infants that is caused by insufficient pulmonary surfactant in alveoli. Pulmonary surfactant is a complex mixture of phospholipids, neutral lipids, and surfactant-specific proteins that is synthesized, packaged, and secreted by alveolar type II cells of the lung. Small respiratory bronchioles and alveoli have limited structural support. The protective liquid layer overlying the epithelium establishes high surface tension that is forceful enough to promote airspace collapse at low alveolar volumes and to oppose reinflation of atelectatic airspaces. Secreted surfactant establishes a phospholipid monolayer at the air-liquid interface that reduces the surface tension, enabling respiratory bronchioles and alveoli to remain open throughout the respiratory cycle. Absent or insufficient surfactant can result from developmental immaturity of alveolar type II cells; spontaneous or inherited mutations of surfactant-related genes; or inactivation of surfactant due to inflammation, chemical modification, or lung injury. Loss of the surfactant monolayer results in high surface tension that contributes to atelectasis of alveoli and respiratory bronchioles. Preterm infants are particularly prone to RDS because alveolar type II cells do not develop until the late second and early in the third trimester, and their numbers and capacity to produce surfactant increase throughout the third trimester. Advances in preventive and rescue treatment strategies, including antenatal glucocorticoids, exogenous surfactant, and continuous positive airway pressure (CPAP), have greatly reduced the impact of RDS on neonatal morbidity and mortality, but RDS remains a particularly vexing problem for extremely low birth weight (ELBW) infants.

II. DIAGNOSIS

A. Risk factors

1. **Lung maturity**, which is distinct from structural lung development, is the most significant risk factor for RDS. By 24 weeks of gestation, structural lung development has advanced sufficiently to provide gas exchange across lung epithelial and endothelial cells and provide a surface area sufficient to meet the oxygen consumption needs of the ELBW infant. However, the fetal lung at that gestation has insufficient numbers of alveolar type II cells to generate enough surfactant to avoid RDS. In contrast, the fetal lung at 36 weeks of gestation generally has sufficient surfactant stores and larger numbers of alveolar type II cells to avoid RDS in most cases. In between, the preparedness of the fetal lung for air breathing depends on the extent of lung maturation, which is influenced by multiple genetic and environmental factors.

2. **Factors that affect lung maturation**

   a. Fetal sex. Male infants are at higher risk for RDS due to the presence of circulating weak fetal androgens that can inhibit the production of surfactant phospholipids.

   b. Maternal diabetes. Poorly controlled maternal diabetes, in the absence of microvascular disease, is associated with RDS due to enhanced production of fetal insulin which inhibits the production of proteins important for surfactant function. By contrast, more advanced maternal diabetes associated with microvascular disease that can limit fetal growth can be somewhat protective due to the stress this causes the fetus.

   c. Fetal stress. The stress of labor, due to the production of endogenous maternal glucocorticoids, may enhance lung maturation. Although this may be advantageous in the short term, inflammation often associated with preterm labor can downregulate the production of many surfactant components thereby increasing the risk of RDS.

   d. Mutations in genes encoding surfactant-related proteins, specifically *SFTPB* (surfactant protein B) and *ABCA3* (ATP binding cassette protein A3), result in severe RDS, typically in term infants, from either dysfunctional surfactant or severely limited production, respectively. Infants with these mutations may only transiently respond to exogenous surfactant administration and will die without lung transplantation. Other mutations of ABCA3, which pumps phospholipid into lamellar bodies, and mutations of surfactant protein C (SFTPC) are associated with progressive interstitial lung disease, often diagnosed beyond the neonatal period.

B. Antenatal testing

1. Because gestational age is a strong predictor of RDS risk, invasive testing (amniocentesis) to confirm lung maturity in amniotic fluid samples is reserved for instances in which surfactant deficiency in addition to other fetal conditions would significantly impact morbidity and mortality. These conditions include fetal anomalies such as congenital diaphragmatic hernia and congenital heart disease where more precise timing of delivery of a near-term infant is desirable. Although the risk of adverse outcomes is low with amniocentesis in

the third trimester, the widespread use of antenatal glucocorticoids has made this procedure unnecessary for most fetuses facing preterm delivery.

2. If lung maturity testing is indicated, the most readily available tests assess the lecithin (disaturated phosphatidylcholine) component of surfactant. Lecithin is the most abundant surfactant phospholipid, and its production is developmentally regulated. However, it is also present in cell membranes, necessitating correction for the presence of contaminants like maternal blood or fetal meconium.

   a. The **lecithin/sphingomyelin (L/S) ratio** corrects for the presence of a neutral lipid in low abundance in surfactant, whereas the **TDx-FLM II** corrects for the presence of albumin in the amniotic fluid sample. In both cases, samples contaminated significantly by blood or meconium can be difficult to interpret. RDS risk is low when the L/S ratio is >2, but notable exceptions to this include maternal diabetes, erythroblastosis fetalis, and intrapartum asphyxia. In these instances, an L/S ratio >2 should be interpreted with caution or another test should be used. The TDx-FLM II has established gestational age–specific cutoffs but in general is predictive of low RDS risk at >55 mg lecithin per gram albumin.

   b. The presence of phosphatidylglycerol (PG) in amniotic fluid is also a marker of lung maturity. This phospholipid appears at later gestational ages than lecithin and is tested by antibody agglutination of PG (**AmnioStat-FLM**).

   c. The presence of **lamellar bodies** in amniotic fluid samples is a rapid and inexpensive test that may be useful in resource-poor settings. Lamellar bodies are membrane-bound organelles in alveolar type II cells that receive, concentrate, and store surfactant constituents for regulated secretion. Upon exocytosis at the plasma membrane, the surfactant within lamellar bodies (not the membrane-bound lamellar bodies themselves) is extruded into the alveolar space and the constituents must unravel and disperse to form the monolayer at the air-liquid interface that lowers surface tension. Secreted surfactant aggregates can be discriminated by light microscopy or fluorescence-activated cell sorting (FACS), and >50,000 surfactant profiles per microliter of amniotic fluid has been correlated with lung maturity. Alternatively, **optical density** of amniotic fluid at 650 nm has been correlated with fetal pulmonary maturity, with readings >0.15 considered mature. Amniotic fluid absorbance is due to surfactant phospholipid components.

C. **Diagnosis.** RDS should be suspected in any preterm infant born at <34 weeks' gestation, with signs of respiratory distress that develop soon after birth. These include tachypnea, retractions, flaring of the nasal alae, grunting, and cyanosis. Blood gas measurement will often demonstrate hypoxemia and hypercarbia.

1. Infants with RDS who are spontaneously breathing may overcome the atelectasis resulting from surfactant deficiency by using a set of physiologic maneuvers to establish functional residual capacity (FRC) and optimize gas exchange. These characteristic signs/symptoms of respiratory

distress are shared by RDS and other respiratory diseases compromising pulmonary function.

a. Tachypnea. Inadequate FRC leads to inadequate tidal volumes. To maintain minute ventilation (the product of tidal volume × respiratory rate), infants with RDS increase respiratory rate.

b. Retractions. To maximize negative inspiratory pressure and thus lung inflation, affected infants use accessory muscles of breathing to supplement diaphragmatic contractions. The high negative inspiratory pressure draws in the highly compliant chest wall of preterm infants resulting in suprasternal, intercostal, and subcostal retractions.

c. Flaring of the nasal alae. To maximize air entry into the lungs in babies who are obligate nose breathers, flaring of the alae nasi reduces the resistance to air flow through the upper airways.

d. Grunting. Grunting is active exhalation against a partially closed glottis and results in a pressure gradient at the level of the vocal cords that provides expiratory distending pressure to stabilize open but surfactant-poor alveoli.

D. Radiographic evidence. RDS in preterm infants is a homogeneous lung disease due to the developmental deficiency of surfactant throughout the lung parenchyma. Typical radiographic findings include low lung volumes, homogeneous microatelectasis that has the appearance of ground glass, and air bronchograms that represent air in larger airways highlighted by the surrounding microatelectasis.

1. Differential diagnosis

a. Transient tachypnea of the newborn (TTN) (see Chapter 32). Excess fetal lung fluid can mimic RDS and can complicate RDS. Signs are indistinguishable from RDS, but TTN often resolves rapidly over the first several hours after birth. Radiographic findings characteristic of retained fetal lung fluid include prominent perihilar streaking (sunburst pattern) due to engorgement of periarterial lymphatics that participate in the clearance of alveolar fluid, and fluid retained in the lateral fissure of the right lung.

b. Pneumonia, especially due to group B *Streptococcus* (GBS). Proinflammatory cytokines elaborated in the course of an infection can inactivate surfactant constituents and downregulate surfactant production. Signs and radiographic findings of GBS sepsis/pneumonia are indistinguishable from RDS; therefore, obtaining blood cultures and initiating antibiotics should be considered.

c. Genetic disorders. Although more common in term and near-term infants, the presentation and radiographic findings are identical to RDS. This category includes mutations of surfactant-specific proteins (including *SFTPB* and *ABCA3*) and disorders of lung development, including alveolar capillary dysplasia with or without misalignment of the pulmonary veins (*FOXF1*), and brain-heart-lung disease (*NKX2-1*). Respiratory signs may be evident at birth or may develop insidiously in a vigorous term infant able to initially spontaneously recruit FRC. However, the infant shows little to no response to the administration of artificial surfactant. Genetic panels that include common mutations are available to aid in making the diagnosis.

III. PREVENTION. The basis for prevention of RDS is the observation that maternal hormones, specifically glucocorticoids, enhance surfactant maturation. Numerous trials have shown that administration of antenatal corticosteroids (ANC) in anticipation of preterm birth is effective in preventing RDS. ANC modifies surfactant availability as well as lung structure, including thinning of alveolar walls. The target population is pregnant women at 24 to 34 weeks of gestation with preterm labor, although emerging evidence suggests some benefit as early as 23 weeks of gestation. A complete course of ANC is considered to be *either* betamethasone at 12 mg intramuscular (IM) q24h × 2 doses *or* dexamethasone 6 mg IM q12h × 4 doses. Meta-analyses have not clearly demonstrated superiority of one drug over the other. No contraindications exist to treatment, including rapidly progressive labor, and animal studies have demonstrated effects on lung structure even after incomplete dosing. However, benefits of prior treatment on lung maturity may diminish if preterm labor stops and pregnancy continues more than a week after ANC use. A second course can be beneficial under such circumstances, but continued redosing has been associated with poor neurodevelopmental outcomes due to deleterious effects of glucocorticoids on brain development. Although the dramatic improvements in RDS and mortality due to ANC in the setting of anticipated preterm birth are unquestioned, outstanding concerns remain over the cardiovascular, metabolic, endocrine, and neurodevelopmental effects of ANC on the developing fetus and infant that continue to drive studies of dosing and steroid choice. These concerns include the observation that neonatal hypoglycemia occurs more often in preterm infants born after exposure to ANC regardless of gestational age.

In addition to ANC maturation of the surfactant system, glucocorticoids also regulate transcription of the subunits of the epithelial sodium channel (ENaC) and facilitate the reabsorption of fetal lung fluid in the lungs of prematurely born infants. Due to the large number of late-preterm infants experiencing respiratory disease due to surfactant immaturity and retained fetal lung fluid, a multicenter randomized controlled trial of a single dose of ANC in women threatening delivery at 34 0/7 to 36 6/7 completed weeks of gestation was done to reduce respiratory morbidity and mortality. Infants born to mothers who received ANC experienced a reduction in the primary outcome composite of severe respiratory outcome that included RDS, TTN, and apnea. This reduction was likely attributable to a reduction in TTN.

IV. MANAGEMENT (see Chapter 29). The key principles of treatment of RDS are to establish and maintain FRC. The most important role of pulmonary surfactant in the alveoli and distal respiratory bronchioles is to maintain a low surface tension that permits these delicate airways to remain patent at low lung volumes. Inadequate or dysfunctional surfactant in infants with RDS leads to an inappropriately high alveolar surface tension, resulting in difficulties recruiting atelectatic alveoli and in progressive atelectasis of recruited airspaces.

A. CPAP has its physiologic basis in the grunting that infants with RDS do to maintain FRC. Application of CPAP via nasal prongs, nasal mask, or face mask enables spontaneously breathing infants to gradually recruit

atelectatic airspaces while maintaining alveolar patency at end expiration despite the absence of surfactant. Meta-analyses of CPAP trials from the 1970s to 1980s demonstrated the effectiveness of CPAP in late-preterm and near-term infants with RDS. More recently, the use of CPAP in VLBW and ELBW infants has reduced the need for mechanical ventilation without increasing the incidence of bronchopulmonary dysplasia (BPD).

1. Practical guidelines

a. Pressure device. Options for application include bubble CPAP, variable flow devices, and mechanical ventilators. Bubble CPAP devices also provide a gentle oscillation of positive pressure that may assist in recruitment and carbon dioxide (CO_2) elimination in addition to supporting alveoli. Whichever device is used, flows of approximately 5 to 10 L/minute are needed to prevent rebreathing and hypercarbia.

b. The development of humidification devices enabling the administration of high-flow oxygen via nasal cannulas has led to their use as a strategy to provide end-expiratory pressure with a patient interface that may be less traumatic than nasal prongs. A single study using an esophageal balloon to measure intrathoracic pressures during high flow rates suggested that the delivered CPAP in centimeter of water (cm H_2O) pressure approximated the liter flow rate in liter per minute (L/minute). One trial that compared nasal CPAP to heated, humidified high-flow nasal cannula (HHHFNC) in infants with an average gestational age of 33 weeks following either mechanical ventilation or CPAP (87%) or as initial therapy (13%) found no difference in the primary outcome of failure requiring intubation within 72 hours of study entry. However, the limited evidence available suggests that HHHFNC should be used with caution, especially as initial therapy in ELBW infants.

c. Patient interface. A variety of nasal prongs and nasal masks can be used to provide an occlusive interface for CPAP delivery. The need for occlusion may lead to pressure necrosis of the nasal septum that can be severe enough to require surgical intervention. This can often be alleviated by alternating interfaces during routine nursing care. Daily rounds should include a discussion of the interface and status of the nasal septum.

d. Initiation of CPAP. Initiate nasal CPAP at 5 to 6 cm H_2O pressure and adjust based on chest radiograph (goal inflation 8 to 9 rib expansion) and oxygen requirement. Achieving optimal FRC should result in a gradual reduction in fraction of inspired oxygen (FiO_2) requirement to 0.21 in the uninjured lung with pure surfactant deficiency as well as normalization of respiratory rate. Monitoring of blood gases in the acute phase of recruitment may be necessary, but once adequate ventilation is achieved and recruitment has been established, noninvasive monitoring is usually sufficient to guide therapy.

e. Weaning strategies. Because successful application of CPAP is defined by achieving and maintaining a normal FRC, weaning of support should initially focus on reduction of supplemental oxygen until oxygen requirements are at least $<30\%$, and preferably $<25\%$. For the preterm infant >32 weeks of gestation, discontinuation of CPAP in favor of

room air or nasal canula oxygen can generally be considered at CPAP 4 to 5 and <25% oxygen concentration. For infants born at <32 weeks of gestation, poor chest wall compliance alone can lead to progressive atelectasis, and longer term use of low CPAP may be advantageous, even when oxygen supplementation is no longer needed. Recent single-center studies report improved lung growth parameters in preterm infants receiving an extended course of CPAP through 32 weeks of gestation. Atelectasis can occur with gradual weaning and discontinuation of CPAP due to insufficient endogenous surfactant stores and/or poor chest wall compliance. Signs of unsuccessful CPAP weaning include increases in oxygen requirement and respiratory rates, as well as retractions.

f. Contraindications. Few contraindications exist to using CPAP. The most important is apnea because the success of this therapy depends on the infant supplying the minute ventilation for normal CO_2 elimination. A trial of CPAP is contraindicated in infants with frank apnea in the delivery room. However, spontaneously breathing infants with respiratory distress or those at high risk for developing RDS (<30 weeks of gestation) may benefit from a trial of CPAP combined with early initiation of caffeine therapy to minimize apnea (see Chapter 31). Air leak is a relative contraindication to CPAP because air leak may worsen in the face of continuous positive pressure.

g. Complications

i. **Overdistention.** Rapid changes in lung compliance as atelectatic regions are recruited and supported, especially after administration of surfactant, can lead to overdistention of airspaces. In turn, this can result in (i) inadequate tidal volumes leading to hypercarbia; (ii) tamponade of the alveolar capillary bed, with ventilation–perfusion mismatch leading to hypercarbia and hypoxemia; and (iii) poor venous return sufficient to reduce cardiac output.

ii. **Air leak.** Although overdistention alone may lead to air leak, more often, air leak is due to large changes in airway pressures at the level of the respiratory bronchiole where airways lose their supporting structure, leading to disruption of the airway wall. This may occur in the context of an infant struggling to breathe or crying against CPAP.

iii. **Underdistention/atelectasis.** Failure to establish FRC will result in persistent need for oxygen supplementation and persistent atelectrauma of poorly supported airspaces. This is often due to difficulty with the patient–device interface (see section IV.A.1.c) and/or an open mouth that allows release of distending pressure. Repositioning patients in a side-lying or prone position to prop the jaw closed, or use of soft chin straps, can be useful.

iv. **Nasal septum trauma** (see section IV.A.1.c)

B. Restore alveolar surfactant. The majority of RDS encountered in the neonatal intensive care unit (NICU) is due to developmental deficiency of surfactant due to premature delivery of an infant with immature lungs. The widespread use of ANC has reduced the incidence and severity of RDS, but the risk remains high when precipitous delivery or other circumstances preclude ANC administration. Fortunately, surfactant maturation continues

postnatally and is often accelerated by the stress of preterm delivery and intensive care. For infants with RDS, exogenous surfactant therapy can acutely supplement insufficient endogenous stores and participate in the natural recycling of alveolar surfactant to enhance production by alveolar type II cells. The combination of ANC and postnatal surfactant administration is more effective in reducing the morbidity and mortality of RDS than either intervention alone. Treatment of RDS in preterm infants is currently the only U.S. Food and Drug Administration (FDA)-approved indication for the use of exogenous surfactant.

1. Practical considerations

a. Prophylaxis versus treatment. Evidence demonstrates an advantage to early treatment of infants before the onset of signs as compared to waiting to establish a diagnosis of RDS. However, universal prophylaxis would lead to many infants being intubated to receive surfactant who either might not develop RDS or who could be successfully managed with CPAP until their own surfactant production was sufficient. Therefore, surfactant should be considered in preterm infants intubated for respiratory failure, infants with early signs of RDS in the immediate perinatal period after a failed trial of CPAP, or in infants for whom CPAP is contraindicated, i.e., apnea. In a normal premature lung, the establishment of FRC should enable reduction of oxygen supplementation to $<30\%$. Therefore, it is reasonable to consider surfactant administration in preterm infants needing $>30\%$ oxygen.

b. Surfactant preparation. Available surfactants include a variety of animal-derived products that are enriched through the addition of phospholipids but preserve the content of the hydrophobic surfactant proteins B and C that contribute to surfactant function (Table 33.1).

c. Dosing and dosing interval. Surfactant is administered to achieve a phospholipid dose that is at least 100 mg/kg (see Table 33.1). The standard dosing interval is every 12 hours for a maximum of three doses. However, in the absence of a therapeutic response or if the initial response is waning, administration before 12 hours should be considered to minimize ventilator-induced lung injury.

d. Administration. Surfactant is typically given to infants with RDS through an endotracheal tube (ETT) that either remains in place for mechanical ventilation or is removed following the surfactant administration to resume CPAP. The ETT should be secured after intubation to avoid malpositioning of the tube during dosing. A chest radiograph is not necessary prior to dosing if the ETT is at a depth appropriate for gestational age and equal breath sounds can be confirmed by auscultation. To minimize reflux up the ETT, administration via a sterile feeding tube inserted into the ETT with the tip at or above the end of the ETT is preferable. Alternatively, the dose can be given via closed in-line suction devices to enable continuous mechanical ventilation. Providing the dose in two to four aliquots and allowing for recovery on mechanical ventilation between aliquots can help to minimize obstruction of the ETT or large airways by the viscous surfactant preparation. Growing experience with MIST (minimally invasive surfactant therapy) and LISA (less invasive surfactant administration) through a thin

Table 33.1. Dosing Information, Source, and Phospholipid and Protein Concentrations for Commonly Used Surfactant Preparations

Trade Name	Active Ingredient	Source	Dosing	Phospholipid Concentration	Protein Concentration
Survanta	Beractant	Bovine lung extract	■ 4 mL/kg (100 mg/kg phospholipid) divided into four-quarter doses through endotracheal tube. Prophylaxis: Give within 15 minutes of birth in infants at risk for surfactant deficiency. Rescue therapy: Give when diagnosis of surfactant deficiency is made. ■ Can use up to four doses, given no more frequently than every 6 hours	25 mg/mL	<1 mg/mL (SP-B and SP-C; does not contain SP-A)
Infasurf	Calfactant	Calf lung lavage fluid	■ 3 mL/kg (105 mg/kg phospholipid) through endotracheal tube for prophylaxis or rescue therapy ■ Can use up to three doses, given 12 hours apart	35 mg/mL	0.7 mg/mL (SP-B and SP-C; does not contain SP-A)
Curosurf	Poractant alfa	Porcine lung extract	■ Initial dose: 2.5 mL/kg through endotracheal tube (200 mg/kg phospholipid) ■ Can use up to two subsequent doses of 1.25 mL/kg administered 12 hours apart (maximum volume 5 mL/kg)	76 mg/mL	1 mg/mL (SP-B and SP-C; does not contain SP-A)

Source: Survanta package insert. Columbus, OH: Abbott Nutrition; Infasurf package insert. Amherst, NY: ONY Inc; Curosurf package insert. Parma, Italy: Chiesi Farmaceutici S.p.A.

SP-A, surfactant protein A; SP-B, surfactant protein B; SP-C, surfactant protein C.

catheter inserted into trachea supports efficacy, but questions remain about safety in the ELBW population. There is limited experience in administering surfactant through a laryngeal mask airway (LMA), and limited evidence exists for LMA use in <1,500-g infants. Early evidence suggests that aerosolization devices for surfactant administration may be beneficial.

e. Complications

i. Airway obstruction. Hypoxemia, bradycardia, and apnea may occur acutely during surfactant administration due to obstruction of large airways until surfactant distributes fully. Divided dose administration and recovery on mechanical ventilation minimize these transient events.

ii. Air leak. More serious complications may result from a rapid increase in lung compliance that occurs as surfactant lowers surface tension, fostering alveolar recruitment. Infants receiving pressure-limited mechanical ventilation may develop pneumothorax as delivered tidal volumes increase as lung compliance decreases in response to surfactant (see Chapter 38). This may be avoided by converting to volume-limited mechanical ventilation (see section IV.C.1.b).

iii. Hemorrhagic pulmonary edema. As compliance improves, pulmonary vascular resistance drops and can result in altered Starling forces that contribute to hemorrhagic pulmonary edema, commonly referred to as pulmonary hemorrhage, especially in the presence of a patent ductus arteriosus that contributes to pulmonary overcirculation (see Chapter 37).

C. Ensure appropriate CO_2 elimination. Although poor oxygenation is most often the dominant feature of RDS, atelectasis also reduces the gas exchange surface area for CO_2, and additional strategies are needed to manage hypercarbia.

1. Practical considerations

a. Caffeine therapy. Successful use of nasal CPAP to treat RDS depends on adequate spontaneous breathing which is facilitated by early use of caffeine (see Chapter 31).

b. Mechanical ventilation (see Chapter 29). Optimal ventilator strategy for infants with RDS includes the application of sufficient positive end-expiratory pressure (PEEP) to allow maintenance of FRC, applying the same guidelines for the use of end-expiratory pressure with CPAP. For infants who fail CPAP, we generally start at the same level of PEEP as provided by nasal CPAP because delivery of end-expiratory pressure via an ETT is more effective than noninvasive application. As discussed earlier, optimization of FRC should result in need for decreased concentration of supplemental oxygen to maintain appropriate oxygen saturation. As with CPAP, complications include overdistention, volutrauma, and air leak.

We typically use volume guaranteed forms of ventilation in infants with RDS, especially during the period of surfactant administration. In volume ventilator modes, the peak inspiratory pressure needed to achieve the set delivered tidal volume decreases as lung compliance drops in response to surfactant treatment, thus reducing volutrauma and air leak.

D. Outcomes. In the presurfactant era, RDS in late-preterm infants typically resolved at 2 to 4 days of age, often preceded by spontaneous diuresis. Improved mortality in ELBW infants has been possible in part due to use of ANC, noninvasive respiratory support with CPAP, and availability of exogenous surfactant, but the time course of RDS has become more difficult to define. In addition, the frequent association of preterm birth with chorioamnionitis or latent inflammation may affect the time to resolution. RDS in infants born at ≥32 weeks' gestational age and without other complications typically resolves fully with no long-term pulmonary sequelae. Infants <32 weeks' gestational age are at risk for BPD; risk increases with decreasing gestational age (see Chapter 34).

E. Future horizons. Current evidence-based practices to prevent and treat RDS are the result of many randomized clinical trials. However, many knowledge gaps remain, including the most appropriate type of and dosing strategy for ANC, the characteristics of patients best suited to noninvasive forms of ventilation for RDS, and the optimal method of noninvasive surfactant administration to reduce complications associated with intubation of ELBW infants. Finally, although there is a stable repertoire of surfactant preparations currently available to treat RDS, innovative additives (budesonide, recombinant human surfactant protein D) attempt to address the deleterious effects of inflammation on the newborn lung.

Suggested Readings

Barkhuff WD, Soll RF. Novel surfactant administration techniques: will they change outcome? *Neonatology* 2019;115(4):411–422.

Gyamfi-Bannerman C, Thom EA, Blackwell SC, et al. Antenatal betamethasone for women at risk for late preterm delivery. *N Engl J Med* 2016;374(14): 1311–1320.

Jobe A. Surfactant for respiratory distress syndrome. *Neoreviews* 2014;15(6): e236–e245.

34 Bronchopulmonary Dysplasia

John T. Benjamin and Erik A. Jensen

KEY POINTS

- Bronchopulmonary dysplasia (BPD) affects 30% to 50% of extremely low birth weight infants and is a strong risk factor for adverse cardiopulmonary health and neurodevelopment in childhood.
- Hallmarks of lung pathology in BPD are arrested lung development and reduced gas exchange surface area.
- Lung immaturity, prenatal and postnatal inflammation, and lung injury from oxygen toxicity and volutrauma associated with mechanical ventilation, coupled with abnormal postinjury repair, contribute to the development of BPD.
- Early initiation of nasal continuous positive airway pressure and caffeine citrate are proven strategies to reduce the risk of developing BPD.
- Corticosteroids, diuretics, and bronchodilators are commonly used to treat respiratory symptoms in BPD, although minimal evidence informs the use of these medications.
- Severely affected infants may require prolonged supplemental respiratory support with home oxygen therapy or invasive mechanical ventilation via tracheostomy.

I. BRONCHOPULMONARY DYSPLASIA (BPD) is one of the most common and severe complications associated with very preterm birth. BPD is a chronic, heterogenous cardiorespiratory illness that develops over the first months of life in preterm infants treated with supplemental respiratory support during the newborn period. BPD predisposes infants to significant respiratory, cardiac, and developmental morbidities that can have adverse health consequences throughout childhood and into adult years.

A. Several diagnostic criteria have been proposed to define the presence and severity of BPD. All widely used criteria define BPD based on treatment with oxygen therapy and/or other respiratory support. The most commonly used criteria define BPD in very preterm infants according to use of supplemental oxygen at 36 weeks' postmenstrual age (PMA). In some clinical and research settings, this definition is modified by performance of an oxygen reduction test to determine objectively an infant's "need" for oxygen therapy.

This maneuver gradually weans nasal cannula flow rates and supplemental oxygen levels while monitoring oxygen saturation (SpO_2). Infants who successfully maintain SpO_2 >90% without supplemental oxygen do not carry the diagnosis of BPD.

B. To characterize BPD severity, a 2001 National Institutes of Health (NIH) consensus conference proposed criteria that categorize BPD as mild, moderate, or severe based on the level of oxygen therapy and the mode of supplemental respiratory support administered at 36 weeks' PMA to very preterm infants treated with oxygen for at least 28 days (Table 34.1). In 2019, investigators from the U.S. Neonatal Research Network (NRN) developed an evidence-based definition that grades BPD severity based only on the mode

Table 34.1. Severity-Based Diagnostic Criteria for Bronchopulmonary Dysplasia (BPD) in Very Preterm Infants (<32 Weeks' Gestation)

2001 NIH Consensus Definition*		2019 Neonatal Research Network Definition†	
BPD Severity	Treatment with O_2 therapy for ≥28 days prior to 36 weeks' PMA *plus* treatment with the support listed below at 36 weeks' PMA‡	BPD Severity	Highest mode of respiratory support administered at 36 weeks' PMA**
Mild	Room air breathing	Grade 1	Nasal cannula with flow ≤2 L/minute
Moderate	Need†† for <30% O_2	Grade 2	Nasal cannula >2 L/minute, nCPAP, NIPPV
Severe	Need†† for ≥30% O_2 and/or positive pressure (PPV, nCPAP)	Grade 3	Invasive mechanical ventilation

*Table adapted from Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *Am J Respir Crit Care Med* 2001;163(7):1723–1729.

†Table adapted from Jensen EA, Dysart K, Gantz MG, et al. The diagnosis of bronchopulmonary dysplasia in very preterm infants. An evidence-based approach. *Am J Respir Crit Care Med* 2019;200(6):751–759.

‡Respiratory support administered at discharge to home is used to define BPD severity if discharge occurs prior to 36 weeks' PMA.

**The 2019 Neonatal Research Network definitions categorizes BPD severity according to the highest mode of respiratory support administered at a PMA of 36 weeks and 0/7 days, irrespective of the prior duration or level of oxygen therapy.

††At the time of development, a physiologic test confirming oxygen requirement was not yet defined. Since then, the oxygen reduction test has been variably used to establish whether an infant "needs" supplemental oxygen therapy.

NIH, National Institutes of Health; PMA, postmenstrual age; nCPAP, nasal continuous positive airway pressure; NIPPV, nasal intermittent positive pressure ventilation; PPV, positive pressure ventilation.

of respiratory support administered at 36 weeks' PMA, regardless of oxygen therapy. In a head-to-head comparison, the 2019 NRN definition was a better predictor of respiratory and neurologic morbidity in early childhood than the 2001 NIH consensus definition.

II. EPIDEMIOLOGY

A. The incidence of BPD is strongly correlated with the degree of immaturity at birth. Approximately 70% to 80% of infants born at 23 to 24 weeks of gestation who survive to 36 weeks' PMA are diagnosed with BPD compared to 20% to 25% of infants born at 28 weeks of gestation and <10% of infants born at 31 weeks of gestation. Greater than 70% of infants born with birth weight <1,000 g develop BPD compared to <30% of infants born weighing 1,000 to 1,500 g.

B. Although prematurity is a major risk factor for BPD, the available evidence indicates that BPD is multifactorial in etiology. Table 34.2 enumerates important risk factors for BPD, some of which are discussed briefly in the following text.

1. **Genetic factors.** Twin studies indicate heritability of BPD with as much as 53% to 79% of the variance in disease susceptibility attributable to genetic factors. Although Genome Wide Association Studies (GWAS) and exome sequencing of BPD patients have identified gene candidates and putative mutations, these results are inconsistent across study populations. Additional studies are needed to understand the genetic predisposition to BPD.
2. Preterm infants with **intrauterine growth restriction (IUGR)** are at high risk for BPD and persistent respiratory dysfunction through school age. **Maternal history of preeclampsia** is an additional antenatal risk factor for BPD, independent of IUGR status. Abnormal placental vascular changes and underperfusion accompany IUGR and pregnancy-induced hypertension and may have deleterious effects on the developing lung that enhance BPD risk.
3. **Antenatal inflammation and chorioamnionitis.** Intrauterine infections are a leading cause of preterm birth and may also contribute to the pathophysiology of BPD. The association between chorioamnionitis and BPD is inconsistent among studies; this may result from use of varying definitions of chorioamnionitis (e.g., clinical vs. histologic chorioamnionitis) and the presence or absence of other risk factors. In a meta-analysis and meta-regression of clinical studies in preterm infants, exposure to chorioamnionitis was associated with a higher risk of BPD, but this effect was modified by gestational age and risk of respiratory distress syndrome (RDS).
4. **Maternal smoking** prior to birth is a risk factor for BPD. Epigenetic changes, altered placental function, and increased fetal/neonatal inflammation are among the postulated mechanisms by which smoking may predispose infants to BPD.
5. **Oxygen supplementation.** Some but not all studies have shown that delivery room resuscitation of preterm infants with higher concentrations of oxygen increases the risk of developing BPD. In a multicenter

Table 34.2. Risk Factors for Bronchopulmonary Dysplasia
Demographic Factors
Gestational age (inverse relationship)
Birth weight (inverse relationship)
White race
Male sex
Antenatal Factors
Genetic predisposition
Intrauterine growth restriction
Preeclampsia and pregnancy induced hypertension
Chorioamnionitis
Maternal smoking
Postnatal Factors
Oxygen therapy
Mechanical ventilation
Patent ductus arteriosus
Neonatal sepsis

randomized controlled trial (RCT), hospitalized preterm infants with a higher SpO_2 (95% to 98%) target had greater supplemental oxygen needs at 36 weeks (BPD diagnosis) and were more likely to need home oxygen therapy compared to those with a lower SpO_2 (91% to 94%) target, suggesting that excessive supplemental oxygen may be deleterious to the developing lung. Insufficient production of the antioxidant enzymes superoxide dismutase, catalase, glutathione peroxidase, and/or deficiency of free radical sinks such as vitamin E, glutathione, and ceruloplasmin may enhance susceptibility of the preterm lung to oxygen toxicity.

6. **Volutrauma from mechanical ventilation.** In preterm infants with respiratory failure, mechanical ventilation may be lifesaving. However, volutrauma from mechanical ventilation can also injure the lung and predispose to BPD. Use of nasal continuous positive airway pressure (CPAP) soon after birth in infants with respiratory insufficiency avoids intubation and ventilation in some infants and reduces the risk of developing BPD.

7. **Persistent left-to-right shunt through the patent ductus arteriosus (PDA)** is a strong risk factor for the development of BPD. Unfortunately, neither prophylactic administration of indomethacin or ibuprofen to close the PDA nor early aggressive surgical intervention reduces BPD risk. Surgical intervention may even lead to worse respiratory outcomes. Although some infants may benefit from medical or interventional closure of the PDA, which patients should be treated and which therapy is most appropriate is uncertain.
8. **Postnatal sepsis.** Similar to antenatal inflammation, postnatal sepsis is also a risk factor for BPD. Endothelial injury, oxidant damage, and inflammation associated with sepsis may lead to lung injury and altered lung development.

III. PATHOGENESIS. The lungs of preterm infants at highest risk for developing BPD are in the late canalicular/early saccular stages of development. During this period, the terminal airspaces and microvasculature in the immature lung expand as it prepares for alveolarization. Preterm birth interrupts the normal progression of lung morphogenesis. Inflammatory injury from prenatal insults such as chorioamnionitis or IUGR and postnatal exposure to mechanical ventilation and excessive oxygen slows this process, resulting in "arrest" in the saccular stage of lung development and a simplified BPD lung that is incapable of normal gas exchange. BPD affects both growth of the distal lung parenchyma and the microvasculature. Lung histopathology in affected infants demonstrates fewer and dilated alveoli and a dysmorphic capillary network. In infants with severe BPD, repeated exposure to volutrauma and high concentrations of oxygen may also result in areas of cellular hyperplasia and peribronchial and interstitial fibrosis, indicating a reparative response to excessive injury in the lung.

IV. THE CLINICAL PRESENTATION in BPD may reveal common signs of respiratory insufficiency and chronic lung injury but may also be reassuring.

A. Physical examination may reveal tachypnea, retractions, and rales on auscultation. However, preterm infants with milder BPD who are receiving sufficient supplemental respiratory support may have findings on examination similar to those without BPD.

B. Arterial blood gas (ABG) analysis may demonstrate hypoxemia and hypercarbia with eventual metabolic compensation for the respiratory acidosis.

C. The **chest radiograph** changes as the disease progresses, but findings may be relatively nonspecific. The initial appearance often shows diffuse haziness, increased interstitial densities, and normal-to-low lung volumes. In more severe disease, chronic changes may include scattered regions of opacification and hyperlucency with superimposed hyperinflation.

D. Cardiac evaluation. In patients with severe BPD and associated pulmonary hypertension (PH), electrocardiogram (ECG) may show persistent or progressive right ventricular hypertrophy if *cor pulmonale* develops. Left ventricular hypertrophy may also develop with systemic hypertension. Echocardiogram may be normal or show signs of PH. If present, the

tricuspid regurgitant (TR) jet may be used to estimate pulmonary arterial pressures. If the TR jet is absent, bidirectional or right-to-left shunting of blood through an open PDA or across a ventricular septal defect suggests high pulmonary vascular resistance. The intraventricular septum, which typically bows into the right ventricle, may be flattened or even bow toward the left ventricle when pulmonary arterial pressure approaches or exceeds the systemic blood pressure. Sustained strain on the right heart leads to right ventricular hypertrophy.

E. Infant pulmonary function testing (iPFT). Increased respiratory system resistance (Rrs) and decreased dynamic compliance (Crs) are hallmarks of BPD. However, iPFT is not typically used in clinical practice in the neonatal intensive care unit.

V. EFFORTS TO PREVENT BPD AND MINIMIZE LUNG INJURY during the neonatal hospitalization are essential to mitigate the risks of long-term respiratory impairments in very preterm infants. Following is a summary of evidence-based therapies to prevent BPD.

A. Pharmacologic therapies

1. **Caffeine citrate** (20 mg/kg loading dose and 5 to 10 mg/kg daily maintenance) is started soon after birth in extremely preterm infants. The Caffeine for Apnea of Prematurity (CAP) trial provided strong evidence of safety and efficacy for BPD prevention. In that trial, caffeine started during the first 10 days after birth in infants with birth weight 500 to 1,250 g reduced the risk of BPD (relative risk, 0.78; 95% confidence interval [CI], 0.70 to 0.86), and led to long-term improvements in motor function and respiratory health. Initiation of caffeine therapy within the first 3 days after birth may result in the greatest reduction in BPD risk.
2. **Intramuscular (IM) vitamin A** (5,000 IU IM, three times per week for the first 28 days of age) reduced the risk of BPD in extremely low birth weight infants (relative risk, 0.85; 95% CI, 0.74 to 0.98) in a large RCT conducted in the 1990s. However, recent observational data have not replicated these findings, and no change was noted in the incidence of BPD during a period of vitamin A shortage. Enteral supplementation with vitamin A in conjunction with standard nutritional administration has not been shown to prevent BPD. If IM vitamin A is available, the decision to administer it should balance its potential modest benefit among contemporary infants with the high cost of available preparations and the need for multiple injections over a 4-week period.
3. **Dexamethasone initiated *during the first postnatal week*** ("early") reduces the risk of BPD but carries significant risk for long-term neurologic injury and should not be used.
4. **Dexamethasone initiated *after the first postnatal week*** reduces the risk of BPD (relative risk, 0.83; 95% CI, 0.71 to 0.97). The long-term neurologic effects of this "late" steroid therapy are less certain. Current guidelines recommend reserving systemic corticosteroid therapy for infants older than a week of age who are at high risk for developing BPD

to balance the short- and long-term risks and benefits of this therapy. However, the optimal drug formulation, dose, duration, and timing of initiation beginning after the first week are uncertain.

5. **Hydrocortisone initiated *during the first postnatal week*** has been shown to reduce the risk of developing BPD but may also increase the risk of sepsis and gastrointestinal perforation in some high-risk infants. Hydrocortisone initiated after the first postnatal week does not appear to reduce BPD risk.
6. **Early use of inhaled budesonide** reduces the risk of BPD in very preterm infants. However, the largest randomized trial to study this therapy identified a higher risk of death in the budesonide-treated infants, suggesting the risks of this therapy do not outweigh the observed benefit for BPD.
7. Meta-analyses of small trials evaluating **azithromycin** and intratracheal instillation of **budesonide plus surfactant** suggest possible benefit for BPD prevention, but larger confirmatory studies are needed to determine the safety and efficacy of these therapies.

B. Respiratory support strategies

1. **Prophylactic initiation of nasal continuous positive airway pressure (nCPAP)** rather than routine intubation and mechanical ventilation after birth in extremely preterm infants provides a small reduction in the risk of death or BPD in extremely preterm infants (relative risk, 0.90; 95% CI, 0.83 to 0.98). The American Academy of Pediatrics recommends early use of nCPAP with selective surfactant administration to reduce BPD risk. Use of nCPAP results in less treatment failure than heated and humidified high-flow nasal cannula in extremely preterm infants and should be used as the first-line noninvasive respiratory support modality. In a large RCT, noninvasive positive pressure ventilation did not prevent BPD at greater rates than nCPAP.
2. For infants who require intubation and mechanical ventilation, **volume-targeted ventilation** as compared to pressure-limited ventilation appears to reduce the incidence of BPD (relative risk, 0.68; 95% CI, 0.53 to 0.87). Compared to pressure-limited mechanical ventilation, high-frequency oscillatory ventilation (HFOV) may also reduce BPD risk but at the possible expense of higher rates of air leak.

C. Endotracheal administration of exogenous surfactant to infants receiving invasive mechanical ventilation reduces the risk of mortality, decreases the severity of RDS, and the decreases frequency of oxygen therapy at 28 days of age. For very preterm infants who fail initial attempts at noninvasive respiratory support, rescue administration of surfactant therapy within the first 2 hours after birth as compared to later ages may reduce the risk of BPD. Techniques for **less invasive surfactant administration (LISA)** involve endotracheal instillation of exogenous surfactant via a thin catheter in spontaneously breathing infants, typically during nCPAP therapy. Initial trial data suggest LISA may further reduce BPD risk when compared to common alternative early respiratory support practices (see Chapter 33).

D. Ineffective or unproven therapies for BPD prevention

1. Administration of **antenatal corticosteroids** to expectant mothers at risk of very preterm delivery reduces neonatal morbidity and mortality (e.g., RDS, intraventricular hemorrhage, necrotizing enterocolitis, early-onset sepsis). However, antenatal steroids have not been shown to reduce the risk of BPD.
2. Although observational data show a strong association between the presence of a **PDA** and the development of BPD, no clear evidence supports medical or interventional closure (e.g., surgery, catheterized occlusion) of a PDA as a means to prevent BPD.
3. **Diuretics** may reduce pulmonary edema and provide short-term improvements in respiratory mechanics in some very preterm infants, but no data indicate that regular use reduces the risk of BPD. Although it is clinically reasonable to avoid excessive fluid administration in very preterm infants, limitation of fluid intake has not shown clear benefit for preventing BPD.
4. **Inhaled nitric oxide (iNO)** is an effective therapy for the treatment of persistent PH of the newborn (PPHN) in near-term and full-term neonates. However, iNO does not prevent BPD when used as an early routine strategy or rescue therapy in very preterm infants.

VI. MANAGEMENT OF INFANTS WITH ESTABLISHED BPD

is almost entirely based on clinical experience, expert opinion, and observational studies. Most infants with BPD will gradually wean from supplemental respiratory support commensurate with gains in longitudinal growth, lung alveolar proliferation, and repair of injured lung. Strategies that may promote clinical stability and aid in recovery among infants with established BPD include several of the following:

A. Although no robust data support the routine use of **diuretics** and **inhaled bronchodilators**, these drug therapies may provide at least short-term benefits in some infants with BPD. Clinicians may consider trials of these agents and use measures such as oxygen requirement, work of breathing on physical examination, or objective assessments of pulmonary mechanics to characterize efficacy. Because of potential adverse effects, particularly with diuretics (electrolyte imbalance, nephrotoxicity, ototoxicity), clinicians should discontinue these agents if no evidence of improvement is observed.

B. Systemic corticosteroids may help facilitate weaning from invasive mechanical ventilation in infants with established BPD or be used as a rescue therapy for acute respiratory decompensations. The safety and long-term neurologic consequences of systemic corticosteroid use in infants with BPD is unknown. It is also uncertain whether intermittent or prolonged therapy with inhaled corticosteroids produces benefit in infants with BPD.

C. Infants with BPD being weaned from respiratory support may need slower transitions to lower support levels than are typically tolerated during the earlier, acute RDS phase of their illness. Some infants may require weekly or even less frequent weans in positive airway pressure levels or nasal cannula flow rates. Work of breathing, ability to tolerate nursing care and

physical and occupational therapy, stability of fraction of inspired oxygen (FiO_2) requirements, and adequacy of growth may all be used to determine readiness for weaning.

D. Nutritional supplementation with sufficient caloric and protein intake to overcome the increased energy expenditure in infants with BPD may help promote weight gain and longitudinal growth. Electrolyte supplementation may be needed to correct losses from diuretic therapy. Some evidence suggests possible benefit from zinc supplementation and regular physical and occupational therapy to improve linear growth.

E. Prolonged supplemental oxygen therapy, with or without positive airway pressure, may be needed to support respiratory health, growth, and development in infants with BPD. Some of the most severely affected infants may need tracheostomy and mechanical ventilation for the first few years of life. Among these infants, earlier placement after term postmenstrual age may improve long-term developmental outcomes, possibly by facilitating earlier, successful initiation of developmentally appropriate activities. However, minimal data are available to help identify which infants with BPD should undergo tracheostomy and when is the optimal time.

VII. IDENTIFICATION AND TREATMENT OF COMPLICATIONS ASSOCIATED WITH BPD

may help mitigate the high risks of morbidity and mortality observed in these infants and improve long-term outcomes.

A. PH develops in 25% of infants with moderate to severe BPD and is associated with poor growth, adverse neurodevelopment, and increased mortality. Along with alveolar simplification, incomplete lung development in extremely preterm infants is associated with fewer and dysmorphic pulmonary vessels. Rarefication of the pulmonary vasculature, along with recurrent episodes of hypoxia-hyperoxia mediated vascular remodeling could result in increased pulmonary vascular resistance and PH. Echocardiography may identify preterm infants at risk for PH as early as 7 days of age. Once a diagnosis of PH is established, supplemental oxygen is provided to keep SpO_2 >92%. Monitoring with echocardiogram may help guide PH-targeted therapy in these patients. iNO is useful to treat acute PH crises and may improve oxygenation in infants with established BPD. However, the efficacy of iNO in long-term treatment of PH associated with BPD has not been determined. Sildenafil, a phosphodiesterase-5 (PDE-5) inhibitor, improves oxygenation in patients with PH-BPD, and is a common first-line agent for chronic PH therapy. When PH does not improve with single-drug therapy, additional medications including endothelial receptor blockers such as bosentan or prostacyclin analogs such as treprostinil may be effective. In BPD patients with PH prior to the initiation of a second PH agent or if PH worsens under dual PH-targeted therapy, cardiac catheterization is helpful to assess vasoactive reactivity, compare pulmonary to systemic blood flow to quantify shunt, and identify vascular abnormalities, such as pulmonary vein stenosis.

B. Upper airway obstruction. Trauma to the nasal septum, larynx, trachea, or bronchi is common after prolonged or repeated intubation and suctioning in BPD patients. Airway abnormalities may include laryngotracheobronchomalacia, granulomas, vocal cord paresis, edema, and subglottic stenosis.

Consultation with otolaryngology specialists may be helpful to evaluate upper airway causes of stridor, persistent wheezing, or repeated extubation failures with fiberoptic bronchoscopy.

C. Systemic hypertension, sometimes with left ventricular hypertrophy, may develop in infants with BPD receiving prolonged oxygen therapy (see Chapter 28). Although the etiology of hypertension in these instances is likely multifactorial, changes in the renin-angiotensin system may be important. Renal ultrasound may identify renal pathologies and umbilical catheter–related thrombosis in some infants. Persistent elevations in systemic pressures require treatment (see Chapter 28, section on Fluid Electrolytes Nutrition, Gastrointestinal, and Renal Issues).

D. Infection. Many preterm infants with BPD require invasive mechanical ventilation and may have indwelling lines for parenteral nutrition and laboratory monitoring, putting them at risk for serious respiratory and systemic infections. Episodes of clinical decompensation should prompt evaluation for potential infectious etiology.

E. Gastroesophageal reflux (GER) and microaspiration may contribute to pulmonary decompensation or delayed recovery in BPD. Acid suppression and promotility drugs are generally ineffective in preterm infants and pose risks for adverse drug effects. Nonpharmacologic management strategies such as optimized positioning, avoidance of excessive feeding volumes, and transpyloric feeding may be beneficial. In older children with severe GER, gastrostomy tube and fundoplication may reduce recurrent aspiration risk until swallow coordination and airway protective mechanisms adequately mature and physiologic GER subsides.

F. Growth failure in BPD may result from inadequate nutrient intake and high energy expenditure. Clinicians should closely monitor growth curves and caloric and micronutrient intake. Periodic surveillance of serum protein, electrolyte, and other nutrition-focused labs may help guide dietary supplementation. Poor growth, particularly when new in onset or acutely worsening, may indicate the need for additional respiratory support. Importantly, growth failure can persist even after apparent clinical resolution of pulmonary disease in infants with BPD and requires routine monitoring throughout the newborn stay and postdischarge period.

VIII. DISCHARGE PLANNING

in infants with BPD should include achievement of cardiorespiratory stability, procurement of any home care support and nursing needs, and assessment of parental readiness (see Chapter 18). Additional considerations include the following:

A. Home oxygen therapy. More than 30% of patients with BPD are discharged home on oxygen therapy. Home supplemental oxygen use is particularly common among infants with greater severity of BPD and who have PH. Although criteria to wean off supplemental oxygen prior to discharge are not well established, a reasonable approach is to discontinue oxygen therapy when the SpO_2 is consistently maintained >92% on low levels of support without significant periods of desaturation. Most patients discharged on oxygen receive <1 L/minute of nasal cannula flow at the time of discharge. In addition to equipment to supply oxygen, a pulse oximeter

or apnea/cardiac monitor for home monitoring should be arranged prior to discharge.

B. Teaching and involvement of parents in caregiving is vital for a smooth transition from the hospital to the home environment. Parents should be taught cardiopulmonary resuscitation and to identify early signs of decompensation. Teaching about equipment use, medication administration, nutritional guidelines, and immunizations should begin when discharge planning is initiated.

C. A predischarge echocardiogram should be considered in infants expected to receive supplemental respiratory support after discharge and those at high-risk for PH. This information may be useful to evaluate subsequent changes in clinical status as an outpatient.

D. Follow-up eye examination should be scheduled as needed. **Outpatient hearing screening** is indicated in infants with BPD owing to the limited diagnostic accuracy of early inpatient testing in this population.

E. Subspecialist and multidisciplinary management. Prior to discharge, baseline evaluations by pulmonology, cardiology, and other subspecialities who will follow the infant as an outpatient can help facilitate transition to home care. Conversations with the primary care physician who will assume care in the outpatient setting may also be helpful, especially if discharge with home oxygen therapy is planned.

IX. OUTPATIENT THERAPY

A. Oxygen supplementation. Home oxygen is usually delivered by tank or an oxygen concentrator. Portable oxygen tanks are also provided to allow mobility. Most BPD patients are weaned off home oxygen by 12 months of age. No widely used guidelines are available for home oxygen weaning, although polysomnography, periodic assessment of SpO_2, room air challenge tests, and assessments of overall respiratory status and growth may all help inform the decision to wean or discontinue oxygen therapy.

B. Medications. Diuretics, inhaled steroids, and inhaled bronchodilators may be used for outpatient management of respiratory signs and symptoms in patients with BPD. Although no evidence-based guidelines on weaning these medications in BPD are available, gradual reductions in the dose or frequency, with transition to use only as needed for acute exacerbations are possible weaning strategies. Sildenafil, bosentan, and prostacyclin analogs like treprostinil may be used for the management of PH. Close follow-up with pediatric cardiology and pulmonary specialists is required to titrate these medications in the outpatient setting.

C. Adequate nutrition. Weight gain and changes in length are sensitive indicators of well-being and should be closely monitored. Infants with BPD may have higher nutritional requirements due to increased respiratory effort and may need greater caloric supplementation (22 to 30 kcal/oz formula or fortified breast milk) to allow optimal growth after discharge.

D. Minimizing cigarette smoke exposure. Because smoking in the home increases respiratory tract illness in children, parents of infants with BPD should be discouraged from smoking and should minimize the child's exposure to smoke-containing environments.

X. CHILD AND ADULT OUTCOMES OF BPD

A. Rates of mortality are increased among children with a history of BPD and rise in frequency with greater severity of disease. More than 20% of very preterm infants with grade 3 BPD as defined by the 2019 NRN criteria die between 36 weeks' PMA and 2 years of age compared to 2% to 3% of those with less severe disease. The presence of PH is an additional risk factor, with 2-year mortality rates ranging as high as 33% to 48% in these infants.

B. Long-term morbidity

1. **Pulmonary.** Tachypnea, cough, and wheezing can persist for months in infants with BPD, and these individuals are at higher risk for poor pulmonary outcomes at later ages as well. Reactive airway disease is common in patients with BPD as are hospitalizations for bronchiolitis and pneumonia. Compared to term-born control infants, children with BPD have substantial impairment in lung function as exhibited by abnormal measures of vital capacity and forced expiratory volume in 1 second (FEV_1). Asthma-like symptoms later in childhood are also more common in survivors with BPD. Although improvement in clinical symptoms often occur as children with BPD age, underlying abnormalities in pulmonary function and chest imaging may persist into adolescence and beyond in these patients. Adult survivors with BPD may experience more rapid declines in age-related loss of lung function and are predisposed to early-onset chronic obstructive pulmonary disease (COPD).
2. **Neurodevelopmental deficits.** BPD is strongly associated with neurodevelopmental deficits in children born preterm. Recurrent episodes of hypoxemia and hypercapnia and respiratory acidosis may potentiate hypoxia-mediated brain injury in these patients. Compared to age-matched preterm controls, patients with BPD are at higher risk for cerebral palsy (CP), even after adjusting for periventricular leukomalacia and major intraventricular hemorrhage. Non-CP motor deficits (both gross motor and fine motor) also occur more frequently in children with BPD compared to gestational age–matched peers resulting in higher needs for interventional services like occupational and physical therapy. Cognitive deficits can also occur and persists from early childhood to school age years.
3. **Growth failure.** Patients with BPD are at increased risk for poor growth after discharge from their birth hospitalization. The degree of long-term growth delay is inversely proportional to gestational age and is likely influenced by BPD severity. Greater work of breathing, poor nutritional states, exposure to diuretic therapy and systemic corticosteroids, and limitations in physical activity may all contribute to poor childhood growth in BPD.

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35 Meconium Aspiration

Susanne Hay

KEY POINTS

- Routine suctioning of nonvigorous infants born through meconium-stained amniotic fluid (MSAF) is not recommended.
- Air leak frequently complicates meconium aspiration syndrome (MAS).
- Meconium inhibits endogenous surfactant activity; rescue doses of surfactant may be indicated in severe MAS.

I. BACKGROUND

A. Cause. Acute or chronic hypoxia and/or infection can result in the passage of meconium *in utero*. In this setting, gasping by the fetus or newly born infant can cause aspiration of amniotic fluid contaminated by meconium. Meconium aspiration before or during birth can obstruct airways, interfere with gas exchange, and cause severe respiratory distress (Fig. 35.1).

B. Incidence. Meconium-stained amniotic fluid (MSAF) complicates approximately 4% to 22% of deliveries The incidence of MSAF is highest in postterm infants (~27% to 38%) and decreases with decreasing gestational age to a nadir (~5%) at ~31 weeks' gestation; it is also elevated in small for gestational age infants. Approximately 3% to 12% of neonates born through MSAF develop meconium aspiration syndrome (MAS), and approximately 30% to 50% of these infants require continuous positive airway pressure (CPAP) or mechanical ventilation. The incidence of MAS varies with factors including obstetrical care/cesarean section rates and population risk, and the overall incidence appears to be decreasing.

II. PATHOPHYSIOLOGY.

Derived from the Greek word "mekonion" (poppy juice), meconium is a tarry, black-green material. It is sterile and odorless and results from the accumulation of debris in the fetal intestine. The components of meconium include water (72% to 80%), desquamated cells from the intestine and skin, gastrointestinal mucin, lanugo hair, fatty material from the vernix caseosa, amniotic fluid, intestinal secretions, blood group–specific glycoproteins, bile, and enzymes including phospholipase A_2.

A. Passage of meconium *in utero*. MSAF occurs more commonly in term or postterm pregnancies and rarely prior to 34 weeks' gestation. MSAF may result from a postterm fetus with rising motilin levels and normal gastrointestinal function, vagal stimulation produced by cord or head compression,

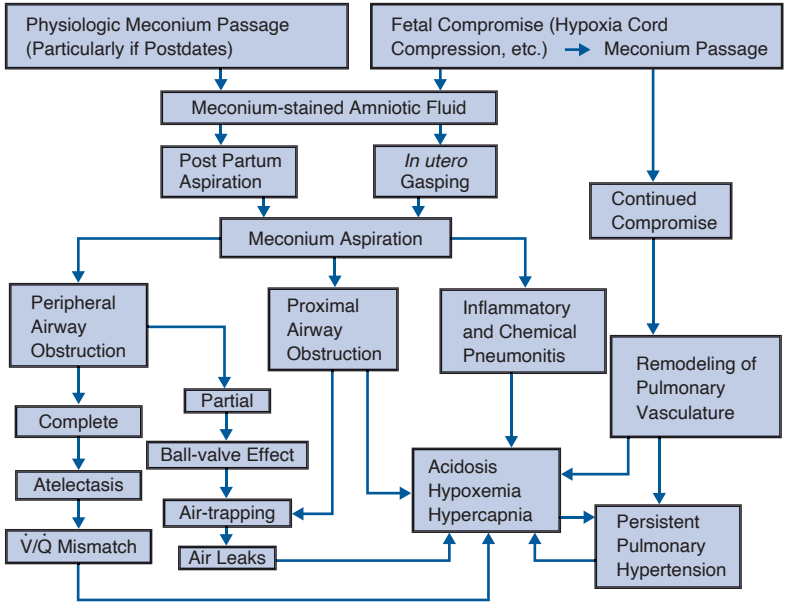

Figure 35.1. Pathophysiology of meconium aspiration. V̇/Q̇, ventilation–perfusion ratio. (Reprinted from Wiswell T, Bent RC. Meconium staining and the meconium aspiration syndrome: unresolved issues. *Pediatr Clin North Am* 1993;40[5]:955–981. Copyright © 1993 Elsevier. With permission.)

or *in utero* fetal stress. Amniotic fluid that is thinly stained is described as *watery*. Moderately stained fluid is opaque without particles, and fluid with thick meconium with particles is sometimes called *pea soup*. Infants born through thick meconium may require more intensive birth resuscitation and ventilation support than others.

B. Aspiration of meconium. In the presence of fetal stress, gasping by the fetus can result in aspiration of meconium before, during, or immediately following delivery. Severe MAS appears to be caused by pathologic intrauterine processes, primarily chronic hypoxia, acidosis, and infection.

C. Effects of meconium aspiration. When aspirated into the lung, meconium may stimulate the release of cytokines and vasoactive substances that result in cardiovascular and inflammatory responses in the fetus and newborn. Meconium itself, or the resultant chemical pneumonitis, mechanically obstructs the small airways, causes atelectasis, and can lead to a "ball-valve" effect with resultant air trapping and possible air leak. Aspirated meconium leads to vasospasm, hypertrophy of the pulmonary arterial musculature, and pulmonary hypertension. This can lead to extrapulmonary right-to-left shunting through the ductus arteriosus or the foramen ovale, resulting in worsened ventilation–perfusion (V̇/Q̇) mismatch and severe arterial hypoxemia. Approximately one-third of infants with MAS develop persistent

pulmonary hypertension of the newborn (PPHN), which contributes to the mortality associated with this syndrome (see Chapter 36). Aspirated meconium also inhibits surfactant function. Several studies suggest that the enzymatic and sterol components of meconium disrupt the surfactant phospholipids and limit the ability for surfactant to lower surface tension.

D. Severity. MAS is considered mild in infants requiring <40% oxygen for <48 hours and moderate in infants requiring >40% oxygen for >48 hours without air leak. MAS is considered severe in infants who require assisted ventilation for >48 hours and is often associated with PPHN.

E. Sequelae. *In utero* passage of meconium in term infants has been associated with an increased risk of perinatal and neonatal mortality, severe acidemia, need for cesarean delivery, need for intensive care and oxygen administration, and adverse neurologic outcome. Preterm infants who pass meconium before delivery have similar adverse effects as well as an increased incidence of severe intraventricular hemorrhage, cystic periventricular leukomalacia, and cerebral palsy.

III. PREVENTION OF MECONIUM ASPIRATION SYNDROME

A. Prevention of passage of meconium *in utero*. Mothers at risk for uteroplacental insufficiency and thus MSAF include those with preeclampsia or increased blood pressure, chronic respiratory or cardiovascular disease, poor intrauterine fetal growth, postterm pregnancy, and heavy smokers. These women should be carefully monitored during pregnancy.

B. Amnioinfusion. The use of amnioinfusion in women whose labor is complicated by MSAF does not reduce neonatal morbidity related to meconium aspiration, although the technique effectively treats repetitive variable fetal heart rate decelerations by relieving umbilical cord compression in labor. A large randomized trial of amnioinfusion for women with thick meconium-stained fluid with or without variable fetal heart rate decelerations showed no reduction of the risk of moderate or severe MAS, perinatal death, or cesarean delivery. However, the study did not have adequate power to determine definitively if amnioinfusion may benefit the group with variable decelerations.

C. Timing and mode of delivery. Elective labor induction as early as 39 weeks' gestation demonstrated a decrease in MAS, and induction of labor is recommended after 41 to 42 weeks' gestation. Infants with MAS are more likely to have been born by cesarean section, but the causal nature of this association is unclear.

IV. MANAGEMENT OF INFANTS DELIVERED THROUGH MECONIUM-STAINED FLUID.

Oropharyngeal and nasopharyngeal suctioning on the perineum and routine tracheal intubation and aspiration of meconium in vigorous infants are not effective in preventing MAS or improving outcomes and are not recommended. According to American Academy of Pediatrics Neonatal Resuscitation Program Guidelines, emphasis should be placed on appropriate interventions to support ventilation and oxygenation as needed, which may

include intubation and suction if the airway is obstructed. If obstructed, the trachea should be suctioned using a suction catheter inserted through the endotracheal tube or directly suctioned through the tube using a meconium aspirator attached to a suction source. The level of suction should be a pressure of 80 to 100 mm Hg.

V. MANAGEMENT OF MECONIUM ASPIRATION SYNDROME

A. Observation. Infants born through MSAF are at risk for meconium aspiration pneumonia and should be observed closely for respiratory distress.

1. The diagnosis of MAS is made in a neonate with respiratory distress born through MASF with characteristic chest radiograph findings and no other explanation for respiratory distress. The classic roentgenographic findings are diffuse, asymmetric patchy infiltrates, areas of consolidation, often worse on the right, and hyperinflation.
2. Monitoring oxygen saturation during the initial hours after birth aids assessment of the severity of the infant's condition and avoids hypoxemia.

B. Care for neonate with MAS

1. Maintain the infant in a neutral thermal environment and minimize tactile stimulation.
2. Assess blood glucose and calcium levels and correct if necessary. Severely depressed infants may have severe metabolic acidosis that may need to be corrected.
3. Evaluate infants with hypoxemia for PPHN and treat as needed (see Chapter 36).
4. Provide specific therapy as needed for hypotension and poor cardiac output, including cardiotonic medications such as dopamine.
5. Provide circulatory support with normal saline or packed red blood cells in patients with marginal oxygenation. In infants with substantial oxygen and ventilator requirements, we usually maintain a hemoglobin concentration above 15 g (hematocrit >40%).
6. Closely monitor renal function (see Chapter 28).
7. Avoid chest physiotherapy because of the potential adverse effect of exacerbating PPHN.
8. Provide airway and oral suctioning if needed to facilitate airway clearance, but potential benefits must be balanced against the risk of hypoxic episodes and subsequent worsening of PPHN.

C. Oxygen therapy. Management of hypoxemia should be accomplished by increasing the inspired oxygen concentration. An indwelling arterial catheter is usually required for blood sampling. It is crucial to provide sufficient oxygen because repeated hypoxic insults may result in ongoing pulmonary vasoconstriction and contribute to the development of PPHN.

D. Assisted ventilation

1. **CPAP.** If fraction of inspired oxygen (FiO_2) requirements exceed 0.40, a trial of CPAP may be considered. CPAP is often helpful, and

the appropriate pressures are individualized for each infant. However, CPAP may sometimes aggravate air trapping and should be used with caution if hyperinflation is apparent clinically or radiographically.

2. **Mechanical ventilation** (see Chapter 29). Infants with severe disease may have substantial gas exchange abnormalities. Mechanical ventilation is indicated for excessive carbon dioxide retention (arterial partial pressure of carbon dioxide [$PaCO_2$] >60 mm Hg) or for persistent hypoxemia (arterial partial pressure of oxygen [PaO_2] <50 mm Hg).
   a. In these infants, higher inspiratory pressures (approximately 30 to 35 cm H_2O) and larger tidal volumes are more often required than in infants with respiratory distress syndrome; the positive end-expiratory pressure (PEEP) selected (usually 4 to 6 cm H_2O) should depend on the individual's response. Adequate expiratory time should be permitted to prevent air trapping behind partly obstructed airways.
   b. Useful starting points are an inspiratory time of 0.4 to 0.5 seconds at a rate of 20 to 25 breaths per minute. Some infants may respond better to conventional ventilation at more rapid rates with inspiratory times as short as 0.2 seconds.
3. High-frequency ventilation with jet or oscillatory ventilators may be effective in infants with severe MAS who fail to improve with conventional ventilation and in those who develop air leak syndromes. **Extracorporeal membrane oxygenation (ECMO)** (see Chapter 39) may be required for infants with refractory respiratory failure.

E. Medications

1. **Antibiotics.** Differentiating between bacterial pneumonia and meconium aspiration by clinical course and chest x-ray findings may be difficult. Although few infants with MAS have documented infections, the use of broad-spectrum antibiotics (e.g., ampicillin and gentamicin) is usually indicated in infants when an infiltrate is seen on chest radiograph. Blood cultures should be obtained to identify bacterial disease, if present, and to determine length of antibiotic course. A small number of studies suggest no difference in infection rates following antibiotic treatment among infants with MAS.
2. **Surfactant.** Endogenous surfactant activity may be inhibited by meconium and MAS is a secondary cause of surfactant deficiency. Surfactant replacement in MAS improves oxygenation, reduces the need for ECMO, and is recommended by the Committee on Fetus and Newborn of the American Academy of Pediatrics.
3. **Corticosteroids.** We do not recommend the use of corticosteroids in MAS. This approach has been proposed to reduce meconium-induced inflammation and to minimize prostaglandin-mediated pulmonary vasoconstriction. Several small randomized controlled trials demonstrated modest improvements in oxygenation and decreased length of NICU stay but no difference in mortality.

F. Complications

1. **Mortality.** Survival of infants with MAS continues to improve, with recent estimates of mortality rates closer to 1% to 2%.

2. **Air leak.** Pneumothorax or pneumomediastinum occurs in approximately 15% to 33% of patients with MAS, and a high index of suspicion is necessary (see Chapter 38). Equipment should be available to evacuate a pneumothorax.
3. **PPHN** is associated with MAS in approximately one-third of cases and contributes to the mortality associated with this syndrome (see Chapter 36). In infants with significant hypoxemia, echocardiography should be performed to ascertain the degree to which right-to-left shunting contributes to the infant's overall hypoxemia and to exclude congenital heart disease. In severely ill infants with MAS and PPHN, inhaled nitric oxide (iNO) reduces the need for ECMO.
4. **Pulmonary sequelae.** A small proportion of survivors require supplemental oxygen at 1 month, and some may have abnormal pulmonary function, including increased functional residual capacity, airway reactivity, and higher incidence of pneumonia.
5. **Neurodevelopmental delays.** There may be an increased incidence of neurologic abnormalities in infants with MAS, although this is based on limited retrospective evidence and the association of MAS with hypoxic ischemic encephalopathy is a potential confounding factor.

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36 Persistent Pulmonary Hypertension of the Newborn

Philip T. Levy

KEY POINTS

- Persistent pulmonary hypertension of the newborn (PPHN) occurs when the physiologic postnatal decline of pulmonary artery pressure (PAP) fails to occur and pulmonary vascular resistance higher than systemic leads to right-to-left shunting and hypoxemia.
- Echocardiography is an essential tool to evaluate pulmonary hypertension (PH) severity, ventricular performance, and hemodynamics of shunting.
- Management includes supportive cardiorespiratory care, pharmacotherapy promoting pulmonary vasodilation, and optimizing ventricular support.
- Oxygen and inhaled nitric oxide (iNO) are targeted evidence-based therapies.

I. DEFINITION. Persistent pulmonary hypertension of the newborn (PPHN) is a condition of postnatal transition that results from failure of the normal decline of pulmonary artery pressure (PAP) following birth. PPHN is characterized by sustained elevation in PAP with increased afterload on the right ventricle (RV), which can lead to RV remodeling, ventricular dysfunction, poor cardiac output (CO), pulmonary-to-systemic shunting, and significant morbidities and mortality among survivors, including chronic pulmonary disease and neurodevelopmental disabilities. The mean PAP (mPAP), calculated from the product of the pulmonary vascular resistance (PVR) and pulmonary blood flow (PBF) plus the pulmonary capillary wedge pressure (PWCP), determines the spectrum of PPHN.

The diagnosis of PPHN is suspected in the setting of severe hypoxemic respiratory failure and impaired oxygenation soon after birth and confirmed with a comprehensive clinical, radiographic, biochemical examination, and echocardiography. Management includes optimizing ventilatory strategies, use of pulmonary vasodilatory therapy (i.e., inhaled nitric oxide [iNO]), and use of extracorporeal membrane oxygenation (ECMO) when appropriate. Collectively, this approach has improved survival of infants with PPHN.

II. PHYSIOLOGY AND PATHOGENESIS

A. Fetal circulation. In the fetus, the highly vascular, low-resistance placenta serves as the organ for gas exchange, receiving oxygenated blood from the maternal circulation and contributing to a lowered fetal systemic vascular resistance (SVR). The lungs receive only a small amount of blood flow due to the vasoconstricted state (high PVR) of the fetal pulmonary vasculature.

B. Transitional circulation. The normal perinatal circulatory transition is characterized by a rapid fall in PVR with relief of alveolar hypoxia and lung expansion accompanying the first breath. The postnatal pulmonary circulation becomes a low-pressure, low-resistance, high-flow system. SVR rises when clamping of the umbilical cord removes the low-resistance placental flow. Increased arterial oxygen content and pH, lowered arterial partial pressure of carbon dioxide ($PaCO_2$), a surge of vasodilator prostaglandins, and release of nitric oxide (NO) cause relaxation of the pulmonary circulation and constriction of the ductus arteriosus (DA). These events raise SVR relative to PVR, cause functional closure of the foramen ovale (FO), and signal the normal perinatal transition in pulmonary and systemic circulations.

C. Hemodynamic profile of PPHN. PPHN physiology mimics the fetal circulation in which PVR exceeds SVR and right-to-left hemodynamic shunting occurs through the FO and/or DA. The altered pulmonary vasculature–RV interactions of PPHN have hemodynamic consequences and in severe cases may lead to RV failure, followed by left ventricular (LV) dysfunction, decreased CO, systemic hypoperfusion, oliguria/anuria, end-organ compromise, and shock.

III. EPIDEMIOLOGIC ASSOCIATIONS AND RISK FACTORS.

PPHN occurs in approximately 2 per 1,000 live births and is most common among full-term and postterm infants.

A. Maternal risk factors found in association with PPHN include advanced maternal age, diabetes mellitus, chorioamnionitis, preeclampsia, urinary tract infection during pregnancy, fever, tobacco use, and selective serotonin reuptake inhibitor (SSRI) consumption during pregnancy.

B. Male infants and those of black, Asian, or Hispanic race are at increased risk.

C. Fetal risk factors include conditions of restrictive lung growth (e.g., congenital diaphragmatic hernia (CDH), oligohydramnios, and neuromuscular disorders) and fetal anemia.

D. Postnatal risk factors include meconium-stained amniotic fluid, respiratory distress syndrome (surfactant deficiency), large for gestational age, post term, cesarean delivery (which may reflect perinatal distress), perinatal asphyxia, large left-to-right shunts (i.e., vein of Galen or coronary artery fistulas), surfactant metabolism disorders, and genetic abnormalities. These can lead to injury of the lung parenchyma and affect the molecular pathways responsible for pulmonary vasomotor tone, leading to PPHN.

PPHN is recognized in 2% to 8% of preterm infants presenting with early respiratory distress syndrome (RDS) and up to 67% of preterm infants with severe RDS, with an incidence of PPHN in preterm infants that is inversely

related to gestational age. The presence of parenchymal lung disease and the immaturity of the NO pathway and gas exchange mechanisms may play roles in its pathogenesis in the preterm infant. Preterm infants with fetal growth restriction, exposure to prolonged rupture of membranes with pulmonary hypoplasia, and chorioamnionitis are also at higher risk of developing PPHN.

IV. CLASSIFICATION.

Classification systems have grouped PPHN based on abnormalities of the pulmonary vasculature (underdeveloped, maldeveloped, or maladapted). Another approach is to categorize the etiology according to the major determinants of elevated PAP, as follows (Fig. 36.1).

A. Vascular maldevelopment with elevated PVR. The most common cause of PPHN is remodeling of the pulmonary vessels with vascular wall thickening

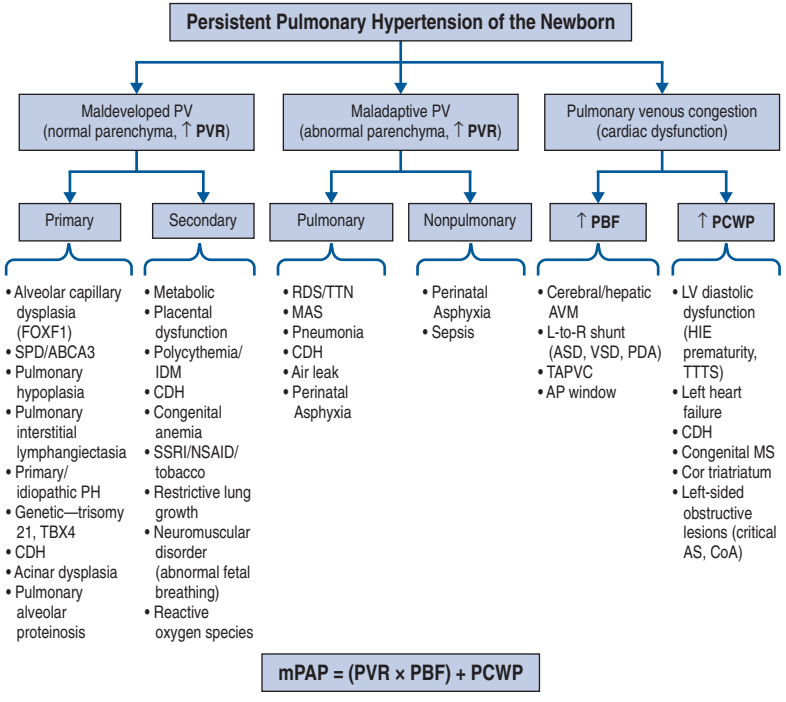

Figure 36.1. Etiologies of persistent pulmonary hypertension of the newborn. PV, pulmonary vein; PVR, pulmonary vascular resistance; PBF, pulmonary blood flow; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; CDH, congenital diaphragmatic hernia; IDM, infant of diabetic mother; SSRI, selective serotonin reuptake inhibitor; NSAID, nonsteroidal anti-inflammatory drugs; RDS, respiratory distress syndrome; TTN, transient tachypnea of the newborn; MAS, meconium aspiration syndrome; AVM, arteriovenous malformation; ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosis; TAPVC, total anomalous pulmonary venous connection; AP, aortopulmonary; LV, left ventricular; HIE, hypoxic-ischemic encephalopathy; TTTS, twin-to-twin transfusion syndrome; MS, mitral stenosis; AS, aortic stenosis; CoA, coarctation of the aorta; mPAP, mean pulmonary arterial pressure.

and smooth muscle hyperplasia, resulting in a decreased cross-sectional area of the pulmonary vascular bed and elevated PVR. The smooth muscle extends to the level of the intra-acinar arteries, preventing the appropriate dilation of the pulmonary vasculature in response to birth-related stimuli and resulting in profound hypoxemia and clear, hyperlucent lung fields. Cellular signaling pathways are also disrupted. Depending on the etiology, elevation in PVR due to maldeveloped pulmonary vasculature may be irreversible. These causes include alveolar capillary dysplasia with misalignment of pulmonary veins, pulmonary interstitial lymphangiectasia, primary surfactant metabolism disorders, CDH, or genetic conditions. Genetic predisposition may play a role in PPHN risk, although familial recurrence is uncommon. Case reports of PPHN cite associations with polymorphisms in genes, including ABCA3, surfactant protein B deficiency, TMEM70 (mitochondrial), CRHR1, ACE, and SPINK5 (Netherton syndrome). Furthermore, PPHN associated with alveolar capillary dysplasia has been linked with mutation of FOXF1. Secondary causes associated with restrictive lung growth and remodeling or vasoconstriction include impaired fetal breathing, oligohydramnios, renal agenesis (i.e., Potter syndrome), placental dysfunction, and underlying metabolic conditions.

B. Vascular maladaptation with elevated PVR. In this category, parenchymal lung disease (e.g., RDS, meconium aspiration, and air leak syndromes) or extraparenchymal disorders (sepsis and perinatal asphyxia) lead to maladaptation of the pulmonary vasculature at birth. In this phenotype, the pulmonary vasculature is structurally normal, but mediators promoting vasoconstriction and negating vasodilation result in abnormal vasoreactivity that affects the reduction of RV afterload and the relationship of PVR to SVR during transition at birth. These mediators contribute to pulmonary vasospasm, whereas other mechanisms suppress endogenous NO production and may lead to endotoxin-mediated myocardial depression and thromboxane-mediated pulmonary vasoconstriction. Although vasospasm is often reversible, prolonged fetal stress and hypoxemia or acute birth asphyxia can lead to remodeling and abnormal muscularization of pulmonary arterioles.

C. Pulmonary venous congestion and left heart dysfunction is a less common etiology. These disorders can produce excessive perfusion to the fetal lung and include the following:

1. Arterial venous connections such as vein of Galen malformations or large coronary artery fistulas, leading to high-output cardiac failure resulting in left-to-right shunting with increased PBF and subsequent ventricular dysfunction.
2. Left-to-right intracardiac and extracardiac shunts in the setting of structurally normal hearts or congenital heart disease (CHD) that result in pulmonary venous congestion and PPHN.
3. Abnormal LV performance due to prematurity with LV diastolic dysfunction, perinatal asphyxia, or twin-to-twin transfusion may lead to increased PCWP, increased pulmonary venous congestion, and PPHN.
4. RV dysfunction due to intrauterine constriction of the DA can result in fetal pulmonary overcirculation, RV failure, and an atrial right-to-left shunt. Treating pulmonary hypertension (PH) associated with these conditions requires improving cardiac function rather than simply lowering PVR.

V. DIAGNOSIS. PPHN should be considered in a cyanotic infant.

A. Physical examination. Cyanosis is the most remarkable feature in an infant with PPHN. Most affected infants present soon after birth with signs of respiratory distress (i.e., tachypnea, retractions, and grunting). Preterm infants may present later. In some infants, the extent of cyanosis might be appreciably different between regions perfused by preductal and postductal vasculature. The cardiac examination is notable for a prominent precordial impulse, a single or narrowly split and accentuated second heart sound, and, sometimes, a systolic murmur consistent with a tricuspid regurgitation jet (TRJ) or a machine-like ductus arteriosus murmur.

B. Diagnostic evaluation typically will include pulse oximetry testing, arterial blood gas (ABG) sampling, chest radiograph, electrocardiogram (ECG), and echocardiogram.

1. **Pulse oximetry assessment and ABG.** A gradient of 10% or more in oxygenation saturation between simultaneous preductal (right upper extremity) and postductal (lower extremity) ABG values or transcutaneous oxygen saturation (SaO_2) measurements documents the presence of a DA right-to-left hemodynamic shunt and, in the absence CHD, suggests PPHN. The absence of differential cyanosis or SaO_2 does not exclude PPHN as a subset of infants with PPHN can have closure of the DA with their hemodynamic shunting occurring only at the FO.
2. The **chest radiograph** can appear normal or show associated pulmonary parenchymal disease, air leak, or CDH. The cardiothymic silhouette is normal or slightly enlarged, and PBF is normal or diminished.
3. The **ECG** most commonly shows RV predominance that is within the range considered normal for age. Less commonly, the ECG might reveal signs of myocardial ischemia or infarction.
4. An **echocardiographic study** should be performed in all infants with suspected PPHN to exclude CHD, document hemodynamic shunting, and assess ventricular function. The most common approach to evaluate severity of PH is by the indirect assessment of elevated RV afterload and estimation of PAP. A ventricular septal wall position that is flattened or bowed to the left on an echocardiogram suggests PH. PAP can also be estimated using continuous-wave Doppler sampling of the velocity of the TRJ, if present. In the absence of a reliable TRJ, estimates of RV systolic time intervals provide supplementary indices for screening and serial follow-up.
5. **Ventricular performance.** Both qualitative and quantitative markers of RV and LV function can be used to assess the ventricular performance to tailor pharmacologic approaches to ventricular dysfunction. Ventricular performance is characterized by three separate techniques: (i) change in cavity dimensions (i.e., LV ejection fraction RV fractional area change), (ii) displacement and velocity of single point along the myocardial wall (i.e., tricuspid annular plane systolic excursion and tissue Doppler velocities), and (iii) deformation of a segment of the wall (i.e., strain analysis).
6. **Hemodynamic shunting.** Color Doppler examination is useful to assess the presence of intracardiac (i.e., FO) and/or extracardiac (i.e.,

DA) hemodynamic shunting. The complete assessment is critical as each could further compromise the efficacy of oxygenation by diverting deoxygenated blood flow from the pulmonary to the systemic vasculature. The presence of an exclusive right-to-left shunt is always abnormal and indicates suprasystemic systolic PAP, whereas a bidirectional shunt indicates near systemic systolic PAP.

C. Other diagnostic considerations. In any infant thought to have PPHN, it is critical to rule out structural CHD, which is sometimes associated with secondary PH. Signs favoring cyanotic CHD over PPHN include fixed hypoxemia, cardiomegaly, grade 3+ murmur, weak pulses, active precordium, pulmonary edema, and persistent preductal and postductal arterial oxygen tension (PaO_2) ≤40 mm Hg.

VI. MANAGEMENT.

PPHN requires immediate appropriate intervention to reverse hypoxemia, improve pulmonary and systemic perfusion, and preserve end-organ function. Management consists of four principal concepts: (i) supportive cardiorespiratory care, (ii) pulmonary vasodilators to decrease afterload, (iii) optimization of ventricular support, primarily RV function; and (iv) ECMO if needed (see Chapter 39). Once stability is achieved, cardiorespiratory support is slowly tapered while closely monitoring the infant's response. The **oxygenation index (OI)**, calculated as OI = 100 × [mean airway pressure × fraction of inspired oxygen (FiO_2)] / PaO_2, is used to assess the severity of PPHN and assist in management. Specific cutoff indicators are suggested below for initiation of iNO (OI >20) and consideration of ECMO support (OI >30).

A. Supportive cardiopulmonary care. Supportive cardiopulmonary approaches may avoid or reverse further increases in RV afterload.

B. Correct metabolic derangements. Biochemical abnormalities contribute to right-to-left shunting with pulmonary vasoconstriction and impairments in cardiac function. Correction of hypoglycemia and hypocalcemia provides adequate substrates for myocardial function and appropriate responses to inotropic agents (see Chapters 40 and 41). Maintaining a neutral acid–base balance with an ideal $PaCO_2$ target of 40 to 50 mm Hg avoids increased PVR associated with acidosis.

C. Supplemental oxygen. Hypoxia is a powerful pulmonary vasoconstrictor. Thus, maintaining oxygenation (normoxemia) with supplemental oxygen is the most important therapy to reduce abnormally elevated PVR. Provide sufficient supplemental oxygen to maintain adequate oxygenation and minimize end-organ underperfusion and lactic acidemia. Monitor preductal and postductal SaO_2 continuously and insert an arterial catheter to monitor blood gases and blood pressure.

D. Mechanical ventilation (see Chapter 29). Mechanical respiratory support is instituted when hypoxemia persists despite maximal administration of supplemental oxygen and/or respiratory failure is demonstrated by marked hypercapnia and acidemia. A common approach is to maintain physiologic PaO_2 and $PaCO_2$ values but avoid hyperventilation. As infants with PPHN often have marked lability, a conservative approach to tapering support is indicated until stability is achieved for 12 to 24 hours. Suggested target

goals are SaO_2 >95%, $PaCO_2$ 40 to 50 mm Hg, and pH 7.30 to 7.40. Important factors to consider when choosing a specific respiratory management strategy are the underlying pulmonary parenchymal abnormality, if any, and the infant's clinical lability or stability.

1. In infants without pulmonary alveolar disease, high intrathoracic pressure impedes CO and elevates PVR. The optimal strategy for this group of infants involves mechanical ventilation with rapid, low-pressure, and short inspiratory time in an effort to minimize elevated intrathoracic pressure and modulate effects of ventilation on pulmonary venous return and CO.
2. In infants with parenchymal pulmonary disease, ventilator strategies should optimize treatment of the primary pulmonary disease. High-frequency oscillatory ventilation (HFOV) or high-frequency jet ventilation (HFJV) may be more effective than conventional mechanical ventilation in these infants.

E. Sedation and analgesia. Severe agitation can lead to catecholamine release that activates pulmonary α-adrenergic receptors and further promotes pulmonary vasoconstriction, asynchronous ventilation, and hypoxemia. An opioid analgesic that minimizes pain, such as fentanyl (1 to 3 μg/kg/hour infusion), is a useful adjunct therapy. Alternatively, morphine sulfate (0.05 to 0.1 mg/kg/hour infusion) can be used if the infant is not hypotensive. Midazolam (0.05 to 0.1 mg/kg/hour infusion) may provide adjunctive sedation in the absence of systemic hypotension. Neuromuscular blockade may be helpful in some infants to synchronize the infant's breathing with mechanical ventilation and minimize their metabolic demands.

F. Circulatory support (see Chapter 40). Optimal CO is necessary to ensure adequate tissue oxygenation and mixed venous oxygen content. Hemodynamic treatment strategies should target the major determinants of altered CO by judicial volume optimization to improve preload, RV afterload reduction to decrease mPAP and PVR (e.g., surfactant administration, ventilation, cardiotropic medications), and/or inotropic support to enhance contractility. In the absence of direct measures of CO, hemodynamic support of infants with PPHN is generally guided by the systolic, diastolic, and mean systemic blood pressures (BPs) needed to elevate PVR and reduce or eliminate the right-to-left hemodynamic shunt. PVR in many infants with PPHN is at or near-normal systemic BP, and initial treatment goals focus on raising systemic BP to levels of 50 to 70 mm Hg (systolic) and 45 to 55 mm Hg (mean). As PVR falls, the infant will tolerate lower BPs and ongoing reassessment of hemodynamic status and revision of the treatment plan are essential.

1. **Preload and volume expansion.** Intravascular volume support can be an important adjunctive therapy for infants with PPHN accompanied by pathophysiologic conditions associated with intravascular volume depletion (e.g., hemorrhage, hydrops, capillary leak) or decreased SVR (i.e., septic shock). Normal saline (0.9% normal saline 10 mL/kg over 20 to 30 minutes) is generally used. Packed red blood cell transfusion is used for anemia associated with hemorrhage (goal hematocrit >40%) or for excessive capillary leak.
2. **Pharmacologic treatment** (Table 36.1) (see Chapter 40). Pharmacologic therapy is directed at ensuring adequate pulmonary and systemic blood flow and maintaining LV and RV function to optimize CO. The

choice of an initial cardiotropic medication or a combination of agents for a particular infant is based on the differential diagnosis and echocardiographic findings, including severity of PH, cardiac function, and shunt physiology. Upper-limit cutoff values for each medication should be discussed before adding a second- or third-line treatment.

a. Dopamine, an endogenous catecholamine precursor of norepinephrine with sympathetic and neuroendocrine properties, is a commonly used cardiotropic agent in neonates with PPHN. Dopamine has both ionotropic and chronotropic effects, and thus can improve cardiac dysfunction and will raise SVR, but may also cause tachycardia. Dopamine is typically started at 2.5 to 5 μg/kg/minute; the infusion rate is titrated to a dose that maintains the mean BP and minimizes right-to-left shunting. The α_1-adrenergic effect of dopamine at higher rates (≥5 μg/kg/minute) may increase PVR and is unlikely to improve PBF due to its potential vasoconstrictive effects on a labile pulmonary vascular bed. When this potential complication occurs with an increasing dose of dopamine and is associated with clinical deterioration, limiting the dose to 7.5 to 10 μg/kg/minute and consideration of second-line agent may be helpful.

b. Dobutamine, a synthetic catecholamine with direct adrenoreceptor agonistic effects, can be used for cardiac dysfunction in the setting of PPHN. It has no impact on PVR but will lower SVR. Although dobutamine is not considered a first-line agent for PPHN in the setting of systemic hypotension, a starting dose of 2.5 to 5 μg/kg/minute may be useful in infants with cardiac dysfunction. At higher doses (5 to 10 μg/kg/minute), dobutamine can be associated with tachycardia and increased myocardial oxygen consumption so that other inotropic agents should be used.

c. Epinephrine is an endogenous catecholamine that stimulates α_1, α_2, β_1, and β_2 adrenoreceptors with dose-dependent hemodynamic effects. Epinephrine has positive inotropic effects (even at lower doses, 0.02 μg/kg/minute) and can raise SVR and can be used when hypotension is refractory to dopamine. Epinephrine is started at a dose of 0.02 to 0.05 μg/kg/minute, and the infusion rate is titrated to maintain a mean BP that minimizes right-to-left shunting. At higher doses, epinephrine may raise PVR and result in hyperglycemia, hyperlactatemia, and tachycardia; as a result, the infusion rate should be limited to 0.1 μg/kg/minute, and a second-line cardiotropic agent could be considered if needed.

d. Norepinephrine, is a potent nonselective adrenergic agent that stimulates both α_1- and α_2-adrenergic receptors, and, as a result, is expected to raise SVR disproportionately to PVR. It has minimal β_1 effects and has little or no changes in heart rate or inotropic effects. If there is no evidence of cardiac dysfunction, then norepinephrine (initial dose of 0.02 to 0.05 μg/kg/minute) can be used for neonates with PPHN as there is growing, but limited data of its association with improved oxygenation in neonates with PPHN. Similar cutoff values as epinephrine can be employed for norepinephrine for when to start a second-line agent.

e. Milrinone, a selective phosphodiesterase-3 inhibitor, has both inotropic and vasodilatory properties. In a newborn with PPHN and cardiac dysfunction, milrinone (dose: 0.33 to 1 μg/kg/minute) may be used with iNO to augment pulmonary vasodilation as well as independently increase RV systolic performance. Because systemic vasodilation is the

Table 36.1. Cardiotropic Medications for Management of Persistent Pulmonary Hypertension of the Newborn

Cardiotropic Agents	Receptors Stimulated	SVR	PVR	Contractility	SV	HR
Dopamine*	α_1, β_1, β_2, D	↑	↑	↑	↑	↑
Dobutamine	α_1, β_1, weak β_2	↓	No effect	↑	↑	↑
Epinephrine*	α_1, α_2, β_1, β_2	↑	↑	↑	↑	↑
Norepinephrine*	α_1, α_2, β_1	↑	↑	No effect	↑	Minimal effect
Milrinone	PDE III inhibitor	↓	↓	↑	↑	↑
Vasopressin	V1, V2	↑	↓	No effect	↑	No effect
Hydrocortisone	Mineralocorticoid, glucocorticoid	↑	No effect	No effect	No effect	↑

Consider upper limit thresholds and cutoff values when combining agents and adding a second-line agent. For example, dopamine of 7.5 μg/kg/minute, epinephrine and norepinephrine of 0.1 μg/kg/minute.

*Dose ranges are based on limited evidence and effects may vary among patients.

	BP (MAP)	Dosage	Physiologic Goal	Pearls + Potential Adverse Cardiovascular Effects
	↑	2–20 μg/kg/minute Start: 5 μg/kg/minute	↑ SVR ↑ MAP ↑ Contractility	<2: D (↑ UOP) 2–6: β_1, D (+ inotrope) >6: α_1, β_1 (↑ SVR) ↑ PVR at higher dose and ↑ HR
	↓	5–20 μg/kg/minute Start: 5 μg/kg/minute	↑ Contractility	Use with cardiac dysfunction. Can cause ↓ SVR Can cause ↑ HR
	↑	0.02–0.5 μg/kg/minute Start: 0.05 μg/kg/minute	↑ SVR ↑ MAP ↑ Contractility	<0.1 (β_1, β_2) – ↑ function >0.1 (β_1, β_{2b}, α_1, α_2) ↑ SVR Caution when HR >160–170 bpm. Lactic acidosis and hyperglycemia
	↑	0.02–0.5 μg/kg/minute Start: 0.05 μg/kg/minute	↑ SVR > PVR ↑ MAP ↓ PA pressure	If function normal, can consider when HR > 160 bpm NE < β_1 activity < Epi Good for septic shock No impact on function
	↓	0.2–1 μg/kg/minute Start: 0.33 μg/kg/minute	↑ Contractility ↓ SVR/PVR ↓ MAP	Not first line with hypotension Use with severe heart dysfunction and stable BP. ↓ PAP and will ↓ SVR Combine with agent that ↑ SVR.
	↑	0.1–1.2 μg /kg/minute Start: 0.1 μg/kg/minute	↑ SVR ↓ PVR ↑ MAP	↑ SVR and ↓ PVR Increase preload Possible first line (not with isolated LV dysfunction) Monitor for hyponatremia.
	↑	1 mg/kg per dose q8h	↑ SVR ↑ MAP	Agent for refractory hypotension Delayed response of 2–8 hours Consider adding with second line.

SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; SV, stroke volume; BP, blood pressure; MAP, mean arterial pressure; UOP, urine output; HR, heart rate; PA, pulmonary artery; NE, norepinephrine; PDE, phosphodiesterase; LV, left ventricle; Epi, epinephrine.

most common adverse effect, milrinone should not be used as a first-line agent to treat hypotension.

f. Arginine vasopressin (AVP), a V1 receptor agonist, selectively vasodilates coronary, cerebral, pulmonary, and renal vascular beds while causing vasoconstriction in other systemic vascular beds.

g. Corticosteroids may be used to manage hypotension in sick neonates. The mechanisms are multifactorial; corticosteroids potentially upregulate myocardial and vascular adrenoreceptors. Hydrocortisone, a combined mineralocorticoid and glucocorticoid, is the most well studied. A typical dose is 2 to 4 mg/kg/day given as 1 mg/kg q8h. This is usually considered as a third-line agent to increase mean BP in neonates with PPHN and hypotension, although is sometimes added when the threshold dose is reached for the first-line agent and the second-line agent is being started. Hydrocortisone increases systemic BP with refractory hypotension within 2 to 6 hours without compromising cardiac function, systemic, or end-organ blood flow.

G. Additional support

1. **Correct anemia.** Packed red blood cell transfusion in an infant with anemia will optimize oxygen delivery.
2. **Correct polycythemia.** Hyperviscosity associated with polycythemia increases PVR, promotes release of vasoactive substances through platelet activation, and reduces pulmonary microvasculature perfusion. Consider partial exchange transfusion in an infant with PPHN whose central hematocrit exceeds 65% (see Chapter 46).
3. **Antibiotic treatment.** An infant with PPHN suspected of possible infection should be evaluated for sepsis and administered antibiotics as appropriate.
4. **Surfactant** administration is useful in cases of secondary surfactant deficiency (RDS) or impairment (i.e., meconium) (see Chapter 43).

H. Pulmonary vasodilator therapy. PPHN-targeted therapy is used for infants with PPHN who fail to respond to general cardiopulmonary supportive care. Oxygen and iNO are the only well-studied pulmonary vasodilators in neonates with PPHN. The efficacy and safety of several newer therapeutic agents used in children and adults with PH have not been adequately tested in neonates with PPHN.

1. **iNO** is the principal therapeutic agent for PPHN. **NO** is a naturally occurring substance produced by endothelial cells and can be delivered through the ventilator circuit. NO diffuses into smooth muscle cells, increases intracellular cyclic guanosine monophosphate (cGMP), relaxes the vascular smooth muscle, and causes pulmonary vasodilation. Because NO is bound by hemoglobin and biologically inactivated, iNO causes little or no systemic vasodilation or hypotension. iNO administered by conventional or high-frequency ventilation in doses of 1 to 20 parts per million (ppm) causes pulmonary but not systemic vasodilation and thus selectively decreases PVR. In a systematic review, iNO reduced the use of ECMO in term infants with severe respiratory failure. iNO is most effective when administered after adequate alveolar recruitment. In infants with diffuse pulmonary disease, this can be accomplished using HFOV and/or surfactant treatment.

a. Initiation. In infants with PPHN and severe respiratory failure, an initial starting dose of 20 ppm is delivered via the ventilator circuit and generally results in an immediate increase in SaO_2. A concentration >20 ppm does not improve response in PPHN and may lead to methemoglobinemia (MetHb), a potential toxicity of iNO treatment.

b. Weaning. As the infant's oxygenation improves, the dose of iNO should be tapered gradually to avoid rebound hypoxemia. Weaning of iNO concentration begins when FiO_2 is weaned to <0.50 to 0.60 and is gradually decreased at intervals no more frequent than every 4 hours, 20 to 15, 15 to 10, 10 to 5 ppm. At this point, infants may be sensitive to smaller decrements so are typically weaned slowly, 1 ppm at a time, from 5 to off, observing the SaO_2 to each change before further weaning.

c. Toxicity. MetHb is a potential complication of iNO therapy but occurs rarely at concentrations of 20 ppm or less. Our approach is to measure methemoglobin level after 24 hours of iNO therapy; if <1%, no further measurements are needed unless there are clinical concerns or an increase in iNO dose. If MetHb is >1%, attempt to lower iNO dose and follow levels.

d. Sildenafil. Sildenafil, a phosphodiesterase type 5 inhibitor that promotes vasodilation, may be considered in resource-limited settings when iNO is not available.

2. **ECMO.** ECMO can be a lifesaving therapy for approximately 75% to 85% of infants with PPHN who fail conventional management with assisted ventilation, iNO, and hemodynamic support (see Chapter 39). Because not all infants with PPHN respond to iNO and some may deteriorate rapidly, critically ill infants with PPHN should be treated at a center in that can provide both iNO and ECMO.

VII. POSTNEONATAL OUTCOMES AMONG INFANTS WITH PPHN. The availability of both iNO and ECMO have helped reduce PPHN-associated mortality to 7% to 10%. Survivors of PPHN remain at risk for medical and neurodevelopmental sequelae. Infants who develop PPHN are at approximately 20% risk of rehospitalization within 1 year of discharge. These infants have a 20% to 46% risk of audiologic, neurodevelopmental, or cognitive impairments and should be referred for neurodevelopmental infant follow-up.

Suggested Readings

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Siefkes HM, Lakshminrusimha S. Management of systemic hypotension in term infants with persistent pulmonary hypertension of the newborn: an illustrated review. *Arch Dis Child Fetal Neonatal Ed* 2021;106(4):446–455.

37 Pulmonary Hemorrhage

Sarah N. Kunz

KEY POINTS

- Pulmonary hemorrhage occurs in 3% to 5% of preterm infants with respiratory distress syndrome (RDS).
- Hemodynamically significant patent ductus arteriosus (PDA) is an important risk factor.
- Treatment is largely supportive.

I. DEFINITION. Pulmonary hemorrhage is defined on **pathologic** examination as the presence of erythrocytes in the alveoli and/or lung interstitium. In infants who survive longer than 24 hours, interstitial hemorrhage predominates. Confluent hemorrhage involving at least two lobes of the lung is termed *massive* pulmonary hemorrhage. Although less agreement exists about the **clinical** definition, pulmonary hemorrhage is typically described as the presence of hemorrhagic fluid in the trachea accompanied by a concurrent respiratory decompensation that requires increased respiratory support.

II. PATHOPHYSIOLOGY. The precise mechanisms underlying pulmonary hemorrhage remain uncertain. Pulmonary hemorrhage likely results from heterogeneous conditions that converge in a common physiologic pathway.

A. Based on studies of lung effluent demonstrating relatively low erythrocyte concentration compared to whole blood, pulmonary hemorrhage is thought to result from hemorrhagic pulmonary edema rather than direct bleeding into the lung.

B. A sudden decrease in intrapulmonary pressure, a consequence of exogenous surfactant administration, leads to increased pulmonary blood flow, which can exacerbate **hemorrhagic pulmonary edema**.

C. Acute left ventricular failure, due to hypoxia or other conditions, may lead to increased pulmonary capillary pressure and injury to the capillary endothelium. This may result in increased leakage of fluid into the interstitium and pulmonary air spaces.

D. Factors that alter the integrity of the epithelial–endothelial barrier in the alveolus or that change the filtration pressure across this membrane may predispose infants to pulmonary hemorrhage.

E. Coagulopathy may worsen pulmonary hemorrhage but is not considered the primary inciting factor.

III. EPIDEMIOLOGY.

Pulmonary hemorrhage complicates the course of 3% to 5% of preterm infants mechanically ventilated for respiratory distress syndrome (RDS). However, autopsy studies demonstrate a much higher incidence of pulmonary hemorrhage in preterm infants (>50%) likely because hemorrhage limited to the interstitial space may not become clinically apparent before death. The majority of pulmonary hemorrhages in preterm infants occur within the first week of life.

IV. PREDISPOSING FACTORS.

Pulmonary hemorrhage has been linked to many predisposing conditions, including extremely preterm gestation, intrauterine growth restriction, intrauterine and intrapartum asphyxia, need for delivery room resuscitation, RDS, patent ductus arteriosus (PDA), infection, and congenital heart disease. Risk factors include conditions predisposing the infant to increased left ventricular filling pressures, increased pulmonary blood flow, compromised pulmonary venous drainage, and poor cardiac contractility. The following factors, which have been implicated in the development of pulmonary hemorrhage, are particularly notable:

A. PDA. The presence of a PDA is a significant risk factor for pulmonary hemorrhage. Increased pulmonary blood flow and compromised ventricular function accompany decreasing pulmonary vascular resistance, leading to pulmonary microvascular injury and hemorrhagic pulmonary edema. In a cohort study of infants born at <29 weeks' gestation, early pharmacologic treatment for PDA was associated with a decreased rate of pulmonary hemorrhage.

B. Exogenous surfactant. Pulmonary hemorrhage may present as a complication of surfactant therapy, likely related to changes in lung compliance and increased pulmonary blood flow. However, the overall benefits of surfactant treatment outweigh the risks.

C. Sepsis. Overwhelming sepsis appears to increase the risk of pulmonary hemorrhage, likely the result of increased pulmonary capillary permeability, and potentially exacerbated by associated thrombocytopenia and coagulopathy.

V. CLINICAL PRESENTATION.

The clinical diagnosis of pulmonary hemorrhage is typically made in a mechanically ventilated infant when sudden cardiorespiratory decompensation occurs in the setting of hemorrhagic fluid in the upper respiratory tract, either spontaneously from the endotracheal tube or upon suctioning. The clinical presentation can be dramatic, and serious cases may present with bradycardia, cyanosis, and hypovolemic shock. Pink or blood-tinged secretions may progress to frank blood from the upper respiratory tract. Only a small percentage of pulmonary hemorrhages observed at autopsy are evident clinically; in the absence of hemorrhagic secretions, respiratory deterioration is usually attributed to other causes.

VI. EVALUATION

A. History and physical examination. A thorough history may help identify predisposing factors such as risks for infection or evidence of a hemodynamically significant PDA. On physical examination, infants with pulmonary

hemorrhage have pink or red frothy fluid in the airway and signs of respiratory decompensation. In the absence of respiratory deterioration, and particularly when blood is noted soon after intubation, isolated bleeding may indicate erosion or ulceration in the upper airway and not represent pulmonary hemorrhage.

B. Radiographic evaluation. The clinical diagnosis of pulmonary hemorrhage may be facilitated by the radiographic changes that accompany it. Nonspecific changes on chest radiograph include diffuse patchy infiltrates or opacification of one or both lungs with air bronchograms. Lung ultrasound may be a useful adjunct in differentiating pulmonary hemorrhage from other causes of respiratory decompensation, although its use is not widespread.

C. Laboratory studies. Laboratory evaluation typically reflects cardiopulmonary compromise and may reveal an associated acidosis (respiratory, metabolic, or mixed), a drop in hematocrit, and an abnormal coagulation profile.

VII. TREATMENT.

Because the underlying pathogenesis remains unclear, treatment is largely supportive. The general approach involves clearing the airways of hemorrhagic fluid, restoring adequate ventilation, and correcting any underlying coagulopathy.

A. Provide positive end-expiratory pressure (PEEP). The use of elevated PEEP of 6 to 8 cm H_2O helps to decrease the efflux of interstitial fluid into the alveolar space and improve gas exchange by increasing the mean airway pressure.

B. Restore hemodynamic stability and correct acidosis. Correct hemodynamic instability with volume resuscitation, including packed red blood cell replacement, and consider the addition of vasoactive medications as needed. Restoration of both adequate ventilation and blood pressure will help to improve acidosis.

C. Correct coagulopathy. Transfusion of fresh frozen plasma, cryoprecipitate, and/or platelets should be directed by the results of laboratory evaluation, as appropriate.

D. Consider echocardiogram. An echocardiographic evaluation may assist in the evaluation of ventricular function, need for vasoactive medications, and the possible contribution of a PDA. Consider pharmacologic or surgical closure of the PDA if hemodynamically significant.

E. Identify other predisposing factors. Additional potential contributing factors such as sepsis must be addressed.

F. Strategy for ventilation. It is uncertain whether using high-frequency ventilation to provide high mean airway pressure while limiting tidal volume excursions is more effective than conventional ventilation to minimize further interstitial and alveolar fluid accumulation.

G. Limit aggressive airway suctioning.

H. Role of surfactant therapy. Surfactant therapy after pulmonary hemorrhage has been considered for continued treatment of primary surfactant deficiency in RDS as well as for treatment of secondary surfactant deficiency

resulting from hemorrhagic airway edema. Following pulmonary hemorrhage, hemoglobin, plasma proteins, and cell membrane lipids present in the airspace may inactivate surfactant. Exogenous surfactant replacement may reverse the inhibition, as demonstrated in the setting of meconium aspiration. Case reports and case series suggest that surfactant may reduce mortality and morbidity from pulmonary hemorrhage. However, a 2020 Cochrane Review failed to identify any randomized controlled trials that address surfactant to treat pulmonary hemorrhage and suggests more studies are needed to recommend a change in clinical practice. Treatment should be decided on a case-by-case basis.

I. **Other adjunct therapies.** Use of therapeutic interventions such as intratracheal epinephrine, cocaine, and hemocoagulase have been reported, although evidence for their use remains inconclusive at this time.

VIII. PROGNOSIS.

The prognosis is difficult to establish, in part due to the difficulty in establishing a clinical diagnosis for this condition. Pulmonary hemorrhage was thought to be uniformly fatal before mechanical ventilation, although this was based on pathologic diagnosis and therefore excluded infants with milder hemorrhages who survived. More recent evidence suggests that the mortality associated with pulmonary hemorrhage in extremely preterm infants remains high; in one study, infants <28 weeks with pulmonary hemorrhage had a mortality rate of 56.9%, compared with 33.7% in infants without pulmonary hemorrhage. In another study, the risk of death or survival with neurosensory impairment at 18 months of age was increased in infants with serious pulmonary hemorrhage.

Suggested Readings

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38 Pulmonary Air Leak

Wendy L. Timpson

KEY POINTS

- Pneumothorax occurs most often in neonates with underlying lung disease receiving positive pressure ventilation, although spontaneous cases also occur.
- Pneumothorax should be considered in any infant with deterioration in respiratory or cardiovascular status.
- Infants with pneumothorax on positive pressure ventilation often require chest tube or pigtail catheter placement.
- Conservative management may be appropriate for clinically stable infants with pneumothoraces.

I. BACKGROUND

A. Risk factors. The primary risk factors for air leak are mechanical ventilation and lung disorders. Risk factors common in preterm infants include oligohydramnios, pulmonary hypoplasia, respiratory distress syndrome (RDS), sepsis, and pneumonia. Surfactant therapy for RDS has markedly decreased the incidence of pneumothorax. Risk factors common in term infants are aspiration of meconium, blood, or amniotic fluid; pneumonia; and congenital malformations. Specific features of mechanical ventilation associated with air leak in newborns include high inspiratory pressure, large tidal volume, and long inspiratory duration.

B. Pathogenesis. Air leak syndromes arise via a common mechanism. Transpulmonary pressures that exceed the tensile strength of the noncartilaginous terminal airways and alveolar saccules damage the respiratory epithelium. Reduced epithelial integrity permits air to enter the interstitium, causing **pulmonary interstitial emphysema (PIE)**. Persistent elevation in transpulmonary pressure facilitates the dissection of air toward the visceral pleura and/or the hilum via the peribronchial and perivascular spaces. In rare circumstances, air can enter the pulmonary veins and result in **air embolism**. Rupture of the pleural surface allows the adventitial air to decompress into the pleural space, causing **pneumothorax**. Following a path of least resistance, air can dissect from the hilum and into the mediastinum, resulting in **pneumomediastinum**, or into the pericardium, resulting in **pneumopericardium**. Air in the mediastinum can decompress into the pleural space, the fascial planes of the neck and skin (**subcutaneous emphysema**), or the retroperitoneum. In

turn, retroperitoneal air can rupture into the peritoneum (**pneumoperitoneum**) or dissect into the scrotum or labial folds.

1. **Elevations in transpulmonary pressure.** The newborn's first breath may cause a negative inspiratory pressure up to 100 cm H_2O. Uneven ventilation due to atelectasis, surfactant deficiency, pulmonary hemorrhage, or retained fetal lung fluid can increase transpulmonary pressure. In turn, this leads to alveolar overdistention and rupture. Similarly, aspiration of blood, amniotic fluid, or meconium can result in alveolar overdistention by obstructing the small airways via a ball-valve mechanism.
2. **In the presence of pulmonary disease, positive pressure ventilation increases the risk of air leak.** The high airway pressure required to achieve adequate oxygenation and ventilation in infants with poor pulmonary compliance (e.g., pulmonary hypoplasia, RDS, inflammation, pulmonary edema) further increases this risk. Excessive transpulmonary pressures can occur when ventilator pressures are not decreased as pulmonary compliance improves. This situation sometimes occurs in infants with RDS after surfactant treatment when compliance increases rapidly. Mechanically ventilated preterm infants who make expiratory efforts against ventilator breaths are also at increased risk for pneumothorax. Close attention to avoiding excessive tidal volume can mitigate this risk and volume-targeted ventilation has been shown to reduce the risk for pneumothorax in preterm infants when compared to pressure-limited modes.
3. **Direct trauma to the airways can also cause air leak.** Laryngoscopes, endotracheal tubes, suction catheters, and malpositioned feeding tubes can damage the lining of the airways and provide a portal for air entry.

II. TYPES OF AIR LEAKS

A. Pneumothorax. Spontaneous pneumothorax occurs in 0.07% of otherwise healthy-appearing neonates. One in 10 infants with a spontaneous pneumothorax is symptomatic. Frequency of air leak increases with decreasing gestational age with rates peaking at 6.3% in infants 500 to 1,500 g. The high inspiratory pressures and uneven ventilation that occur in the initial stages of lung inflation may contribute to this phenomenon. Pneumothorax is more common in newborns treated with positive pressure ventilation for underlying pulmonary disease.

Clinical signs of pneumothorax range from insidious changes in vital signs to the complete cardiovascular collapse that often accompanies a tension pneumothorax. Rising intrathoracic pressure leads to decreased lung volume, mediastinal shift, compression of the large intrathoracic veins, and increased pulmonary vascular resistance. The net effect is increased central venous pressure, decreased preload, and, ultimately, diminished cardiac output. A pneumothorax must be considered in any infant receiving positive pressure ventilation, particularly mechanically ventilated infants, who develop alterations in hemodynamics, pulmonary compliance, or oxygenation and ventilation.

1. **Diagnosis**
   a. **Physical examination** findings may include the following:
      i. Signs of respiratory distress including tachypnea, grunting, flaring, and retractions
      ii. Cyanosis
      iii. Chest asymmetry with expansion of the affected side
      iv. Shift in the point of maximum cardiac impulse
      v. Diminished or distant breath sounds on the affected side
      vi. Alterations in vital signs. With smaller collections of extrapulmonary air, compensatory increases may occur in heart rate and blood pressure. As the amount of air in the pleural space increases, central venous pressure rises, and severe hypotension, bradycardia, apnea, hypoxia, and hypercapnia may occur.

   b. Arterial blood gases. Changes in arterial blood gas measurements are nonspecific but sometimes reflect a decreased partial pressure of oxygen (PO_2) and increased partial pressure of carbon dioxide (PCO_2). The pH may be low as PCO_2 rises or with metabolic acidosis due to poor cardiac output with tension pneumothorax.

   c. Chest radiograph. Anteroposterior (AP) views may show a hyperlucent hemithorax, a separation of the visceral from the parietal pleura, flattening of the diaphragm, or mediastinal shift. A cross-table lateral view can detect small collections of intrapleural air beneath the anterior chest wall; however, an AP view is needed to determine laterality. A lateral decubitus view, with the side of suspected pneumothorax up, may be helpful in detecting a small pneumothorax and may help differentiate skinfolds, congenital lobar emphysema, congenital pulmonary airway (cystic adenomatoid) malformations, and surface blebs that occasionally give the appearance of intrapleural air.

   d. Transillumination. A high-intensity fiberoptic light source may demonstrate a pneumothorax. This technique is less sensitive in infants with chest wall edema or severe PIE, in extremely small infants with thin chest walls, or in full-term infants with thick chest walls.

   e. Needle aspiration. In a rapidly deteriorating clinical situation, thoracentesis may confirm the diagnosis and be therapeutic (see section II.A.2.b).

2. **Treatment.** Note that prior to any procedure, a "time out" should be done with all team members to confirm the correct patient, diagnosis, and laterality (side affected) (see Chapter 69, Common Neonatal Procedures).

   a. Conservative therapy. Close observation may be sufficient for infants who are asymptomatic. The extrapulmonary air will usually resolve in 24 to 48 hours. Oxygen should only be administered if the baby develops hypoxemia and should be targeted to the desired saturation limits. No evidence supports the use of 100% oxygen to hasten the resolution of pneumothorax. Furthermore, unnecessary oxygen exposure can lead to free radical injury.

   b. Needle aspiration. Thoracentesis with a "butterfly" needle or intravenous (IV) catheter with an inner needle is the first-line treatment for a symptomatic pneumothorax. Needle aspiration may be curative in infants, particularly those not receiving positive pressure ventilation and is

frequently a temporizing measure in mechanically ventilated infants. In infants with severe hemodynamic compromise, thoracentesis may be a life-saving procedure.

i. Attach a 23G or 25G butterfly needle or 22G or 24G IV catheter to a 10- to 20-mL syringe fitted with a three-way stopcock.

ii. Identify the second intercostal space (ICS) in the midclavicular line and prepare the overlying skin with an antibacterial solution.

iii. Insert the needle firmly into the ICS just above the superior edge of the third rib to minimize the chance of lacerating an intercostal artery located on the inferior surface of the ribs. Advance the needle perpendicular to the chest wall while an assistant applies continuous suction with the syringe. A rapid flow of air into the syringe occurs when the needle enters the pleural space. Once the pleural space has been entered, stop advancing the needle. This will reduce the risk of puncturing the lung while the remaining air is evacuated. When the flow of air stops, the needle should be removed, and pressure held over the site to minimize blood loss. Transillumination immediately prior to, and following, thoracentesis can be useful to estimate efficacy.

iv. A continuous air leak can be aspirated while a chest tube is being inserted (see section II.A.2.c). The "butterfly" needle can be left in place, or if an IV catheter is used, the needle can be removed, and the plastic catheter left in place for further aspiration. A short piece of IV extension tubing attached to the IV catheter hub through a T-piece connector will allow flexibility during repeated aspiration. It is important to remember that if the infant is spontaneously breathing, a needle left in place can serve as a conduit for air entry into the pleural space with negative pressure generated during inspiration. To prevent this, the butterfly tubing should be clamped or the stopcock left in the "off" position. This is less of a concern for babies who are receiving positive pressure ventilation.

c. Chest tube drainage. Chest tube drainage is often needed to evacuate pneumothoraces that develop in infants receiving positive pressure ventilation. Frequently, these air leaks are continuous and can result in severe hemodynamic compromise if left untreated.

i. Insertion of a chest tube

a) Select a chest tube of the appropriate size; French size 10 (smaller) and 12 (larger) catheters are adequate for most infants.

b) Position the infant with the lateral chest wall of the affected side facing up. Take care to note the ipsilateral nipple to avoid damage to breast tissue during the procedure. Inspect the chest tube to gauge the depth of insertion relative to the size of the infant to ensure that the side ports will be positioned deep to the chest wall.

c) Prepare the chest area with an antiseptic solution. The subcutaneous tissues overlying the fourth to sixth rib at the midaxillary line can be infiltrated with a 1% lidocaine solution for analgesia with care not to obscure landmarks needed to guide

the procedure. Additionally, a narcotic for pain management should be administered.

d) In the midaxillary line at the sixth ICS, parallel to the rib, make a small incision (0.5 to 1.0 cm) through the skin. An alternative site is in the anterior-superior portion of the chest wall; however, this approach has a risk of injury to the internal mammary artery and other regional vessels and thus is the less preferred option.

e) With a small curved hemostat, dissect the subcutaneous tissue overlying the rib. Make a subcutaneous track to the fourth ICS. Take care to avoid the nipple area, the pectoralis muscle, and the axillary artery.

f) Enter the pleural space with the closed hemostat in the fourth ICS at the intersection of the nipple line and the anterior axillary line. Guide the tip over the top of the rib to avoid trauma to the intercostal artery. Push the hemostat through the intercostal muscles and parietal pleura. Listen for a rush of air to indicate pleural penetration; a "pop" may be felt. Spread the tips to widen the opening and leave the hemostat in place. A chest tube with a trochar in the center can be used but is not recommended because it increases the risk of lung or vascular injury. A trochar is not necessary to penetrate the chest wall of very preterm infants.

g) Grasp the end of the chest tube with the tips of the hemostat. The chest tube and the hemostat should be in a parallel orientation. Direct the chest tube through the skin incision, into the pleural opening, and between the opened tips. After the pleural space has been entered, direct the chest tube anteriorly and cephalad by rotating the curved points of the hemostat. Release the hemostat and advance the chest tube a few centimeters. Be certain that the side ports of the chest tube are in the pleural space. Direct the chest tube to the location of the pleural air. The anterior pleural space is generally most effective for infants in the supine position.

h) Palpate the chest wall around the entry site to confirm that the chest tube is not in the subcutaneous tissues.

i) Attach the chest tube to a Heimlich valve (for transport) or an underwater drainage system such as a Pleur-evac. Apply negative pressure (10 to 20 cm H_2O) to the underwater drainage system.

j) Using 3-0 or 4-0 silk, close the skin incision with a purse-string suture around the tube or a single interrupted suture on either side of the tube. Secure the chest tube by wrapping and then tying the skin suture tails around the tube.

k) Cover the insertion site with petrolatum gauze and a small, clear, plastic, adhesive surgical dressing. Avoid extensive taping or large dressings because they interfere with chest examination and may delay the discovery of a displaced chest tube.

l) Obtain AP and lateral chest radiographs to confirm tube position and ascertain drainage of the pleural air.

m) Radiographs may reveal that a chest tube is ineffective in evacuating extrapulmonary air. The most common cause of failure is tube placement in the posterior pleural space or the subcutaneous tissue. Other causes for ineffective drainage are tubes that perforate the lung, diaphragm, or mediastinum. Extrapulmonary air not in the pleural space, such as a pneumomediastinum or subpleural pulmonary pseudocyst, will not be drained by a chest tube. Complications of chest tube insertion include hemorrhage, lung perforation, cardiac tamponade, and phrenic nerve injury.

ii. Insertion of a pigtail catheter. Pigtail catheters may be a less traumatic and faster way to relieve a pneumothorax and may be preferred to chest tube placement in premature infants. Furthermore, once pigtail catheters are in position, they are less painful than rigid chest tubes and their use could reduce narcotic exposure. Pigtail catheters are inserted using a modified Seldinger technique.

a) Select an appropriately sized catheter; 8 (smaller) or 10 (larger) French are typically adequate.

b) Position the infant with the lateral chest wall of the affected side facing up. Take care to note the ipsilateral nipple to avoid damage to breast tissue during the procedure. Inspect the catheter to gauge the depth of insertion relative to the size of the baby to ensure that the side ports will be positioned deep to the chest wall, noting that the catheter will spontaneously curl back into a "pigtail" position upon removal of the insertion guide wire. Some catheters have depth markings that are useful to determine goal insertion depth, whereas others do not, in which case a sterile skin marker can be used.

c) Prepare the chest area with an antiseptic solution. The subcutaneous tissues overlying the sixth ICS at the midaxillary line can be infiltrated with a 1% lidocaine solution for analgesia with care not to obscure landmarks needed to guide the procedure. Additionally, administer a narcotic for pain management.

d) Insert an 18G needle or an 18G IV catheter into the pleural space in the midaxillary line, just superior to the sixth rib to avoid the intercostal artery that runs inferior to the rib. An assistant should use a three-way stopcock affixed to a 10- or 20-mL syringe to continuously draw back during insertion. Extraction of air indicates entry into the pleural space; however, in most cases, the needle must be advanced 1 to 2 mm deeper to ensure that the full bevel has entered the pleural space.

e) Inspect the guide wire to identify the insertion depth that will be needed to reach the pleural space. Remove the three-way stopcock and advance the guide wire through the catheter to a point just beyond its tip. The needle or IV catheter is then removed while holding the guide wire in place, and a dilator is advanced over the wire. Insert the pigtail catheter into the pleural space over the guide wire and advance until the curve of the catheter is inside the chest, ideally positioned anteriorly and superiorly.

f) Remove the guide wire and secure the catheter with sterile adhesive strips in a chevron fashion. Additional anchoring can be achieved with an overlying clear sterile adhesive, taking care to avoid obscuring the insertion area, as it should be monitored for position and evidence of infection while the pigtail is in position.

g) Connect to an evacuation device as with chest tube placement. Confirm proper positioning and adequate air evacuation by radiography.

d. Removal of a chest tube or pigtail catheter. When the infant's lung disease has improved and the chest tube has not drained air for 24 to 48 hours, discontinue suction and leave the drainage device under water seal. If radiographic examination shows no reaccumulation of extrapulmonary air in the next 12 to 24 hours, the drainage device should be removed. A narcotic is given for pain control prior to removal. To reduce the chance of introducing air into the pleural space, cover the chest wound with a small occlusive dressing during removal. Remove the drainage device during expiration in spontaneously breathing infants and during inspiration in mechanically ventilated infants. A manual mechanical breath for ventilated infants can ensure removing the drainage device during the inspiratory phase.

e. Persistent pneumothorax refractory to routine measures. Minimizing positive pressure is critical to optimize pleural healing and reduce risk for ongoing air leak. High-frequency ventilation (HFV) can be used to minimize tidal volume and improve air leaks in mechanically ventilated infants. In patients with severe air leaks, oxygen supplementation is often increased so that mean airway pressure can be minimized, although this intervention must be balanced with risks for free radical damage secondary to oxygen exposure in very preterm infants. Interventional radiology may be needed to place catheters under ultrasound or fluoroscopic guidance to drain air collections that are inaccessible by standard techniques.

3. Complications

a. Profound ventilatory and circulatory compromise can occur and, if untreated, result in death.

b. Intraventricular hemorrhage may result, possibly secondary to a combination of fluctuating cerebrovascular pressures, impaired venous return, hypercapnia, hypoxia, and acidosis.

c. Inappropriate antidiuretic hormone secretion may occur.

B. PIE. PIE occurs most often in mechanically ventilated, extremely preterm infants with RDS or sepsis. Interstitial air can remain localized but commonly spreads to involve significant portions of one or both lungs. Interstitial air can dissect toward the hilum and the pleural surface via the adventitial connective tissue surrounding the lymphatics and pulmonary vessels. This can compromise lymphatic drainage and pulmonary blood flow. PIE alters pulmonary mechanics by decreasing compliance, increasing residual volume and dead space, and enhancing ventilation–perfusion mismatch. Rupture of interstitial air into the pleural space and mediastinum can result in pneumothorax and pneumomediastinum, respectively.

1. **Diagnosis**
   a. PIE frequently develops in the first 48 hours after birth.
   b. PIE may be accompanied by hypotension, bradycardia, hypercarbia, hypoxia, and acidosis.
   c. PIE has two radiographic patterns: cyst-like and linear. Linear lucencies radiate from the lung hilum. Occasionally, large cyst-like blebs give the appearance of a pneumothorax.
2. **Treatment**
   a. If possible, attempt to decrease mean airway pressure by lowering peak inspiratory pressure, positive end-expiratory pressure (PEEP), and inspiratory time. HFV can be used in infants with PIE to avoid large tidal volumes. Volume-targeted ventilation may be a useful mode to minimize trauma as lung compliance changes.
   b. Positioning the infant with the affected lung dependent may improve unilateral PIE.
   c. Minimize endotracheal suctioning and manual positive pressure ventilation.
   d. Severe localized PIE that has failed to improve with conservative management may require collapse of the affected lung by selective bronchial intubation or occlusion or, rarely, surgical resection.
3. **Complications.** PIE may precede more severe complications such as pneumothorax, pneumopericardium, or an air embolism. It is also a harbinger of chronic lung disease in the very preterm infant.

C. Pneumomediastinum. Mediastinal air can develop when pulmonary interstitial air dissects into the mediastinum or when direct trauma occurs to the airways or the posterior pharynx.

1. **Diagnosis**
   a. Physical examination. Heart sounds may be distant.
   b. Chest radiograph. Air collections are central and usually elevate or surround the thymus. This results in the characteristic "spinnaker sail" sign. A pneumomediastinum is best appreciated on lateral view.
2. **Treatment**
   a. Pneumomediastinum is of little clinical importance, and specific drainage procedures are usually unnecessary.
   b. Rarely, cardiorespiratory compromise may develop if the air is under tension and does not decompress into the pleural space, the retroperitoneum, or the soft tissues of the neck. This situation may require surgical mediastinotomy drainage. If the infant is mechanically ventilated, reduce mean airway pressure when possible.
3. **Complications.** Pneumomediastinum is often associated with other types of air leak.

D. Pneumopericardium. Pneumopericardium is the least common form of air leak in newborns but is a common cause of cardiac tamponade. Asymptomatic pneumopericardium is occasionally detected as an incidental finding on a chest radiograph. Most cases occur in preterm infants with RDS treated with mechanical ventilation, preceded by PIE and pneumomediastinum. The mortality rate for critically ill infants who develop pneumopericardium is high.

1. **Diagnosis.** Pneumopericardium should be considered in mechanically ventilated newborn infants who develop acute or subacute hemodynamic compromise.
   a. Physical examination. Although infants may initially have tachycardia and decreased pulse pressure, hypotension, bradycardia, and cyanosis may ensue rapidly. Auscultation reveals muffled, distant, or absent heart sounds. A pericardial knock (Hamman sign) or a characteristic mill wheel–like murmur (bruit de moulin) may be present.
   b. Chest radiograph. AP views show air surrounding the heart. Air under the inferior surface of the heart is diagnostic. However, small pericardial air collections may not be easily visualized, especially in the neonate with significant lung disease obscuring the cardiac silhouette.
   c. Transillumination. A high-intensity fiberoptic light source may illuminate the substernal region. Flickering of the light with the heart rate may help differentiate pneumopericardium from pneumomediastinum or a medial pneumothorax.
   d. Electrocardiogram (ECG). Decreased voltages, manifesting as a shrinking QRS complex, are consistent with pneumopericardium.
2. **Treatment.** Pediatric cardiology, if available, should be consulted when the diagnosis is made.
   a. Conservative management. Asymptomatic infants not receiving positive pressure ventilation can be managed expectantly. Vital signs are closely monitored (especially changes in pulse pressure). Frequent chest radiographs are obtained until the pneumopericardium resolves.
   b. Needle aspiration. Cardiac tamponade is a life-threatening event that requires immediate pericardiocentesis.
      i. Prepare the subxiphoid area with antiseptic solution.
      ii. Attach a 20G to 22G IV catheter with an inner needle to a short piece of IV extension tubing that, in turn, is connected to a three-way stopcock and a 20-mL syringe.
      iii. In the subxiphoid space, insert the catheter at a 30- to 45-degree angle and toward the infant's left shoulder.
      iv. Have an assistant aspirate with the syringe as the catheter is advanced.
      v. Once air is aspirated, stop advancing the catheter.
      vi. Slide the plastic catheter over the needle and into the pericardial space.
      vii. Remove the needle, reattach the IV tubing to the hub of the plastic catheter, evacuate the remaining air, and withdraw the catheter.
      viii. If air leak persists, prepare for pericardial tube placement.
      ix. If blood is aspirated, immediately withdraw the catheter to avoid lacerating the ventricular wall.
      x. The complications of pericardiocentesis include hemopericardium and laceration of the right ventricle or left anterior descending coronary artery.
   c. Continuous pericardial drainage. Pneumopericardium often progresses to cardiac tamponade and may recur. A pericardial tube may be needed for continuous drainage.

3. **Complications.** Ventilated infants who have a pneumopericardium drained by needle aspiration frequently (80%) have a recurrence. Recurrent pneumopericardium can occur days after apparent resolution of the initial event.

E. Other types of air leaks

1. **Pneumoperitoneum.** Intraperitoneal air may result from extrapulmonary air that decompresses into the abdominal cavity. Usually, the pneumoperitoneum is of little clinical importance, but it must be differentiated from intraperitoneal air resulting from a perforated viscus. Rarely, pneumoperitoneum can impair diaphragmatic excursion and compromise ventilation. In these cases, continuous drainage may be necessary.
2. **Subcutaneous emphysema.** Subcutaneous air can be detected by palpation of crepitus in the face, neck, or supraclavicular region. Large collections of air in the neck, although usually of no clinical significance, can partially occlude or obstruct the compressible, cartilaginous trachea of the premature infant.
3. **Systemic air embolism.** An air embolism is a rare but usually fatal complication of pulmonary air leak. Air may enter the vasculature either by disruption of the pulmonary venous system or by inadvertent injection through an intravascular catheter. The presence of air bubbles in blood withdrawn from an umbilical artery catheter can be diagnostic.

Suggested Readings

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39 Extracorporeal Membrane Oxygenation

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KEY POINTS

- Extracorporeal membrane oxygenation (ECMO) is used to support neonates with severe but reversible respiratory, circulatory, or cardiac failure and may be used as an adjunct to conventional cardiopulmonary resuscitation (CPR) for neonates with cardiac arrest (ECMO to support CPR).
- Venovenous ECMO (VV ECMO) only supports oxygenation and ventilation; venoarterial ECMO (VA ECMO) supports both gas exchange and circulation.
- Common complications of ECMO include mechanical failure of the ECMO circuit and components, cannulation site and visceral bleeding, infection, intracranial hemorrhage, and renal failure.

I. BACKGROUND. Extracorporeal membrane oxygenation (ECMO) is a modified form of cardiopulmonary bypass that can provide gas exchange and circulatory support for neonates with cardiac or respiratory failure unresponsive to conventional medical therapies.

The Extracorporeal Life Support Organization (ELSO), the largest repository of ECMO information worldwide, documents >40,000 ECMO runs used to support neonates for respiratory, cardiac, and extracorporeal cardiopulmonary resuscitation (ECPR) indications, worldwide, from the inception of the registry to 2020 (Tables 39.1 and 39.2). Improved ventilatory strategies and availability of inhaled nitric oxide (iNO) have reduced the use of ECMO for neonatal respiratory failure.

II. ECMO CIRCUIT. The following components are required to provide ECMO support: drainage (venous) and reinfusion (arterial) cannulae, ECMO blood pump (roller or centrifugal), oxygenator, and circuit pressure and flow monitors. Roller pump ECMO circuits require a reservoir (bladder) to collect blood from the venous drainage. Heat exchanger and ultrafiltration systems are optional components. Type of pump and components that make an ECMO circuit vary widely among ECMO programs.

Table 39.1. Outcomes for Neonatal Extracorporeal Membrane Oxygenation by Indication

Neonatal Indication	Total ECMO Runs	Survived ECLS	Survival to Discharge or Transfer
Respiratory	32,634	28,627 (87%)	23,860 (73%)
Cardiac	8,993	6,216 (69%)	3,899 (43%)
ECPR	2080	1,463 (70%)	883 (42%)

ECPR refers to neonatal patients placed emergently on ECMO during cardiopulmonary resuscitation.

ECPR, extracorporeal cardiopulmonary resuscitation; ECLS, extracorporeal life support.

Source: Published by the Extracorporeal Life Support Organization. *Extracorporeal Life Support Organization: ECMO and ECLS*. Ann Arbor, MI: Extracorporeal Life Support Organization; 2020. With permission.

Table 39.2. Neonatal Respiratory Runs by Diagnosis during 2015–2020 from Extracorporeal Life Support Organization (ELSO) Report 2020

Neonatal Categories	Total Runs	Survived to Discharge
MAS	658	91%
CDH	1,331	53%
PPHN/PFC	533	72%
Sepsis	107	51%
RDS	28	85%
Pneumonia	22	45%
Air leak syndrome	5	80%
Other	1,337	71%

MAS, meconium aspiration syndrome; CDH, congenital diaphragmatic hernia; PPHN, persistent pulmonary hypertension of the newborn; PFC, persistent fetal circulation; RDS, respiratory distress syndrome.

Source: Extracorporeal Life Support Organization. *Extracorporeal Life Support Organization: ECMO and ECLS*. Ann Arbor, MI: Extracorporeal Life Support Organization; 2020. Data through July 2020.

III. INDICATIONS AND CONTRAINDICATIONS

A. Respiratory failure. The indications for neonatal ECMO include potentially reversible respiratory failure with a high predicted risk mortality with continuation of conventional support therapies. ECMO can also be considered for patients with life-threatening air leaks not manageable with optimal ventilatory support and chest drainage.

1. **Oxygenation index (OI)** is a commonly used objective measure of the severity of respiratory failure and is calculated as follows: OI = mean airway pressure (MAP) × fraction of inspired oxygen (FiO_2)/arterial partial pressure of oxygen (PaO_2) × 100. It is essential to document OIs from serial blood gases over time because the OI may vary. Although ECMO indications may vary among centers, commonly used criteria include two OIs of >40 within 1 hour, one OI of 60 on high-frequency ventilation, or one OI of 40 combined with cardiovascular instability. Other criteria for ECMO suggested by the ELSO guidelines include (i) acute decompensation with partial pressure of arterial oxygen <40 mm Hg in a patient with hypoxic respiratory failure; (ii) evidence of right ventricle dysfunction in neonates with pulmonary hypertension; or (iii) inadequate oxygen delivery as characterized by rising lactate, metabolic acidosis, or end-organ dysfunction. For neonates hospitalized in centers where ECMO is not available, an OI of 20 should prompt early referral to an ECMO center.
2. Congenital heart disease should be excluded by echocardiography in any newborn with severe hypoxemia (see Chapter 41). In particular, total anomalous pulmonary venous return (TAPVR) can mimic neonatal respiratory distress syndrome (RDS) due to lung congestion from impaired drainage of the pulmonary veins into the left atrium. Reduced pulmonary blood flow in an infant on venoarterial ECMO (VA ECMO) support makes the diagnosis of TAPVR difficult and may require cardiac catheterization to establish or rule out.

B. Cardiac failure. ECMO provides biventricular support for neonates with cardiac failure. Indications are cardiac failure despite maximal hemodynamic support and a potentially reversible underlying condition. ECMO is used to support children with congenital heart disease including for preoperative stabilization, postoperative cardiac failure and pulmonary hypertension, and failure to wean from cardiopulmonary bypass after cardiac surgery. Other cardiac indications for ECMO include neonatal myocarditis, cardiomyopathy, and support for high-risk interventional cardiac catheterization procedure.

C. ECMO to support ECPR. ECMO can be offered in centers with a rapid response ECMO team in the setting of a witnessed cardiorespiratory arrest from a potentially reversible cause. Response times from the arrest to cannulation are ideally <30 minutes. ECPR requires a readily accessible "clear-primed circuit" (primed with crystalloid fluids rather than with blood products) and an ECMO team available 24/7. Effective cardiopulmonary resuscitation (CPR) before cannulation is essential for a favorable outcome.

D. *Ex utero* intrapartum treatment (EXIT) to ECMO procedure. Indications for this procedure include severe airway obstruction from large neck masses or mediastinal tumors, lung tumors, and severe congenital diaphragmatic hernia (CDH), and a multidisciplinary team is required that includes the ECMO team, maternal–fetal medicine specialists, and neonatologist. The vessels are cannulated during a cesarean section while the newborn remains on placental support.

E. Contraindications. ECMO should be offered only for reversible conditions. Contraindications include lethal chromosomal disorders (including trisomy 13 and 18), irreversible preexisting severe brain damage, large intraventricular hemorrhage (IVH) or intraparenchymal hemorrhage, uncontrollable bleeding, and vessels too small for ECMO cannulation. Relative contraindications include weight <2 kg due to cannula size limitations (except for thoracic cannulations), gestational age <34 weeks due to increased risk of IVH, irreversible end-organ failure, severe coagulopathy, progressive chronic lung disease, and continuous CPR for more than an hour or poor-quality CPR before ECMO support.

IV. PHYSIOLOGY

A. ECMO flow. Venous drainage through the drainage ECMO cannula provides preload to the pump. In roller pump ECMO circuits, venous drainage is passive into a reservoir, whereas in centrifugal pumps, negative pressure created by the spinning rotor results in active venous drainage. Cessation of venous drainage (due to cannula malposition, intravascular hypovolemia, cardiac tamponade, or pneumothorax) causes slowing of the pump speed; in roller pump ECMO circuits, this is mediated through a servo mechanism. This prevents negative pressure that may lead to air in the circuit. Excessive negative drainage pressure can also cause hemolysis. Flow is determined by venous return and the ECMO pump speed. In the centrifugal pump ECMO circuits, resistance to pump outflow from high systemic vascular resistance or small arterial cannula may reduce ECMO flow.

B. VA ECMO. VA ECMO supports heart and lung function and is used for primary cardiac failure or respiratory failure with secondary cardiac failure. In VA ECMO, the blood is drained from a central vein (usually the internal jugular vein), oxygenated, and returned to the arterial circulation (common carotid artery). Total cardiac output (CO) is the sum of the native CO and the pump flow generated by the circuit:

$$CO_{total} = CO_{native} + CO_{circuit}.$$

C. Venovenous ECMO (VV ECMO). VV ECMO only supports lung function and is used for isolated respiratory failure. In VV ECMO, blood is drained from a central vein, oxygenated, and returned to the right atrium, allowing native cardiac function to circulate this oxygenated blood to the body. A proportion of oxygenated blood returned to the heart is immediately recirculated back into the ECMO circuit while the rest goes to the right side of the heart, into the pulmonary vascular bed, into the left side

of the heart, and into the systemic circulation. VV ECMO can be used in infants with respiratory failure and hemodynamic instability, when the instability is attributed only to the hypoxemia. In this case, VV ECMO usually rapidly reverses hypoxia and acidosis and improves hemodynamics. VV ECMO avoids accessing the carotid artery and thus is thought to lower the risk of neurologic injury. With venovenous dual-lumen (VVDL) ECMO, a specially designed double-lumen cannula provides drainage and return through the same cannula. VV ECMO requires that the internal jugular vein is large enough to accommodate a 12-French double-lumen cannula. When hypotension, metabolic acidosis, or cardiac failure persists on VV ECMO support, converting to VA ECMO is considered. Conversion to VA ECMO may also be needed if technical difficulties result in significant recirculation in the venous cannula.

D. Oxygen delivery. Oxygen delivery is the product of CO and arterial oxygen content. Arterial oxygen content is determined by the gas exchange in the membrane oxygenator, gas exchange from the neonate's lung, and hemoglobin level.

E. Carbon dioxide (CO_2) removal. CO_2 removal is achieved by the membrane of the ECMO circuit and the patient's lung. The amount of CO_2 removed depends on the arterial partial pressure of CO_2 ($PaCO_2$) of blood circulating through the membrane, the surface area of the membrane, and the gas flow through the membrane lung ("sweep gas flow"). ECMO settings are adjusted as physiologic pulmonary function and tidal volume improve and the $PaCO_2$ decreases. CO_2 removal is extremely efficient during ECMO, so that additional CO_2 may need to be added to the circuit to prevent hypocarbia and respiratory alkalosis.

F. Cerebral perfusion. Initiation of VA ECMO rapidly restores cerebral perfusion due to shock, although the large-bore cannulas placed in internal jugular vein and common carotid artery for ECMO can impair cerebral venous drainage and arterial perfusion to the brain. Collateral circulation through the circle of Willis generally maintains cerebral blood flow to both sides of the brain. The carotid artery is frequently ligated after decannulation from ECMO and, although is sometimes reconstructed, does not appear to impact neurologic outcome.

G. Renal perfusion. During VA ECMO, CO is largely from nonpulsatile flow into the patient from the ECMO circuit. Animal models suggest that renal perfusion is similar during VA ECMO and VV ECMO. However, unclamping the bridge during VA ECMO directs flow away from the patient and may be associated with decreased blood pressure and renal and cerebral perfusion.

V. MANAGEMENT

A. Pre-ECMO. In preparation for cannulation, the following should be available: central venous access; arterial catheter for monitoring; ECMO equipment; cross-matched blood and blood products; intravenous fluids; and medications for intravenous administration including sedatives, heparin,

antibiotics, resuscitation medications, and inotrope infusions. Initial laboratory evaluation includes complete blood count, electrolyte and coagulation profile, renal and liver function tests, and head ultrasound examination. An echocardiogram is obtained before ECMO to rule out structural cardiac abnormalities. An ECMO team including neonatologist, cannulating surgeon, nurses, and ECMO specialist is assembled, and team member roles and responsibilities are assigned.

B. Membrane. An appropriate neonatal-sized membrane is used. A widely used membrane is a hollow fiber polymethylpentene oxygenator. The total volume of a neonatal ECMO circuit is 600 mL.

C. ECMO priming. Patients placed on ECMO emergently can be started on a crystalloid solution-primed circuit instead of priming with blood and blood products. In this case, the crystalloid solution from the ECMO circuit dilutes the neonate's blood volume after deployment and causes a decrease in hematocrit and oxygen-carrying capacity. The hematocrit is later restored by using ultrafiltration and packed red blood cell (PRBC) transfusion.

D. Blood priming. For nonemergent ECMO, a blood primed circuit is used. Components for blood priming a roller pump neonatal circuit are 500 mL of PRBC (cytomegalovirus [CMV] negative, <7 days old), 200 mL of fresh frozen plasma (FFP), 2 units of cryoprecipitate, and 2 units of platelets (not concentrated). Heparin, sodium bicarbonate, and calcium gluconate are added to the circuit. Once the circuit is fully primed, the following laboratory measurements (target ranges in parentheses) are obtained from the circuit before connecting the patient: pH (7.35 to 7.45), PCO_2 (35 to 45 mm Hg), PO_2 (>300 mm Hg), HCO_3 (22 to 24 mEq/L), Na^+ (>125 mEq/L), K^+ (<8 mEq/L), and ionized Ca^{++} (>0.8 mEq/L). Hyperkalemia of the ECMO circuit is treated with calcium and bicarbonate administration into the circuit.

E. Cannulation. The ECMO cannulation is performed by cardiac or pediatric surgeons at the bedside, in the cardiac catheterization laboratory, or in the operating room. Cannulation can be performed either by a cutdown approach or percutaneous technique. Ultrasound can guide access to the vessels for percutaneous cannulation, and wire confirmation can be obtained by either echocardiography or fluoroscopy prior to vessel dilation and cannula insertion. The infant is anesthetized and muscle relaxed for the cannulation, and heparin 50 to 100 units/kg is administered before cannulation. Appropriate cannula sizes are as follows: for the venous side, 8- to 14-French cannula, and for the arterial side, 8- to 10-French or a 12- to 16-French VVDL cannula. Generally, the vein is cannulated first followed by the artery, after which ECMO can start. Once the patient is on ECMO, we confirm that both venous and arterial cannula are in good position by chest x-ray and give 2 units of platelets and 2 units of cryoprecipitate.

F. On **initiation of ECMO**, the neonate may become markedly hypertensive. As hypertension and anticoagulation are significant risk factors for intracranial hemorrhage, prompt recognition and treatment of hypertension

is essential. Hydralazine 0.1 to 0.4 mg/kg per dose or sodium nitroprusside infusion can be used to treat hypertension.

G. ECMO therapy. ECMO pump flow rate is generally 100 to 150 mL/kg/minute in newborns. Sweep gas flow rate is adjusted based on arterial blood gases. A safety check is conducted every 4 hours. This safety check includes searching for blood clots and circuit inspection for leaks. Normothermia is maintained, and temperature is regulated by adjustments in the heat exchanger water temperature. The following laboratory studies are used for monitoring: (i) coagulation tests (activated clotting time [ACT]), activated partial thromboplastin time (aPTT), or anti-factor Xa activity; (ii) lactate levels; (iii) complete blood count, platelets, whole blood electrolytes, ionized calcium, and creatinine; (iv) antithrombin III (AT III); and (v) liver function tests, alkaline phosphatase, lactate dehydrogenase (LDH), bilirubin, albumin, prealbumin, and total protein.

H. Blood gas monitoring. Arterial blood gas targets are PaO_2 >60 mm Hg and $PaCO_2$ 40 to 45 mm Hg. If PaO_2 is <60 mm Hg, the sweep gas to the ECMO membrane can be increased. If the fraction of delivered oxygen (FDO_2) is already maximized at 1.0, increasing the ECMO pump flow rate or increasing the patient's hematocrit may be helpful to increase oxygen delivery. On VV ECMO, it may be necessary to increase the ventilator settings to assist with oxygenation and ventilation.

I. Anticoagulation. Anticoagulation is used in all patients to prevent clot formation. Heparin is the most widely used anticoagulant, although testing and management approaches vary among centers. Each ECMO program should develop and use an anticoagulation management policy to provide safe and effective anticoagulation for ECMO patients. If heparin-induced thrombocytopenia (HIT) is confirmed, a synthetic direct thrombin inhibitor (argatroban or bivalirudin) can be used as an alternative anticoagulant during ECMO.

J. Blood products. We maintain prothrombin time (PT) at <17 seconds. If PT is >17 seconds, we administer FFP at a dose of 20 mL/kg. Fibrinogen levels are kept >100 mg/dL; for levels <100 mg/dL, we administer 1 to 2 units per 10 kg cryoprecipitate. We maintain platelet count >100,000 with platelet transfusion. We keep the hematocrit >35% to facilitate oxygen delivery.

K. Bleeding management. Cannulation site, surgical, and visceral bleeding are common in ECMO patients and may require surgical management. Coagulation abnormalities should be promptly identified and corrected. Anticoagulant use can be paused until bleeding is controlled. ε-Aminocaproic acid (Amicar) lowers the incidence of hemorrhagic complications associated with ECMO, including intracranial and postoperative hemorrhage. Adverse effects include increased clot formation in the circuit. Patients considered to be at high risk for bleeding complications are those who are <37 weeks' gestational age or who have had sepsis, prolonged hypoxia, or acidosis (pH 7.1) before ECMO, or grade 1 or 2 IVH. These infants can be given prophylactic Amicar as a loading dose (100 mg/kg) followed by a 30 mg/kg/hour infusion. We assess the patient for continued risk of

bleeding complications after 72 hours of Amicar and continue treatment if these risks still exist. Postoperative hemorrhage or bleeding from surgical sites should be managed by the surgical team. Factor VII at 90 μg/kg can be used in the setting of severe bleeding. A standby primed ECMO circuit should be readily available when anticoagulation is paused or when Amicar or factor VII is administered because of the risk of clot formation within the ECMO circuit.

L. Antibiotics. We routinely administer prophylactic antibiotics to lower the risk of infection while on ECMO therapy. Infections occur in about 5% of all ECMO runs.

M. Analgesia and sedation. Patients are sedated with an opioid/benzodiazepine combination. We typically use morphine and midazolam infusions, initiated at 0.05 mg/kg/hour and titrated to achieve the desired analgesia and sedation. Fentanyl can be used during cannulation but should not be used during ECMO because the ECMO membrane absorbs fentanyl, leading to suboptimal analgesia.

N. Fluids and nutrition. Dextrose and amino acid solution (parenteral nutrition) can be administered through the circuit. Lipid should be administered directly to the patient and not through the circuit and should not exceed 1 g/kg/day to prevent lipid accumulation and embolism in the circuit.

O. Ultrafiltration. Ultrafiltration is considered for urine output of $<$0.5 mL/kg/hour, positive fluid balance $>$500 mL per 24 hours, and failed diuretic therapy and can also be used to remove volume following blood product transfusion. The goal is to normalize fluid balance in patients who have excessive positive fluid balance by placing an ultrafilter in line with the ECMO circuit.

P. Head imaging. Head ultrasound examinations are performed before ECMO, if possible, and serially during the ECMO run. Electroencephalograms are performed when seizure activity is suspected. A magnetic resonance imaging (MRI) of the brain can be considered after the ECMO run is completed.

Q. Ventilator strategy. The ventilator strategy on VA ECMO is a lung protective strategy with the goals to maintain functional residual capacity (FRC) and reduce ventilator-induced lung injury. Centers vary in approach but focus on settings that limit volutrauma, barotrauma, atelectrauma, and oxygen toxicity. General guidelines include limiting peak inspiratory pressure (PIP) to 15 to 20 cm H_2O, maintaining stable positive end-expiratory pressure (PEEP) (5 to 10 cm H_2O), lowering respiratory rate, limiting FiO_2 to $<$0.4, and keeping inspiratory time to 0.5 to 1 second. On VV ECMO, ventilator settings are adjusted to achieve adequate gas exchange because the patient's own lungs contribute to oxygenation and ventilation.

Endotracheal suctioning is performed routinely. Signs of improving lung function during ECMO include (i) better gas exchange, (ii) gradual resolution of pulmonary edema on chest radiographs, and (iii) improved lung mechanics and increased expired tidal volumes as pulmonary edema resolves.

R. Weaning and cycling. Weaning from VA ECMO involves gradually reducing the ECMO support and evaluating hemodynamics and gas exchange accomplished by native heart and lung function. Ventilator settings are increased, and sweep gas flow is reduced; the flow of the ECMO pump is weaned to 100 mL/minute in 10 to 20 mL decrements. Mixed venous oxygen saturation (SVO_2) is monitored, and serial arterial blood gases and lactate levels are obtained to assess tolerance to weaning. "Cycling" means transiently removing the patient from the ECMO circuit. In VA ECMO, the venous and arterial cannulas are clamped, the bridge is opened, and the ECMO blood flow "cycles" from the arterial to the venous side through the bridge, without perfusing the patient. In VV ECMO, the ventilator settings are increased above the resting settings and the sweep gas flow is interrupted ("capped") while the circuit continues to flow.

S. Decannulation. When the patient's heart or lung disease has improved enough to tolerate minimal inotropic support or moderate ventilator settings, we consider decannulation. For patients with primary respiratory failure, our criteria for decannulation are PIP <30 cm H_2O; PEEP 5 cm H_2O; respiratory rate 25 breaths per minute; $FiO_2 = 0.4$; PaO_2 >60 mm Hg; $PaCO_2$ 40 to 50 mm Hg; and pH <7.5. At the time of decannulation from VA ECMO, the common carotid artery and jugular vein are ligated.

We consider discontinuation of ECMO support for lack of recovery when the disease process becomes irreversible or when there is uncontrollable bleeding, neurologic event (devastating neurologic examination, significant intracranial hemorrhage), or multiorgan system failure.

VI. SPECIAL SITUATIONS DURING EXTRACORPOREAL MEMBRANE OXYGENATION SUPPORT

A. ECMO-circuit change. We consider changing the entire ECMO circuit in the following circumstances: (i) premembrane pressures exceed 350 mm Hg with no change in postmembrane pressure, or the circuit is extensively thrombosed by visual inspection of the tubing; (ii) CO_2 removal is impaired despite maximum sweep gas flow rate and the circuit is extensively clotted; (iii) there is a gas-to-blood leak; and (iv) there is extensive platelet consumption. A new ECMO circuit may help to correct a persistent coagulopathy or platelet consumption. If a circuit needs to be changed, a new circuit is primed, the patient is cycled off ECMO, the old circuit is cut away, and the new circuit is connected, with care taken to keep air out of the system and to maintain strict sterile barriers. Patient hemodynamics and gas exchange are managed conventionally for the brief period of time off ECMO.

B. Lung biopsy. Irreversible causes of respiratory failure such as alveolar capillary dysplasia (ACD) or other forms of pulmonary hypoplasia are usually not known prior to ECMO support. If pulmonary function does not improve after a prolonged period (usually 1 to 2 weeks of ECMO support),

a lung biopsy can be performed through a thoracotomy. Lung biopsy during ECMO and anticoagulation carries a significant risk of hemorrhage and should be performed by an experienced pediatric surgical team.

C. Left-sided heart failure and left atrial decompression. If left ventricular contractility is severely impaired, arterial blood will not be ejected through the left ventricular outflow tract, leading to an increase in both left ventricular end-diastolic pressure and left atrial pressures. This may lead to significant pulmonary edema from left atrial hypertension and to intravascular and intracardiac thrombosis secondary to stasis. In this circumstance, the left atrium may have to be decompressed ("vented") into the venous side of the ECMO circuit. This is achieved either by creating an atrial septostomy in the cardiac catheterization lab or, if the patient is already cannulated through the open chest, by inserting a cannula directly into the left atrium through the pulmonary vein.

VII. COMPLICATIONS

A. Mechanical. Common mechanical problems include clots in the circuit (most common in oxygenator, bladder, and bridge), cannula problems, oxygenator failure, and air in the circuit. Rupture of tubing is a rare but potentially significant problem. Poor venous return to the circuit causes the pump to slow or shut down. Causes for poor venous return from the patient to the ECMO circuit include hypovolemia, pneumothorax, or tamponade physiology. Mechanical reasons for poor venous return related to the ECMO circuit are poor catheter position, small venous catheter diameter, excessive tubing length, kinked tubing, and insufficient hydrostatic column length (height of patient above pump head). Initially, fluids are administered while other reasons for poor return are ruled out.

B. Cardiovascular. Hemodynamic instability during ECMO may be a result of hypovolemia, vasodilation during septic inflammatory response, arrhythmias, and pulmonary embolism. Volume overload, especially in the setting of capillary leak, may worsen chest wall compliance and further compromise gas exchange. Both hypotension and hypertension can occur during neonatal ECMO and require vasoactive support to optimize blood pressure.

C. Neurologic. Sequelae resulting in neurologic damage often originate from acidosis and hypoxia before commencement of ECMO. Small intracranial hemorrhages are managed by optimizing clotting factors and using Amicar. Larger intracranial hemorrhages may force discontinuation of anticoagulation or ECMO support. Clinical seizures are also common, occurring in 9% of neonates on ECMO and may require investigation with electroencephalography (EEG), consultation with neurology, and medical management.

D. Renal. Renal failure may warrant dialysis, and fluid overload may require hemofiltration during the ECMO run. According to ELSO registry data, hemofiltration was used in 16% of all neonatal ECMO runs.

VIII. OUTCOME

A. Survival. The 2020 International Summary Extracorporeal Life Support registry of the ELSO reported a total of 32,634 ECMO runs (84% survival) worldwide for neonatal respiratory support. Common indications for ECMO included CDH, persistent pulmonary hypertension of the newborn (PPHN), meconium aspiration syndrome (MAS), sepsis, and neonatal RDS (see Table 39.2).

B. Neurodevelopment. Neurodevelopment was assessed 7 years after completion of the U.K. Collaborative ECMO trial. Although both the ECMO and conventional therapy groups had developmental problems and impaired neurologic outcome, the ECMO group performed better in each task. Both groups had progressive sensorineural hearing loss and difficulties with learning and processing. Cognitive skills were not different, with cognitive level within the normal range for 76% of the children in each group. Among the survivors, 55% in the ECMO group and 50% in the conventional group were without disabilities. This study suggests that the underlying disease is the major influence on morbidity and that the beneficial effect of ECMO persists after 7 years. Neonates surviving to hospital discharge following ECMO support require long-term neurodevelopmental follow-up.

Suggested Readings

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40 Shock

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KEY POINTS

- Shock remains an important cause of neonatal mortality and morbidity.
- Early diagnosis and recognition of the underlying pathophysiology are key to successful management.
- Shock in neonates may be due to lower vascular tone (distributive shock), inadequate blood volume (hypovolemic shock), decreased cardiac function (cardiogenic shock), restricted blood flow (obstructive shock), and inadequate oxygen delivery (dissociative shock).
- Treatment for shock involves addressing the underlying etiology and managing its cardiovascular and systemic effects. Fluids, inotropes, vasopressors, and hydrocortisone replacement are used to treat neonatal shock.

I. DEFINITION. Shock is defined as acute circulatory dysfunction resulting in an imbalance between tissue oxygen and nutrient delivery and oxygen demand, leading to tissue hypoxia and cellular dysfunction. Shock remains an important cause of neonatal mortality and morbidity. Its prognosis depends on the duration and severity and the extent of vital organ damage. Shock can lead to long-term morbidity including severe neurologic compromise due to cerebral ischemia and reperfusion injury. Therefore, recognizing shock promptly and initiating a goal-targeted therapy that addresses its underlying pathophysiology and maintains hemodynamic stability are essential. In the extremely premature newborn, the lowest acceptable blood pressure (BP) that may be associated with end-organ damage is not well established; therefore, the appropriate time for intervention remains controversial.

II. PATHOPHYSIOLOGY OF NEONATAL SHOCK. Myocardial dysfunction, abnormal peripheral vasoregulation and hypovolemia are often the primary underlying pathophysiologic processes of neonatal shock. This is often complicated by relative adrenal insufficiency commonly seen in premature infants.

The neonatal myocardium has fewer contractile elements and more connective tissue compared to older children. Therefore, is highly sensitive to changes in afterload.

Pathophysiology of shock in newborns is unique because it overlaps with the physiologic transition and hemodynamic changes from fetal circulation to neonatal circulation at birth. Suprasystemic pulmonary vascular resistance (PVR) may remain elevated, especially in the presence of ongoing hypoxia and acidosis from sepsis, leading to persistent pulmonary hypertension (PPHN).

In addition to PPHN, neonatal shock may be associated with closure of the ductus arteriosus in a ductal-dependent congenital heart lesion, requiring prostaglandin infusion to open and maintain patency of the ductus arteriosus (PDA).

Evidence suggests low cortisol levels in sick term, late-preterm, and preterm infants. Adrenal insufficiency and decreased vascular responsiveness to catecholamines can contribute to vasopressor resistant shock. Low-dose steroids have been found to improve cardiovascular status in infants with vasopressor resistant shock, further supporting the role of relative adrenal insufficiency.

III. ETIOLOGY.

Shock in neonates may be due to lower vascular tone (distributive shock), inadequate blood volume (hypovolemic shock), decreased cardiac function (cardiogenic shock), restricted blood flow (obstructive shock), and inadequate oxygen delivery/releasing capacity (dissociative shock). Distributive shock, with or without myocardial dysfunction, is the most frequent cause of hypotension, especially in preterm infants.

A. Distributive shock. Changes in vascular tone in neonates can result in decreased flow to tissues due to the following:

1. Impaired vasoregulation from increased or dysregulated endothelial nitric oxide (NO) production in the perinatal transitional period, particularly in the preterm neonate
2. Neurologic injury such as in patients with severe perinatal asphyxia which may affect neurovascular pathways
3. Sepsis-related release of proinflammatory cascades that lead to vasodilation
4. Anaphylactic shock is more common in children and rarely affects neonates.

B. Hypovolemic shock. The following conditions can reduce circulating blood volume:

1. Placental hemorrhage, as in abruptio placentae or placenta previa
2. Fetal-to-maternal hemorrhage
3. Twin-to-twin transfusion
4. Intracranial hemorrhage
5. Massive pulmonary hemorrhage (often associated with PDA)
6. Blood loss due to disseminated intravascular coagulation (DIC) or other severe coagulopathies
7. Plasma leak into the extravascular compartment, as seen with low oncotic pressure states or capillary leak syndrome (e.g., sepsis)
8. Dehydration due to excessive insensible water loss or inappropriate diuresis as commonly observed in extremely low birth weight (ELBW) infants

C. Cardiogenic shock due to myocardial dysfunction. Decreased cardiac output either due to poor myocardial function or diverted flow through accessory channels results in cardiogenic shock. Some common causes of neonatal cardiogenic shock include the following:

1. Congenital heart disease
2. Post-PDA ligation syndrome
3. Intrapartum asphyxia leading to myocardial depression
4. Bacterial or viral myocarditis. Congenital viral infections such as enterovirus are more likely to cause severe myocarditis.
5. Fetal or neonatal arrhythmias compromising cardiac output
6. Large arteriovenous malformations (AVMs) such as an intracranial AVM that divert a considerable amount of cardiac output away from the systemic circulation
7. Metabolic abnormalities (e.g., hypoglycemia) or cardiomyopathy seen in infants of diabetic mothers

D. Obstructive shock. Restricted venous inflow or arterial outflow will rapidly decrease cardiac output and lead to profound shock. Types of obstructions to blood flow include the following:

1. **Venous obstructions**
   - **a.** Cardiac anomalies including total anomalous pulmonary venous return, cor triatriatum, tricuspid atresia, mitral atresia
   - **b.** Acquired inflow obstructions can occur from intravascular air or thrombotic embolus.
   - **c.** Increased intrathoracic pressure caused by high airway pressures, pneumothorax, pneumomediastinum
   - **d.** Cardiac tamponade due to pericardial effusion or pneumopericardium
2. **Arterial obstructions**
   - **a.** Cardiac anomalies including pulmonary stenosis or atresia, aortic stenosis or atresia
   - **b.** Vascular anomalies such as coarctation of the aorta or interrupted aortic arch
   - **c.** Hypertrophic subaortic stenosis due to ventricular hypertrophy seen in infants of diabetic mothers with compromised left ventricular (LV) outflow
   - **d.** PPHN leading to decreased pulmonary flow due to high PVR

E. Dissociative shock. Caused by inadequate oxygen delivery or inadequate oxygen-releasing capacity

1. Severe anemia
2. Methemoglobinemia

IV. DIAGNOSIS

At the onset of shock, the initial "compensated phase" is characterized by compensatory mechanisms that increase tissue oxygen extraction, leading to maintenance of adequate BP by diverting blood away from the skin, muscles, and other nonessential organs. This compensation allows BP

to remain within the normal range and maintain perfusion to vital organs. During compensated shock, clinical findings may be subtle and difficult to identify. These infants have decreased systemic blood flow but a normal BP due to a transient increase in systemic vascular resistance (SVR). They have decreased peripheral perfusion (cold, pale skin with delayed capillary refill), tachycardia to maintain cardiac output, weak peripheral pulses and narrow pulse pressure (raised diastolic BP), ileus (decreased splanchnic circulation), and oliguria (decreased renal perfusion). If the clinical condition that results in shock remains unabated or if the underlying etiology is severe (e.g., sudden tension pneumothorax), compensatory mechanisms are usually insufficient to maintain BP and systemic hypotension ensues. The "uncompensated phase" of shock is characterized by hypotension and decreased perfusion to vital organs which may be evident by the development of lactic acidosis. Lack of perfusion to the brain may cause changes in consciousness and lethargy. Lack of coronary perfusion increases the risk of cardiac arrest. In preterm infants, the associated decrease in brain blood flow and oxygen supply during hypotension predisposes to intraventricular/cerebral hemorrhages and periventricular leukomalacia with long-term neurodevelopmental disability. In addition, in ELBW infants, the vasculature of the cerebral cortex may respond to transient myocardial dysfunction/shock with vasoconstriction rather than vasodilatation, further diminishing cerebral perfusion and increasing the risk of neurologic injury.

The physiologic response to increased SVR is altered in septic shock with the release of inflammatory mediators causing vasodilation and increased capillary permeability. In such cases, hypotension and wide pulse pressure is an early indicator of shock.

Monitoring vital signs and indicators of organ dysfunction may be helpful in diagnosing and monitoring shock, but the initiation of treatment should not be delayed. Conventional parameters commonly used in clinical practice are capillary refill time, urine output, heart rate, presence of lactic acidosis, mixed venous saturation, and arteriovenous oxygen difference. These clinical signs are subjective and nonspecific. Even if their predictive values, which are poor at baseline, improved by combining one or more variables, they are still unable to provide physiologic details. Invasive BP monitoring can offer continuous real-time assessment of cardiovascular well-being. However, lack of consensus definition of hypotension in neonates continues to be a major barrier for such assessment and does not represent an accurate measure of tissue perfusion. The relation between BP and systemic blood flow is complex in the very low birth weight (VLBW) infant, especially in the first few days of life. Autoregulation ensures adequate perfusion to vital organs in states of hypoperfusion. However, cerebral autoregulation may be lacking in the VLBW infants transitionally at birth or during period of illness. Unlike adults and pediatric patients, shock in newborn infants is often recognized in the uncompensated phase by the presence of hypotension, which may be too late. Uncompensated shock results in inadequate oxygen delivery to the tissues so that cellular metabolism becomes predominantly anaerobic, producing lactic and pyruvic acid. Hence, metabolic acidosis often indicates inadequate circulation.

Investigations should focus on identifying the underlying etiology of shock based on clinical and physiologic findings. The routine methods of evaluation used in the adult and pediatric populations are often invasive and not

feasible in neonates. Therefore, the importance of noninvasive technologies for hemodynamic monitoring in neonates. Such evaluations may include bedside focused echocardiography to assess cardiac function and loading conditions (preload and afterload) and cardiac output as well as appropriate laboratory studies to evaluate the presence of infection, anemia, dehydration, etc. Flow in the superior vena cava (SVC) provides an excellent assessment of the blood flow to the upper body and has been used to assess response to therapeutic interventions to reverse shock.

Other noninvasive technologies to assess cardiac output in neonates such as electrical cardiometry, bioimpedance, and the ultrasonic cardiac output monitor (USCOM) are useful tools for trending and longitudinal assessments purposes.

Near-infrared spectroscopy (NIRS) may help with assessing the peripheral perfusion and cerebral oxygenation. Although the utilization of this device in the management of shock has not been studied extensively in neonates, it is used quite commonly in postoperative cardiac patients to measure adequate oxygen delivery, end-organ perfusion, and response to therapeutic interventions. Clinical applicability still rests with trend monitoring rather than absolute numbers. There remains paucity of data in preterm and term infants when interventions should be warranted based on NIRS. Moreover, NIRS has not been yet associated with improved short- or long-term outcomes in the neonatal population.

V. TREATMENT. Treatment for shock involves addressing the underlying etiology; instituting goal-oriented, time-sensitive interventions; and managing its cardiovascular and systemic effects. Neonatal cardiovascular physiology is complex and dynamic. The definite goal is to restore blood flow and oxygen delivery to tissues. Fluids, inotropes, vasopressors, and hydrocortisone replacement are used to treat shock in neonates.

A. Fluid therapy. The initial approach is usually to administer crystalloids such as normal saline. An infusion of 10 to 20 mL/kg of isotonic saline solution is used to treat suspected hypovolemia. If the shock is due to anemia with or without blood loss, then red blood cell transfusions or fresh frozen plasma for DIC may be better alternatives to normal saline. Use of albumin solutions has been proposed as an alternative to normal saline infusion as they may improve intravascular oncotic pressures, but there is no evidence that they are superior to normal saline and is currently not recommended. In contrast to outcomes with early aggressive fluid resuscitation in older populations, there is insufficient evidence to support early volume expansion in VLBW infants. In hypotensive preterm neonates, it is recommended that a slow and single bolus of saline is given and, if further intervention is necessary, to begin vasoactive medications. The neonatal literature is limited to small studies. Moderate increase in both SVC flow and LV output have been shown in neonates with low systemic blood flow.

B. Supportive treatment. Correction of negative inotropic factors such as hypoxia, acidosis, hypoglycemia, and other metabolic derangements will improve cardiac output. In addition, hypocalcemia frequently occurs in infants with circulatory failure, especially in settings of large amounts of

volume replacement. In this setting, administration of calcium frequently produces a positive inotropic effect. Calcium gluconate 10% (100 mg/kg) can be infused slowly if ionized calcium levels are low.

C. Medications

1. **Inotropes** are used to improve cardiac function and include the following:
   a. Sympathomimetic amines are commonly used in infants. The advantages include rapidity of onset, ability to control dosage, and ultrashort half-life.
      i. **Dopamine** activates receptors in a dose-dependent manner and its effects on PVR should be considered. At low doses (0.5 to 2 μg/kg/minute), dopamine stimulates peripheral dopamine receptors and increases renal, mesenteric, and coronary blood flow with little effect on cardiac output. In intermediate doses (5 to 9 μg/kg/minute), dopamine has positive inotropic and chronotropic effects increasing both LV output and mean arterial pressure. The increase in myocardial contractility may depend in part on myocardial norepinephrine stores.
      ii. **Dobutamine** is a synthetic catecholamine with relatively cardioselective inotropic effects. In doses of 5 to 15 μg/kg/minute, dobutamine increases cardiac output by increasing stroke volume in a dose-dependent fashion with little effect on heart rate. Dobutamine can decrease SVR and is often used with dopamine to improve cardiac output and SVR in cases of decreased myocardial function as its inotropic effects, unlike those of dopamine, are independent of norepinephrine stores. In a randomized blinded trial, SVC flow was increased by 35% in preterm neonates receiving dobutamine as compared to a 1% decrease in neonates treated with dopamine.
      iii. **Epinephrine** has potent inotropic and chronotropic effects in the 0.05 to 0.3 μg/kg/minute doses. At these doses, it increases cardiac output and has β2-adrenergic effects in the peripheral vasculature with little α-adrenergic effect resulting in lower SVR. It is not a first-line drug in newborns; however, it may be effective in patients who do not respond to dopamine. Epinephrine is an effective adjunct therapy to dopamine because cardiac norepinephrine stores are readily depleted with prolonged and high-rate dopamine infusions.
   b. Milrinone is a phosphodiesterase-III inhibitor that enhances intracellular cyclic adenosine monophosphate (cAMP) content preferentially in the myocardium leading to increase in cardiac contractility. It improves diastolic myocardial function more readily than dobutamine. Milrinone also lowers PVR and SVR by increasing cAMP levels in vascular smooth muscle often necessitating the use of volume and dopamine.
2. **Vasopressor therapy** is used to increase SVR and improve BP which should restore perfusion to vital organs. Such medications include the following:
   a. Dopamine in high doses (10 to 20 μg/kg/minute) causes vasoconstriction by releasing norepinephrine from sympathetic vesicles as well as acting directly on α-adrenergic receptors. Neonates have reduced

releasable stores of norepinephrine. Dopamine-resistant shock commonly responds to norepinephrine or high-dose epinephrine. Norepinephrine may be the preferred agent in shock associated with low SVR.

b. Norepinephrine. A potent α-agonist with some β1 effects; the first-line agent in adult and pediatric vasodilatory (warm) shock

c. Vasopressin has primarily been studied in adults for the treatment of shock, with limited experience in neonates. It is an endogenous neuropeptide involved in the postnatal regulation of fluid homeostasis but also plays a significant role in maintaining vascular tone. Vasopressin deficiency may occur in catecholamine-resistant hypotension in the evolution of sepsis and hence its reported efficacy in vasodilatory shock. There is insufficient data for the use of vasopressin in neonates. It is not routinely used to treat shock in infants but may be a therapeutic option to consider in the setting of abnormal peripheral vasoregulation.

3. **Hydrocortisone replacement.** Corticosteroids may be useful in infants with hypotension refractory to volume expansion and vasopressors, especially among premature infants. Hydrocortisone stabilizes BP through multiple mechanisms. It induces the expression of the cardiovascular adrenergic receptors that are downregulated by prolonged use of sympathomimetic agents and also inhibits catecholamine metabolism. After hydrocortisone administration, there is a rapid increase in intracellular calcium availability, resulting in enhanced responsiveness to adrenergic agents. The BP response is evident as early as 2 hours after hydrocortisone treatment. For refractory hypotension, hydrocortisone can be used at a dose of 2 to 4 mg/kg/day. If efficacy is noted, the dose can be repeated every 6 to 8 hours for 2 to 5 days. Occasionally, hypotension will recur after stopping corticosteroid therapy, requiring a longer duration of therapy with a slow dosage wean.

VI. TYPICAL CLINICAL SCENARIOS OF SHOCK IN NEONATES

A. VLBW neonate in the immediate postnatal period

1. Physiology includes poor vasomotor tone, immature myocardium that is more sensitive to changes in afterload, and dysregulated NO production.
2. What level of BP defines hypotension in the VLBW infants remains unknown. In general, a mean BP that equals the baby's gestational age in weeks is the definition most widely used but unfortunately is the one with the least amount of supportive evidence.
3. Recommended therapy is dobutamine or dopamine and judicious use of volume if hypovolemia is suspected. It is important not to give large-volume infusions due to their association with increased risk of bronchopulmonary dysplasia and intraventricular hemorrhage reported in premature infants. Hydrocortisone may be considered for dopamine-resistant hypotension.

B. Perinatal hypoxic-ischemic injury in full-term neonates

1. Physiology results in transient myocardial ischemia with decreased LV systolic performance.

2. Therapeutic hypothermia increases SVR/afterload by peripheral vasoconstriction.
3. The recommended cardiovascular agent should improve cardiac contractility without further exacerbating vasoconstriction. Dobutamine is usually the preferred agent.
4. Milrinone can be considered to provide afterload reduction and inotropic effects.

C. Septic shock

1. Physiology involves relative hypovolemia, myocardial dysfunction, peripheral vasodilation, and increased pulmonary pressures secondary to acidosis and hypoxia.
2. There is a strong inverse relationship between the incidence of sepsis and both gestational age and birth weight.
3. Therapy includes volume resuscitation with crystalloid (10 to 20 mL/kg) which should be repeated as needed and administration of dopamine, norepinephrine, or vasopressin. A functional echocardiogram should be obtained for hemodynamic assessment to evaluate cardiac function, SVC flow, cardiac output, and intracardiac shunting. Consider extracorporeal membrane oxygenation (ECMO) in infants >34 weeks' gestation if they do not respond to these interventions.

D. Preterm neonate with patent ductus arteriosus

1. Physiology includes ductal "steal" compromising vital organ perfusion and increase in left-to-right shunt as PVR declines. The high volume of pulmonary venous return to the left heart may not be tolerated. The inability of the immature LV to increase its force of contraction may lead to a decrease in cardiac output, increase in venous pressure, and, therefore, increased risk of pulmonary hemorrhage.
2. Typically it presents with low diastolic BP and normal or elevated systolic BP.
3. Recommended therapy should be targeted to augment LV systolic performance without increase in SVR. Dobutamine seems preferable than dopamine for these reasons. However, no randomized clinical trials comparing these two treatment strategies have been yet performed in premature infants. Ventilatory strategies to increase PVR by increasing positive end-expiratory pressure (PEEP), maintaining permissive hypercarbia, and avoiding hyperoxygenation may contribute to hemodynamic stability until a definitive therapy is achieved.

E. Preterm neonates with "pressor-resistant" hypotension

1. A proportion of VLBW infants become dependent on medium to high doses of vasopressors beyond the first postnatal days. Etiologies include relative cortisol deficiency, adrenal insufficiency, and downregulation of adrenergic receptors.
2. Consider low-dose hydrocortisone (2 to 4 mg/kg/day for 2 to 5 days in three to four divided doses); some centers routinely measure a serum cortisol level prior to treatment, but there is poor correlation with

cortisol levels and the degree of hypotension in VLBW infants. Studies support the efficacy of hydrocortisone in raising BP within 2 hours of administration, yet the long-term neurologic effects of this treatment in the VLBW infant remain to be investigated. Due to a published report of possible increased incidence of intestinal perforation in infants who have been treated with indomethacin who are also treated with hydrocortisone, the concurrent use of these drugs cannot be recommended.

Suggested Readings

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41 Cardiac Disorders

Felina K. Mille and Chitra Ravishankar

KEY POINTS

- The incidence of congenital heart disease is 0.6% to 0.8% of all live births.
- If not diagnosed prenatally, patients with critical congenital heart lesions present in the newborn period.
- Prompt recognition and treatment of critical congenital heart disease can be lifesaving.

I. INTRODUCTION. Outcomes for patients with congenital heart disease have improved significantly over the last several decades. Advancements in echocardiography, medical therapy, interventional cardiology, and surgical management have yielded reduced morbidity and mortality, even for children with the most complex heart lesions. Today, many patients with significant congenital heart disease are identified prenatally. A subset of prenatally diagnosed patients and those who are identified postnatally remain at risk for significant instability, end-organ injury, and death. Thus, early recognition and stabilization of the neonate with critical congenital heart disease is essential. This chapter is an overview of the initial evaluation and management, by neonatologists and pediatricians, of neonates and infants suspected of having congenital heart disease.

II. INCIDENCE AND SURVIVAL. The reported incidence of congenital heart defects varies between 0.6% and 0.8% of live births, resulting in nearly 40,000 infants born with congenital heart disease each year in the United States alone. This incidence has remained constant over the past several decades. Approximately 25% of congenital heart defects are considered critical, or requiring intervention in the first year of life. These, along with their relative incidence, are summarized in Table 41.1. Approximately 70% of patients with critical congenital heart disease are identified prenatally, but lesions involving the outflow tracts and aorta, such as transposition of the great arteries and coarctation, may be missed during routine fetal imaging. Advances in diagnostic imaging, cardiac surgery, and intensive care have reduced the operative risks of many complex lesions; the hospital mortality following all forms of neonatal cardiac surgery has significantly decreased in the past decade.

III. TIMING OF PRESENTATION. The normal fetal connections between the systemic and pulmonary circulations, the patent foramen ovale (PFO) and patent ductus arteriosus (PDA), close in the first few days of life. Additionally, pulmonary

Table 41.1. Forms of Critical Congenital Heart Disease along with Relative Incidence and Genetic Associations

	Incidence (per 10,000 births)	Associations
Hypoplastic left heart syndrome	2–3	Turner syndrome
Aortic stenosis	3	Turner syndrome
Aortic coarctation	4	Turner syndrome; Williams syndrome
Interrupted aortic arch	0.2	22q11.2 deletion
Tetralogy of Fallot (TOF)	3	Trisomy 21; consider 22q11.2 deletion if right aortic arch or TOF/pulmonary atresia (PA)/MAPCAs.
PA with intact ventricular septum	0.4–0.8	
Pulmonary stenosis	6–8	Noonan syndrome; Alagille
Tricuspid atresia	0.5–1.2	
Ebstein anomaly	0.5	
D-Transposition of the great arteries	2.3–4.7	Rarely syndromic, 22q11.2 deletion if aortic arch anomaly
TAPVC	0.6–1.2	Heterotaxy syndrome
Complete AV canal defect	2	Trisomy 21
Truncus arteriosus	0.5–1.5	>20% have 22q11.2 deletion.

MAPCAs, multiple aortopulmonary collateral arteries; TAPVC, total anomalous pulmonary venous connection.

vascular resistance drops significantly within 72 hours of delivery and continues to fall during the first 6 to 8 weeks of life. These changes account for the typical timing of presentation in postnatally diagnosed patients with critical congenital heart disease. The differential diagnosis of patients presenting in the immediate postnatal, early neonatal, or infant period are summarized below and shown graphically in Figure 41.1. The diagnostic evaluation, stabilization, and management of each lesion are described in more details later in the chapter.

A. Immediate postnatal. Critical congenital heart disease should be in the differential diagnosis of the neonate presenting soon after birth with hypoxemia or shock. In *D-transposition of the great arteries (D-TGA),* the aorta

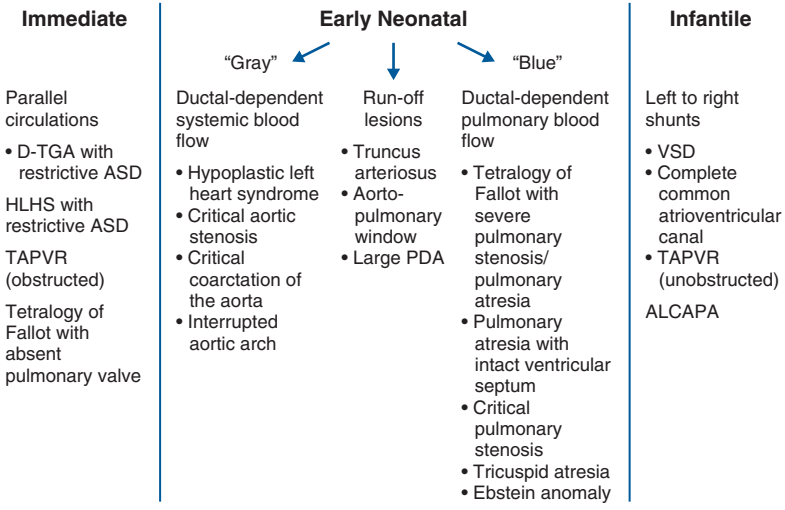

Figure 41.1. Schematic representation of the differential diagnosis of congenital heart disease based on age of presentation. Patients with D-transposition of the great arteries (D-TGA), hypoplastic left heart syndrome (HLHS) with inadequate atrial communication, and obstructed total anomalous pulmonary venous return (TAPVR) present with hypoxemia after birth. Those with ductal-dependent systemic or pulmonary blood flow present at the time of ductal constriction. Run-off lesions result in congestive heart failure (CHF) as pulmonary vascular resistance (PVR) falls during the first days of life. Finally, patients with significant left-to-right shunts and anomalous left coronary artery from the pulmonary artery (ALCAPA) become symptomatic as PVR continues to fall during the first few weeks of life. ASD, atrial septal defect; PDA, patent ductus arteriosus; VSD, ventricular septal defect.

arises from the right ventricle (RV) and the pulmonary artery arises from the left ventricle. This creates two parallel circulations, and mixing is required in order for oxygenated blood to reach the body. The PFO is the primary location of mixing, and if it is inadequately sized, the patient may become profoundly hypoxemic. Maintenance of the PDA with prostaglandin E_1 (PGE_1) infusion encourages atrial shunting, but frequently, this is insufficient and an emergent transcatheter balloon atrial septostomy is required to stabilize the patient. Patients with D-TGA and restrictive PFO may have a "reverse differential cyanosis," where the preductal saturation is lower than the postductal saturation. Thus, monitoring preductal saturation, which reflects oxygen supply to the brain and the heart, is critical.

In *total anomalous pulmonary venous connection* (*TAPVC*), the pulmonary veins drain abnormally to the systemic or coronary venous system. If the drainage pathway is obstructed, the patient develops pulmonary edema, associated hypoxemia, shock, and evidence of refractory pulmonary hypertension. This is a cardiac surgical emergency, and the patient may require preoperative extracorporeal support if immediate cardiac surgical intervention is not available.

A rare form of *tetralogy of Fallot*, marked by *absence of the pulmonary valve* leads to early postnatal respiratory failure in the setting of marked pulmonary artery dilation and associated tracheobronchomalacia. The ductus

arteriosus is often absent in this disorder, and patients may benefit from prone positioning.

B. Early neonatal. This group of cardiac defects includes those in which patency of the ductus arteriosus is necessary to maintain systemic (*left-sided obstructive lesions*) or pulmonary (*right-sided obstructive lesions*) blood flow. As a result of the expected ductal constriction and closure, the neonate with ductal-dependent systemic blood flow will develop cardiogenic shock and acidosis. Patients may present with tachypnea, poor feeding, lethargy, listlessness, and metabolic acidosis. Those with ductal-dependent pulmonary blood flow, will become progressively hypoxemic and may progress to shock. Patients with large run-off lesions, such as *truncus arteriosus* and large *aortopulmonary window*, may also present with congestive heart failure (CHF) in the first week of life. As pulmonary vascular resistance drops, blood preferentially shunts to the pulmonary circulation and may result in systemic hypoperfusion.

C. Infantile. As the pulmonary vascular resistance continues to fall over the first 6 to 8 weeks of life, infants with moderate to large *ventricular septal defects* (*VSDs*), *complete common atrioventricular canal* (*CAVC*) defects, and large PDA may present with symptoms of pulmonary overcirculation in the setting of increased left-to-right shunting.

IV. CLINICAL MANIFESTATIONS OF CONGENITAL HEART DISEASE.

Key clinical findings in the neonate which may require cardiac evaluation include cyanosis, CHF, cardiovascular collapse or shock, and heart murmur.

A. Cyanosis. Cyanosis (blueness of the skin and mucous membranes) is a common presenting sign of congenital heart disease in the neonate and represents hypoxemia or decreased arterial oxygen saturation. However, depending on the skin complexion, clinically apparent cyanosis is usually not visible until there is >3 g/dL of desaturated hemoglobin in the arterial system. Therefore, the degree of visible cyanosis depends on both the severity of hypoxemia (which determines the percentage of oxygen saturation) as well as the hemoglobin concentration. For example, consider two infants with similar degrees of hypoxemia—each having an arterial oxygen saturation of 85%. The polycythemic newborn (hemoglobin of 22 g/dL) will have 3.3 g/dL (15% of 22 g/dL) desaturated hemoglobin and have more visibly apparent cyanosis than the anemic infant (hemoglobin of 10 g/dL) who will only have 1.5 g/dL (15% of 10 g/dL) desaturated hemoglobin. True or central cyanosis should be a generalized finding (i.e., not acrocyanosis, blueness of the hands and feet only, which is a normal finding in a neonate) and can often best be appreciated in the mucous membranes.

Because identifying cyanosis by visual inspection can be challenging, routine preductal and postductal pulse oximetry screening is mandated in 49 U.S. states as well as Washington, D.C., before neonatal discharge. In a 2012 meta-analysis, pulse oximetry screening had 76.5% sensitivity and 99.9% specificity for identifying significant congenital heart disease. There were few false positives, which were further reduced if screening was performed after 24 hours of age. It is not clear if routine pulse oximetry screening has changed the rates of late diagnosis or mortality in patients with critical congenital heart disease. The differential diagnosis of neonatal cyanosis includes lung, cardiac, and systemic pathology (Table 41.2).

Table 41.2. Differential Diagnosis of Cyanosis in the Neonate
Primary Cardiac Lesions
Decreased pulmonary blood flow, intracardiac right-to-left shunt
Critical pulmonary stenosis
Tricuspid atresia
Pulmonary atresia/intact ventricular septum
Tetralogy of Fallot
Ebstein anomaly
Total anomalous pulmonary venous connection with obstruction
Normal or increased pulmonary blood flow, intracardiac mixing
Hypoplastic left heart syndrome
Transposition of the great arteries
Truncus arteriosus
Tetralogy of Fallot/pulmonary atresia
Complete common atrioventricular canal
Total anomalous pulmonary venous connection without obstruction
Other single-ventricle complexes
Pulmonary Lesions (Intrapulmonary Right-to-Left Shunt) (see Chapters 32–38)
Primary parenchymal lung disease
Aspiration syndromes (e.g., meconium and blood)
Respiratory distress syndrome
Pneumonia
Airway obstruction
Choanal stenosis or atresia
Pierre Robin syndrome
Tracheal stenosis
Pulmonary sling
Absent pulmonary valve syndrome
(continued)

Table 41.2. ***(Continued)***

Pulmonary Lesions (Intrapulmonary Right-to-Left Shunt) (see Chapters 32–38)
Extrinsic compression of the lungs
Pneumothorax
Pulmonary interstitial or lobar emphysema
Chylothorax or other pleural effusions
Congenital diaphragmatic hernia
Thoracic dystrophies or dysplasia
Hypoventilation
Central nervous system lesions
Neuromuscular diseases
Sedation
Sepsis
Pulmonary arteriovenous malformations
Persistent Pulmonary Hypertension (see Chapter 36)
Cyanosis with Normal PO_2
Methemoglobinemia
Polycythemia* (see Chapter 46)

*In the case of polycythemia, these infants have plethora and venous congestion in the distal extremities, which gives the appearance of distal cyanosis; these infants actually are not hypoxemic (see text).
PO_2, partial pressure of oxygen.

B. CHF. CHF in the neonate (or in a patient of any age) is a *clinical* diagnosis made based on the presence of certain signs and symptoms rather than on radiographic or laboratory findings, which may corroborate the diagnosis. CHF occur when the heart struggles to meet the metabolic demands of the tissues. Clinical findings are frequently due to homeostatic mechanisms attempting to compensate for this imbalance. In early stages, the neonate may be tachypneic and tachycardic with an increased respiratory effort, rales, hepatomegaly, and delayed capillary refill. In contrast to adults, edema is rarely seen. Diaphoresis, feeding difficulties, and growth failure may be present. *Hydrops fetalis* is an extreme form of intrauterine CHF (see Chapter 5). When heart failure develops in the first weeks of life, the differential diagnosis includes (i) a structural lesion causing severe pressure and/or volume overload, (ii) a primary myocardial lesion causing myocardial dysfunction, or (iii) arrhythmia. Table 41.3 summarizes the differential diagnoses of CHF in the neonate.

Table 41.3. Differential Diagnosis of Congestive Heart Failure in the Neonate

Pressure Overload
Aortic stenosis
Coarctation of the aorta
Volume Overload
Left-to-right shunt at level of great vessels
Patent ductus arteriosus
Aorticopulmonary window
Truncus arteriosus
Tetralogy of Fallot, pulmonary atresia with multiple aorticopulmonary collaterals
Left-to-right shunt at level of ventricles
Ventricular septal defect
Common atrioventricular canal
Single ventricle without pulmonary stenosis (includes hypoplastic left heart syndrome)
Arteriovenous malformations
Combined Pressure and Volume Overload
Interrupted aortic arch
Coarctation of the aorta with ventricular septal defect
Aortic stenosis with ventricular septal defect
Myocardial Dysfunction
Primary
Cardiomyopathies
Inborn errors of metabolism
Genetic
Myocarditis

(continued)

Table 41.3. *(Continued)*
Myocardial Dysfunction
Secondary
Sustained tachyarrhythmias
Perinatal asphyxia
Sepsis
Severe intrauterine valvular obstruction (e.g., aortic stenosis)
Premature closure of the ductus arteriosus
Anomalous left coronary artery from the pulmonary artery (ALCAPA)

C. Shock. The most time-sensitive presentation of the neonate with congenital heart disease is circulatory collapse. Neonates with either cyanosis or CHF may progress to shock when tissue oxygen demand exceeds delivery. These neonates will present with hypotension, metabolic acidosis, and cardiorespiratory failure. The differential diagnosis of neonatal shock is broad, but congenital heart disease should be considered. In this scenario, emergency treatment of circulatory shock should precede cardiac diagnostic studies.

D. Heart murmur. Heart murmurs are common in the newborn period. Physiologic murmurs may be heard during the transition from fetal circulation, specifically the closing of the PDA. Other transient murmurs include very small muscular VSDs or peripheral branch pulmonary artery stenosis due to blood flow turbulence at the pulmonary artery branches that disappears as the branches grow. However, harsh, loud, systolic, and diastolic murmurs may represent cardiac pathology and should be evaluated. Semilunar valve stenosis (systolic ejection murmurs) and atrioventricular valvular insufficiency (blowing holosystolic murmurs) tend to be noted very shortly after birth. In contrast, murmurs due to left-to-right shunt lesions (a VSD murmur or continuous PDA murmur) may not be heard until the second to fourth week of life, when the pulmonary vascular resistance has decreased and the left-to-right shunt increases. Therefore, the *age of the patient* when the murmur is first noted and the *character of the murmur* provide important clues to the nature of the malformation.

E. Fetal echocardiography. It is increasingly common for infants to be born with a diagnosis of probable congenital heart disease due to the widespread use of obstetric ultrasonography and fetal echocardiography. Prenatal diagnosis can guide plans for prenatal care, site and timing of delivery, as well as immediate perinatal care of the infant. The recommended timing for fetal echocardiography is 18 to 20 weeks' gestation, although reasonable images can be obtained as early as 16 weeks, and transvaginal ultrasonography may be used for diagnostic purposes in fetuses in the first trimester. Indications for fetal echocardiography are summarized in Table 41.4. It is important

Table 41.4. Indications for Fetal Echocardiography
Fetus-Related Indications
Suspected congenital heart disease on screening ultrasonography
Fetal chromosomal anomaly
Fetal extracardiac anatomic anomaly
Fetal cardiac arrhythmia
Persistent bradycardia
Persistent tachycardia
Irregular rhythm
Nonimmune hydrops fetalis
Mother-Related Indications
Congenital heart disease
Maternal metabolic disease
Diabetes mellitus
Phenylketonuria
Maternal rheumatic disease (such as systemic lupus erythematosus)
Maternal environmental exposures
Alcohol
Cardiac teratogenic medications
Amphetamines
Anticonvulsants
Phenytoin
Trimethadione
Carbamazepine
Valproate
Isotretinoin
Lithium carbonate
Maternal viral infection
Rubella
Family-Related Indications
Previous child or parent with congenital heart disease
Previous child or parent with genetic disease associated with congenital heart disease

to note, however, that most cases of congenital heart disease occur in pregnancies without known risk factors. Coarctation of the aorta, small VSD and atrial septal defect, TAPVC, and mild aortic or pulmonary stenosis are abnormalities that may be missed by fetal echocardiography. It is important to consider that the expected PDA can mask a coarctation, and the fetal circulation requires a PFO for survival that can make the presence of an atrial septal defect uncertain. In general, in complex congenital heart disease, the main abnormality is noted; however, the full extent of cardiac malformation may be better determined on postnatal examinations.

Fetal tachyarrhythmias or bradyarrhythmias (intermittent or persistent) may be detected on routine obstetric screening ultrasound examinations; this should prompt more complete fetal echocardiography to rule out associated structural heart disease, assess fetal ventricular function, and further define the arrhythmia.

Fetal echocardiography has allowed for improved understanding of the *in utero* evolution of some forms of congenital heart disease. This, in turn, has led to the development of fetal cardiac intervention. This progress represents a promising new method of treatment for congenital heart disease.

V. EVALUATION OF THE NEONATE WITH SUSPECTED CONGENITAL HEART DISEASE

A. Initial evaluation

1. Physical examination

a. Inspection. The infant's general appearance, color, perfusion, and mental status should be thoroughly assessed. Cyanosis may be noted by inspecting the oral mucosa. Mottling of the skin or an ashen, gray color suggests severe cardiovascular compromise and shock. Particular attention should be paid to the respiratory pattern, including the rate, work of breathing, and use of accessory muscles. Tachypnea may represent compensation for pulmonary edema or metabolic acidosis. A careful search for other anomalies is essential because 25% of patients with congenital heart disease have at least one extracardiac malformation. Table 41.5 summarizes malformation and syndromes commonly associated with congenital heart disease.

b. Palpation. Palpation of the *distal extremities* with attention to temperature and capillary refill is imperative. Although cool extremities with delayed capillary refill can be seen in sepsis or dehydration, this finding should also raise suspicion of critical congenital heart disease. While palpating the distal extremities, note the presence and character of the distal pulses. Diminished or absent lower extremity pulses are suggestive of aortic arch obstruction. Palpation of the precordium may provide important information suggesting congenital heart disease. A hyperdynamic precordium suggests a significant left-to-right shunt.

c. Auscultation. This part of the exam should be performed systematically. First, listen to the heart rate to determine if it is regular and appropriate for the patient's age. Second, listen carefully to the heart sounds. The second heart sound is important because its split indicates the presence of two semilunar valves. This can be difficult in neonates

Table 41.5. Chromosomal Anomalies, Syndromes, and Associations Commonly Associated with Congenital Heart Disease

	Approximate Incidence or Mode of Inheritance	Extracardiac Features	Cardiac Features
Chromosomal Anomalies			
Trisomy 21 (Down syndrome)	1/660	Facies (brachycephaly, flattened occiput, midfacial hypoplasia, mandibular prognathism, upslanting palpebral fissures, epicanthal folds, Brushfield spots, large tongue); simian creases, clinodactyly with short fifth finger; pronounced hypotonia	40%–50% have cardiac defects, CAVC, VSD most common, also TOF, ASD, PDA; complex congenital heart disease is very rare.
45,X (Turner syndrome)	1/2,500	Lymphedema of hands, feet; short stature; short-webbed neck; facies (triangular with downslanting palpebral fissures, low-set ears); shield chest	25%–45% have cardiac defects, coarctation; bicuspid aortic valve most common
Trisomy 13 (Patau syndrome)	1/5,000	SGA; facies (midfacial hypoplasia, cleft lip and palate, microphthalmia coloboma, low-set ears); brain anomalies (microcephaly holoprosencephaly); aplasia cutis congenita of scalp; polydactyly	≥80% have cardiac defects; VSD most common
Trisomy 18 (Edward syndrome)	1/3,000 (female:male = 3:1)	SGA; facies (dolichocephaly, prominent occiput, short palpebral fissures, low-set posteriorly rotated ears, small mandible); short sternum; rocker bottom feet; overlapping fingers with "clenched fists"	≥95% have cardiac defects; VSD most common (sometimes multiple); redundant valvular tissue with regurgitation often affecting more than one valve (polyvalvular disease)

Single-Gene Defects			
Noonan syndrome	AD	Facies (hypertelorism, epicanthal folds, downslanting palpebral fissures, ptosis); low-set ears; short webbed neck with low hairline; shield chest, cryptorchidism in men	50% have cardiac detect, usually pulmonary valve stenosis, also ASD, hypertrophic CM.
Holt-Oram syndrome	AD	Spectrum of upper limb and shoulder girdle anomalies	≥50% have cardiac defect, usually ASD or VSD.
Alagille syndrome	AD	Cholestasis; facies (micrognathism, broad forehead, deep-set eyes); vertebral anomalies, ophthalmologic abnormalities	Cardiac findings in 90%. Peripheral pulmonic stenosis is most common.
Gene Deletion Syndromes			
Williams syndrome (deletion 7q11)	1/7,500	SGA, FIT; facies ("elfin" with short palpebral fissures, periorbital fullness or puffiness, flat nasal bridge, stellate iris, long philtrum, prominent lips); fussy infants with poor feeding, friendly personality later in childhood; characteristic mental deficiency (motor more reduced than verbal performance)	50%–70% have cardiac defect, most commonly supravalvular aortic stenosis; other arterial stenoses also occur, including PPS, CoA, renal artery, and coronary artery stenoses.
DiGeorge syndrome (deletion 22q11)	1/6,000	Thymic hypoplasia/aplasia; parathyroid hypoplasia/aplasia; cleft palate or velopharyngeal incompetence	IAA and conotruncal malformations including truncus, TOF

(continued)

Table 41.5. Chromosomal Anomalies, Syndromes, and Associations Commonly Associated with Congenital Heart Disease *(Continued)*

	Approximate Incidence or Mode of Inheritance	Extracardiac Features	Cardiac Features
Associations			
VACTERL		Vertebral defects, anal atresia, cardiac defects, TE fistula, radial and renal anomalies, limb defects	Approximately 50% have cardiac defect, most commonly VSD.
CHARGE		Coloboma, heart defects, choanal atresia, growth and mental deficiency, genital hypoplasia (in men), ear anomalies and/or deafness	50%–70% have cardiac defect, most commonly conotruncal anomalies (TOF, DORV, truncus arteriosus).

CAVC, complete atrioventricular canal; VSD, ventricular septal defect; TOF, tetralogy of Fallot; ASD, atrial septal defect; PDA, patent ductus arteriosus; SGA, small for gestational age; AD, autosomal dominant; CM, cardiomyopathy; FIT, failure to thrive; PPS, peripheral pulmonary stenosis; CoA, coarctation of the aorta; IAA, interrupted aortic arch; TE, tracheoesophageal; DORV, double outlet right ventricle.

with fast resting heart rates. The presence of an S3 or S4 gallop is more obvious and indicative of a neonate in crisis. A systolic ejection click suggests aortic or pulmonary valve stenosis. The presence and intensity of systolic murmurs suggest the type and severity of the underlying anatomic diagnosis. When associated with pathology, they are associated with (i) semilunar valve or outflow tract stenosis, (ii) shunting through a septal defect, or (iii) atrioventricular valve regurgitation. Diastolic murmurs are *always* indicative of cardiovascular pathology.

2. **Four-extremity blood pressure.** Measurement of blood pressure should be taken in bilateral upper and lower extremities. The lower extremities should be equivalent because both are located distal to any aortic arch obstruction. A difference between leg blood pressures is likely due to sampling and not indicative of disease. Automated blood pressure cuffs are most commonly used today, but in a small neonate with pulses that are difficult to palpate, manual blood pressure measurement with Doppler amplification may be necessary. A systolic pressure that is $\geq$10 to 15 mm Hg higher in the upper body compared to the lower body is abnormal and suggests coarctation of the aorta, aortic arch hypoplasia, or interrupted aortic arch. It should be noted that a systolic blood pressure gradient is quite specific for an arch abnormality but not sensitive; a systolic blood pressure gradient will not be present in the neonate with an arch abnormality in whom the ductus arteriosus is patent and nonrestrictive. Therefore, the lack of a systolic blood pressure gradient in newborn does *not* conclusively rule out coarctation or other arch abnormalities, but the presence of a significant systolic pressure gradient is diagnostic of an aortic arch abnormality.
3. **Pulse oximetry.** As noted earlier, preductal and postductal pulse oximetry measurements should be performed in all neonates. Values $<$95% should prompt cardiac evaluation. A preductal to postductal saturation difference of $>$5% to 10% is strongly suggestive of congenital heart disease or severe pulmonary hypertension with right-to-left shunting through the PDA.
4. **Chest x-ray.** A frontal and lateral view (if possible) of the chest should be obtained. In infants, particularly newborns, the size of the heart may be difficult to determine due to an overlying thymus. Nevertheless, useful information can be gained from the chest x-ray. In addition to heart size, notation should be made of visceral and cardiac situs (dextrocardia and *situs inversus* are frequently accompanied by congenital heart disease). The aortic arch side (right or left) often can be determined; a right-sided aortic arch is associated with congenital heart disease in $>$90% of patients. Dark or poorly perfused lung fields suggests decreased pulmonary blood flow, whereas diffusely opaque lung fields may represent increased pulmonary blood flow or significant left atrial hypertension/pulmonary venous congestion.
5. **Electrocardiogram (ECG).** The neonatal ECG reflects the patient's *in utero* hemodynamics. Therefore, the normal newborn ECG is notable for right ventricular predominance (Fig. 41.2). As many forms of congenital heart disease have minimal prenatal hemodynamic effects, the ECG is frequently "normal for age" despite significant structural

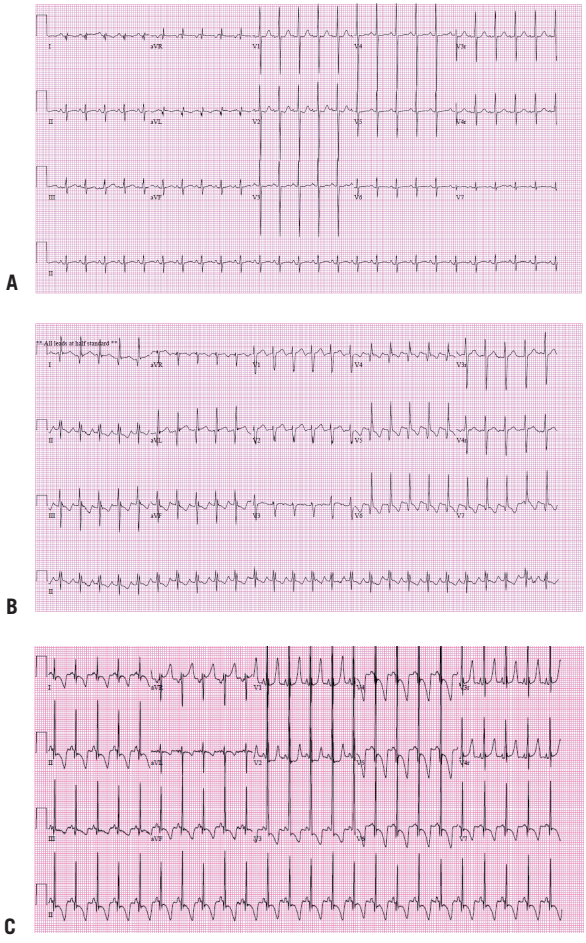

Figure 41.2. **A:** Normal neonatal electrocardiogram (ECG) showing slight rightward axis and upright p wave, which is typical of a newborn. By day of life (DOL) 3, the T wave in V_1 should flip downward. **B:** ECG of a patient with anomalous left coronary artery from the pulmonary artery (ALCAPA) showing evidence of left-sided ischemia, including Q waves in lead I and lateral precordial leads with T-wave inversion in V_3–V_6. **C:** Pathognomonic ECG for Pompe disease showing short PR interval and massive voltages consistent with biventricular hypertrophy with strain.

pathology (e.g., transposition of the great arteries, tetralogy of Fallot). The ECG will evolve after birth in response to changing physiology and the resulting changes in chamber size and thickness that occur. Although rare, several forms of congenital and acquired heart disease in the neonate are associated with pathognomonic ECG findings that should not be missed (Fig. 41.3).

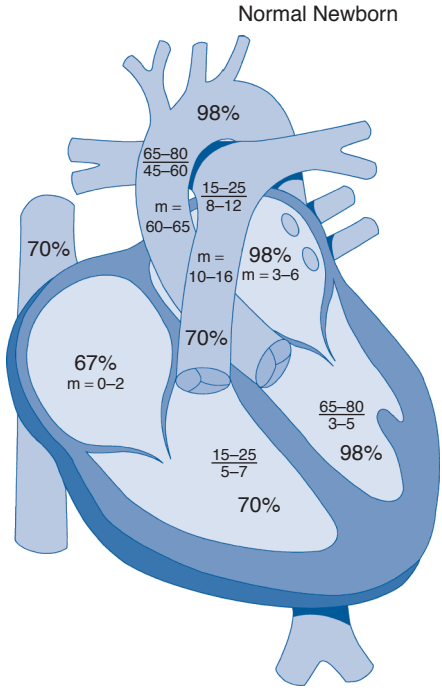

Figure 41.3. Typical hemodynamic measurements obtained at cardiac catheterization in a newborn, term infant without congenital or acquired heart disease. In this (and subsequent diagrams), oxygen saturations are shown as percentages, and typical hemodynamic pressure measurements in mm Hg are shown. In this example, the transition from fetal to infant physiology is complete; the pulmonary vascular resistance has fallen, the ductus arteriosus has closed, and there is no significant shunt at the foramen ovale. m, mean value.

Because most findings on a neonate's ECG would be abnormal in an older child or adult, it is essential to refer to age-specific charts of normal values for most ECG parameters. Refer to Tables 41.6 and 41.7 for normal ECG values in term and premature neonates.

When interpreting an ECG, the following determinations should be made: (i) rate and rhythm; (ii) P, QRS, and T axes; (iii) intracardiac conduction intervals; (iv) evidence for chamber enlargement or hypertrophy; (v) evidence for pericardial disease, ischemia, infarction, or electrolyte abnormalities; and (vi) if the ECG pattern fits with the clinical picture. When the ECG is abnormal, one should also consider incorrect lead placement; a simple confirmation of lead placement may be done by comparing QRS complexes in limb lead I and precordial lead V_6—each should have a similar morphology if the limb leads have been properly placed. The ECG of the premature infant is somewhat different from that of the term infant (see Table 41.7).

Table 41.6. Electrocardiogram Standards in Newborns

	Age (Days)			
Measure	**0–1**	**1–3**	**3–7**	**7–30**
Term infants				
Heart rate (bpm)	122 (99–147)	123 (97–148)	128 (100–160)	148 (114–177)
QRS axis (degrees)	135 (91–185)	134 (93–188)	133 (92–185)	108 (78–152)
PR interval, II (seconds)	0.11 (0.08–0.14)	0.11 (0.09–0.13)	0.10 (0.08–0.13)	0.10 (0.08–0.13)
QRS duration (seconds)	0.05 (0.03–0.07)	0.05 (0.03–0.06)	0.05 (0.03–0.06)	0.05 (0.03–0.08)
V_1, R amplitude (mm)	13.5 (6.5–23.7)	14.8 (7.0–24.2)	12.8 (5.5–21.5)	10.5 (4.5–18.1)
V_1, S amplitude (mm)	8.5 (1.0–18.5)	9.5 (1.5–19.0)	6.8 (1.0–15.0)	4.0 (0.5–9.7)
V_6, R amplitude (mm)	4.5 (0.5–9.5)	4.8 (0.5–9.5)	5.1 (1.0–10.5)	7.6 (2.6–13.5)
V_6, S amplitude (mm)	3.5 (0.2–7.9)	3.2 (0.2–7.6)	3.7 (0.2–8.0)	3.2 (0.2–3.2)

Preterm infants				
Heart rate (bpm)	141 (109–173)	150 (127–182)	164 (134–200)	170 (133–200)
QRS axis (degrees)	127 (75–194)	121 (75–195)	117 (75–165)	80 (17–171)
PR interval (s)	0.10 (0.09–0.10)	0.10 (0.09–1.10)	0.10 (0.09–0.10)	0.10 (0.09–0.10)
QRS duration (s)	0.04	0.04	0.04	0.04
V_1, R amplitude (mm)	6.5 (2.0–12.6)	7.4 (2.6–14.9)	8.7 (3.8–16.9)	13.0 (6.2–21.6)
V_1, S amplitude (mm)	6.8 (0.6–17.6)	6.5 (1.0–16.0)	6.8 (0.0–15.0)	6.2 (1.2–14.0)
V_6, R amplitude (mm)	11.4 (3.5–21.3)	11.9 (5.0–20.8)	12.3 (4.0–20.5)	15.0 (8.3–21.0)
V_6, S amplitude (mm)	15.0 (2.5–26.5)	13.5 (2.6–26.0)	14.0 (3.0–25.0)	14.0 (3.1–26.3)

Source: Reprinted by permission from Springer: Davignon A, Rautaharja P, Boiselle E, et al. Normal ECG standards for infants and children. *Pediatr Cardiol* 1980;1(2):123–131. Reprinted from Sreenivasan VV, Fisher BJ, Liebman J, et al. Longitudinal study of the standard electrocardiogram in the healthy premature infant during the first year of life. *Am J Cardiol* 1973;31(1):57–63. Copyright © 1973 Elsevier. With permission.

Table 41.7. Electrocardiogram Findings in Premature Infants (Compared to Term Infants)

Rate
Slightly higher resting rate with greater activity-related and circadian variation (sinus bradycardia to 70, with sleep not uncommon)
Intracardiac conduction
PR and QRS duration slightly shorter
Maximum QT_c <0.44 s (longer than for term infants, QT_c <0.40 s)
QRS complex
QRS axis in frontal plane more leftward with decreasing gestational age
QRS amplitude lower (possibly due to less ventricular mass)
Less right ventricular predominance in precordial chest leads

Source: From Thomaidis C, Varlamis G, Karamperis S. Comparative study of the electrocardiograms of healthy fullterm and premature newborns. *Acta Paediatr Scand* 1988;77(5):653–657. Reproduced by permission of John Wiley & Sons, Inc.

6. **Hyperoxia test.** A hyperoxia test should be considered in all neonates with suspected critical congenital heart disease, especially if echocardiographic evaluation is not immediately available.

   This test assesses for a fixed, intracardiac right-to-left shunt. The arterial oxygen tension should be measured in room air (if tolerated) followed by repeat measurements with the patient receiving 100% inspired oxygen. The arterial partial pressure of oxygen (PaO_2) should be measured directly through arterial puncture. **Pulse oximetry cannot be used** as in a patient receiving 100% inspired oxygen, a value of 100% oxygen saturation may be obtained with an arterial PaO_2 ranging from 80 (abnormal) to 680 torr (normal).

   Measurements should be made at both "preductal" and "postductal" sites and the exact site of PaO_2 measurement must be recorded. Markedly higher oxygen content in the upper versus the lower part of the body can be suggestive of aortic arch obstruction or pulmonary hypertension with right-to-left ductal shunting. "Reverse differential cyanosis," with elevated lower body saturation and lower upper body saturation, occurs in children with transposition of the great arteries with an abnormal pulmonary artery to aortic shunt due to coarctation, interruption of the aortic arch, or suprasystemic pulmonary vascular resistance.

   When a patient breathes 100% oxygen, an arterial PaO_2 of >250 torr in both upper and lower extremities virtually eliminates critical cyanotic heart disease. An arterial PaO_2 of <100 torr in the absence of obvious

lung disease is most likely due to intracardiac right-to-left shunting and is virtually diagnostic of cyanotic congenital heart disease. Patients who have an arterial PaO_2 between 100 and 250 torr may have structural heart disease with complete intracardiac mixing and greatly increased pulmonary blood flow, as is occasionally seen with single-ventricle complexes such as hypoplastic left heart syndrome. *The neonate who "fails" a hyperoxia test is very likely to have congenital heart disease involving ductal-dependent systemic or pulmonary blood flow and should receive PGE_1 until an echocardiographic diagnosis can be made.*

B. Stabilization and transport. Infants with suspected congenital heart disease require early stabilization, echocardiographic evaluation, and often, transport to a medical center with cardiac surgical or interventional capacity.

1. Initial resuscitation. For the neonate who presents with evidence of decreased cardiac output or shock, initial attention is devoted to the basics of advanced life support. A stable airway must be established and maintained as well as adequate ventilation. Reliable vascular access is essential, optimally including an arterial line. Volume resuscitation, inotropic support, and correction of metabolic acidosis are required with the goal of improving cardiac output and tissue perfusion. Patients with limited oxygen delivery frequently benefit from sedation and paralysis to minimize oxygen demand.

2. PGE_1. The neonate who "fails" a hyperoxia test or presents in shock within the first 3 weeks of life is highly likely to have congenital heart disease. These patients may have ductal-dependent systemic or pulmonary blood flow or a PDA that aids in intercirculatory mixing. *PGE_1 infusion should be initiated as soon as critical congenital heart disease is suspected, even before a definitive anatomic diagnosis is made.*

PGE_1 causes apnea in 10% to 12% of neonates, usually within the first 6 hours of administration. Therefore, the infant who will be transferred to another institution while receiving PGE_1 may require intubation prior to transport, and all neonates on PGE_1 infusion require continuous cardiorespiratory monitoring. In addition, PGE_1 may cause peripheral vasodilation and hypotension. A separate intravenous (IV) line should be secured for volume administration in any infant receiving PGE_1, especially those who require transport.

Specific information regarding other adverse reactions, dose, and administration of PGE_1 is in section VIII.A.

Rarely, a patient's clinical status may worsen after beginning PGE_1. This is usually due to lesions with left atrial hypertension: hypoplastic left heart syndrome with a restrictive PFO, infradiaphragmatic total anomalous pulmonary venous return (TAPVR), transposition of the great arteries with intact ventricular septum and a restrictive PFO, and some cases of Ebstein anomaly (see section VI.B.5). In these lesions, deterioration on PGE_1 is often a helpful diagnostic finding, and *urgent* plans for echocardiography and possible interventional catheterization or surgery should be made.

3. Inotropic agents. Continuous infusions of inotropic agents, usually the sympathomimetic amines, can improve myocardial performance

as well as perfusion of vital organs and the periphery. Care should be taken to replete intravascular volume before institution of vasoactive agents. *Dopamine* is a precursor of norepinephrine and stimulates β1, dopaminergic, and α-adrenergic receptors in a dose-dependent manner. Dopamine can be expected to increase mean arterial pressure, improve ventricular function, and improve urine output with a low incidence of side effects at doses <10 μg/kg/minute. Low-dose *epinephrine* may also improve inotropy, especially in patients with diminished ventricular function, but the minimal necessary dose needed should be used to minimize increases in myocardial oxygen demand. See section VIII.B for details of administration of inotropic agents and additional pharmacologic agents.

4. **Transport.** After initial stabilization, the neonate with suspected congenital heart disease often needs to be transferred to an institution that provides subspecialty care in pediatric cardiology and cardiac surgery. A successful transport involves two transitions of care for the neonate: (i) from the referring hospital staff to the transport team and (ii) from the transport team staff to the accepting hospital staff. The need for accurate, detailed, and complete communication of information between all of these teams cannot be overemphasized. If possible, the pediatric cardiologist who will be caring for the patient should be included in the discussions of care while the neonate is still at the referring hospital.

   Reliable vascular access should be secured for the neonate receiving continuous infusions of PGE_1 or inotropic agents. Umbilical lines placed for resuscitation and stabilization should be left in place for transport; the neonate with congenital heart disease may potentially require cardiac catheterization through this route. Particular attention should be paid to the patient's airway and respiratory effort before transport. Intubation should be considered, especially in patient on PGE_1 infusion.

5. **Acid–base status and oxygen delivery should be checked with an arterial blood gas before transport.** Supplemental oxygen at or near 100% is often not the inspired oxygen concentration of choice for the neonate with congenital heart disease (see section VI for details of lesion-specific care). This is particularly important for those infants with ductal-dependent systemic blood flow and complete intracardiac mixing with single-ventricle physiology because supplemental oxygen may increase pulmonary blood flow at the expense of systemic blood flow.

   Finally, it is important to remember that hypotension is a late finding of shock in neonates. Therefore, other signs of incipient decompensation, such as persistent tachycardia and poor tissue perfusion, are important to note and treat before transport. Before leaving the referring hospital, the patient's current hemodynamic status (distal perfusion, heart rate, systemic blood pressure, acid–base status, etc.) should be reassessed and relayed to the receiving hospital team.

C. Diagnosis evaluation

1. **Echocardiography.** Transthoracic echocardiography is the primary diagnostic tool for anatomic definition in pediatric cardiology. Echocardiography provides information about the structure and function of

the heart and great vessels in a timely fashion. Although not an invasive test *per se*, a complete echocardiogram on a newborn suspected of having congenital heart disease may take an hour or more to perform and may therefore not be well tolerated by a sick and/or premature newborn. Temperature instability due to exposure during this extended time of examination may be a problem in the neonate. Extension of the neck for suprasternal notch views of the aortic arch may be problematic, particularly in the neonate with respiratory distress or with a tenuous airway. Therefore, in sick neonates, close monitoring by a medical staff person other than the one performing the echocardiogram is essential, with attention to vital signs, respiratory status, temperature, etc.

2. **Cardiac catheterization**

a. Indications (Table 41.8). Neonatal cardiac catheterization is rarely necessary for anatomic definition of intracardiac structures but is useful to define the anatomy of the distal pulmonary arteries, aortopulmonary collaterals, and certain types of coronary artery anomalies. Increasingly, catheterization is performed for catheter-directed therapy of congenital lesions. See Figure 41.3 for normal newborn oxygen saturation and pressure measurements obtained during cardiac catheterization.

b. Interventional catheterization. Since the first balloon dilation of the pulmonary artery reported by Kan in 1982, balloon valvuloplasty has become the procedure of choice in many types of valvar lesions, even extending to critical lesions in the neonate. Balloon valvuloplasty is considered the initial treatment of choice for both pulmonary and aortic stenosis, with >90% immediate success rate in the neonate. Other neonatal catheterization procedures include balloon atrial septostomy, radiofrequency (RF) perforation of the pulmonary valve in pulmonary atresia with intact ventricular septum, device closure of the persistent ductus arteriosus and in the current era stenting of PDA for defects with ductal-dependent pulmonary blood flow and as part of the hybrid procedure in neonates with hypoplastic left heart syndrome.

VI. "LESION-SPECIFIC" CARE FOLLOWING ANATOMIC DIAGNOSIS

A. Ductal-dependent systemic blood flow. Commonly referred to as *left-sided obstructive lesions*, this group of lesions includes a spectrum of hypoplasia of the left-sided structures of the heart ranging from isolated coarctation of the aorta to hypoplastic left heart syndrome. These infants may present in cardiovascular collapse as the ductus arteriosus closes or more insidiously with symptoms of CHF (see section IV.B). All infants with ductal-dependent systemic blood flow require prostaglandin to maintain ductal patency. Additional care varies somewhat with each lesion but often includes treatment of shock, stable vascular access, intubation, and mechanical ventilation with positive end-expiratory pressure to overcome pulmonary venous desaturation from pulmonary edema, inotropic support, sedation, and, sometimes, neuromuscular blockade to limit systemic oxygen demand.

1. **Aortic stenosis** (Fig. 41.4). Abnormalities of the aortic valve may range from a bicuspid, nonobstructive, functionally normal valve to a unicuspid, markedly deformed, and severely obstructive valve, which greatly limits

Table 41.8. Indications for Neonatal Catheterization
Interventions
Therapeutic
Balloon atrial septostomy
Balloon pulmonary valvuloplasty
Balloon aortic valvuloplasty*
Coil embolization of abnormal vascular communications
Radiofrequency perforation of the atretic pulmonary valve*
Device closure of the patent ductus arteriosus*
Stent implant in the ductus arteriosus*
Anatomic Definition (Not Visualized by Echocardiography)
Coronary arteries
Pulmonary atresia/intact ventricular septum
Transposition of the great arteries
Tetralogy of Fallot
Aortic to pulmonary artery collateral vessels
Tetralogy of Fallot
Pulmonary atresia
Distal pulmonary artery anatomy
Hemodynamic Measurements
*These interventions have alternative surgical options, and utilization is based on institutional experience.

systemic cardiac output. By convention, "severe" aortic stenosis is defined as a mean systolic gradient from left ventricle to ascending aorta of 40 to 50 mm Hg. "Critical" aortic stenosis results from severe anatomic obstruction with accompanying left ventricular failure and/or shock, regardless of the measured gradient. Patients with critical aortic stenosis have severe obstruction present *in utero* (usually due to a unicuspid, "platelike" valve), with resultant left ventricular hypertrophy and, frequently, endocardial fibroelastosis. Associated left-sided abnormalities such as mitral valve disease and coarctation are not uncommon. Following closure of the PDA, the left ventricle must supply all of the systemic cardiac output. Patients may develop left ventricular failure, clinical CHF, or shock.

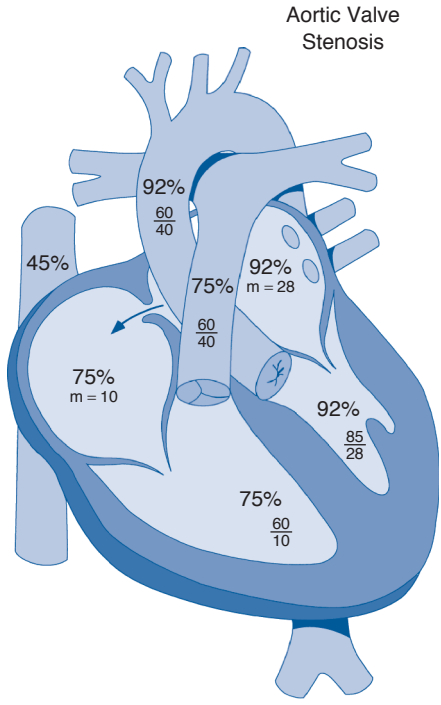

Figure 41.4. Critical aortic valve stenosis with a closed ductus arteriosus. Typical anatomic and hemodynamic findings include (i) a morphologically abnormal, stenotic valve; (ii) poststenotic dilatation of the ascending aorta; (iii) elevated left ventricular end-diastolic pressure and left atrial pressures contributing to pulmonary edema (mild pulmonary venous and arterial desaturation); (iv) a left-to-right shunt at the atrial level (note increase in oxygen saturation from superior vena cava to right atrium); (v) pulmonary artery hypertension (also secondary to the elevated left atrial pressure); and (vi) only a modest (25 mm Hg) gradient across valve. The low measured gradient (despite severe anatomic obstruction) across the aortic valve is due to a severely limited cardiac output, as evidenced by the low mixed venous oxygen saturation (45%) in the superior vena cava. m, mean value.

Following anatomic definition of left ventricular size, mitral valve, and aortic arch anatomy by echocardiography, cardiac catheterization or surgery should be performed as soon as possible to perform aortic valvotomy. With either type of therapy, patient outcome will depend largely on (i) the degree of relief of the obstruction, (ii) the degree of aortic regurgitation, (iii) associated cardiac lesions (especially left ventricular size), and (iv) the severity of end-organ dysfunction secondary to the initial presentation (e.g., necrotizing enterocolitis or renal failure). All patients with aortic stenosis will require lifelong follow-up because stenosis frequently recurs.

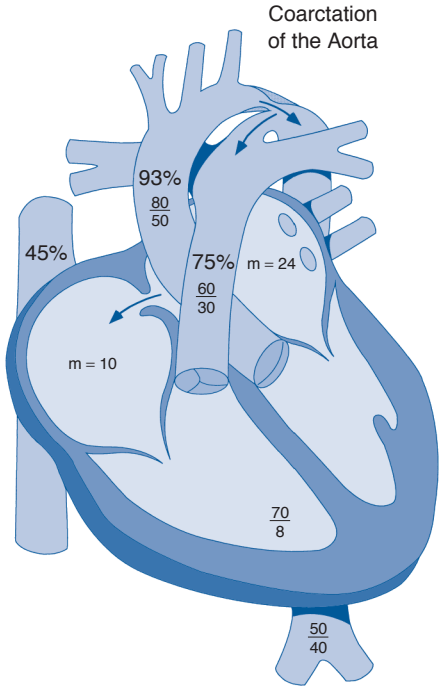

Figure 41.5. Coarctation of the aorta in a critically ill neonate with a nearly closed ductus arteriosus. Typical anatomic and hemodynamic findings include (i) "juxtaductal" site of the coarctation, (ii) a bicommissural aortic valve (seen in 80% of patients with coarctation), (iii) narrow pulse pressure in the descending aorta and lower body, and (iv) a bidirectional shunt at the ductus arteriosus. As in critical aortic stenosis (see Fig. 41.4), there is an elevated left atrial pressure, pulmonary edema, a left-to-right shunt at the atrial level, pulmonary artery hypertension, and only a moderate (30 mm Hg) gradient across the arch obstruction. The low measured gradient (despite severe anatomic obstruction) across the aortic arch is due to low cardiac output. m, mean value.

2. **Coarctation of the aorta** (Fig. 41.5) is an anatomic narrowing of the descending aorta, most commonly at the site of insertion of the ductus arteriosus (i.e., "juxtaductal"). Additional cardiac abnormalities are common, including bicuspid aortic valve (present in 80% of patients) and VSD (present in 40% of patients). In addition, hypoplasia or obstruction of other left-sided structures including the mitral valve, the left ventricle, and the aortic valve are not uncommon and must be assessed during the initial echocardiographic evaluation.

   In utero, systemic blood flow to the lower body is through the PDA. Following ductal closure in the newborn with a critical coarctation, the left ventricle must suddenly generate adequate pressure and volume to pump the entire cardiac output past a significant point of obstruction.

This sudden pressure load may be poorly tolerated by the neonatal myocardium, and the neonate may become rapidly and critically ill because of lower body hypoperfusion. *In some infants, PGE_1 is unsuccessful in opening the ductus arteriosus, so ductal patency and left ventricular function should be reassessed early.*

In infants with symptomatic coarctation, surgical repair is performed as soon as the infant has been resuscitated and medically stabilized. Usually, the procedure is performed through a left lateral thoracotomy incision, although a median sternotomy may be required if the aortic arch is diffusely hypoplastic or if there is a large, coexisting VSD which requires repair. Alternatively, a pulmonary artery band may be placed at the time of coarctation repair to protect from excessive pulmonary blood flow until the VSD can be addressed at a later age.

3. **Interrupted aortic arch** (Fig. 41.6) consists of atresia of a segment of the aortic arch. There are three anatomic subtypes of interrupted aortic arch based on the location of the interruption: distal to the left subclavian artery (type A), between the left subclavian artery and the left carotid artery (type B), and between the innominate artery and the left carotid artery (type C). Type B is the most common variety. More than 99% of these patients have a VSD; abnormalities of the aortic valve and narrowed subaortic regions are associated anomalies.

   Infants with interrupted aortic arch are completely dependent on a PDA for lower body blood flow and, therefore, become critically ill when the ductus closes. Immediate management is similar to that described for coarctation (see section VI.A.2); PGE_1 infusion is essential. All other resuscitative measures will be ineffective if blood flow to the lower body is not restored. Pre- and postductal oxygen saturations should be monitored. High concentrations of inspired oxygen may result in low pulmonary vascular resistance, a large left-to-right shunt, and a "run-off" during diastole from the lower body to the pulmonary circulation. Inspired oxygen levels should therefore be minimized, aiming for normal (95%) oxygen saturations in the *upper* body.

   Surgical reconstruction should be performed as soon as metabolic acidosis has resolved, end-organ dysfunction is improving, and the patient is hemodynamically stable. The repair typically entails a corrective approach through a median sternotomy, with arch reconstruction (usually an end-to-end anastomosis) and closure of the VSD.

4. **Hypoplastic left heart syndrome** (Figs. 41.7A and 41.7B) represents a heterogeneous group of anatomic abnormalities in which there is a small-to-absent left ventricle with hypoplastic to atretic mitral and aortic valves. Before surgery, the RV supplies both the pulmonary and systemic blood flows (through the PDA) with the proportion of cardiac output going to either circuit dependent on the relative resistances of these vascular beds.

   As the pulmonary vascular resistance begins to fall (see Fig. 41.7A), blood flow is preferentially directed to the pulmonary circulation at the expense of the systemic circulation. As systemic blood flow decreases, stroke volume and heart rate increase as a mechanism to preserve systemic cardiac output. The RV becomes progressively volume overloaded

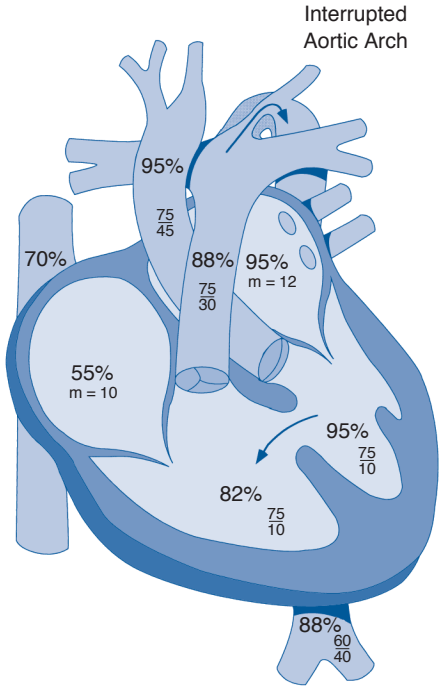

Figure 41.6. Interrupted aortic arch with restrictive patent ductus arteriosus. Typical anatomic and hemodynamic findings include (i) atresia of a segment of the aortic arch between the left subclavian artery and the left common carotid (the most common type of interrupted aortic arch—break "type B"), (ii) a posterior malalignment of the conal septum resulting in a large ventricular septal defect and a narrow subaortic area, (iii) a bicuspid aortic valve occurs in 60% of patients, (iv) systemic pressure in the right ventricle and pulmonary artery (due to the large, nonrestrictive ventricular septal defect), (v) increased oxygen saturation in the pulmonary artery due to left-to-right shunting at the ventricular level, (vi) "differential cyanosis" with a lower oxygen saturation in the descending aorta due to a right-to-left shunt at the patent ductus. Note the lower blood pressure in the descending aorta due to constriction of the ductus; opening the ductus with prostaglandin E_1 (PGE_1) results in equal upper and lower extremity blood pressures but continued "differential cyanosis." m, mean value.

with mildly elevated end-diastolic and left atrial pressures. The infant may be tachypneic or in respiratory distress, and hepatomegaly may develop. The greater proportion of pulmonary venous return in the mixed ventricular blood results in mildly decreased systemic arterial oxygen saturation (frequently in the high 80% range to low 90% range), and visible cyanosis may be mild or absent. Not infrequently, these infants are discharged from the nursery as normal newborns. A goal of neonatal pulse oximetry screening is to detect this desaturation before discharge.

At this point, the continued fall in pulmonary vascular resistance results in a progressive increase in pulmonary blood flow and relative

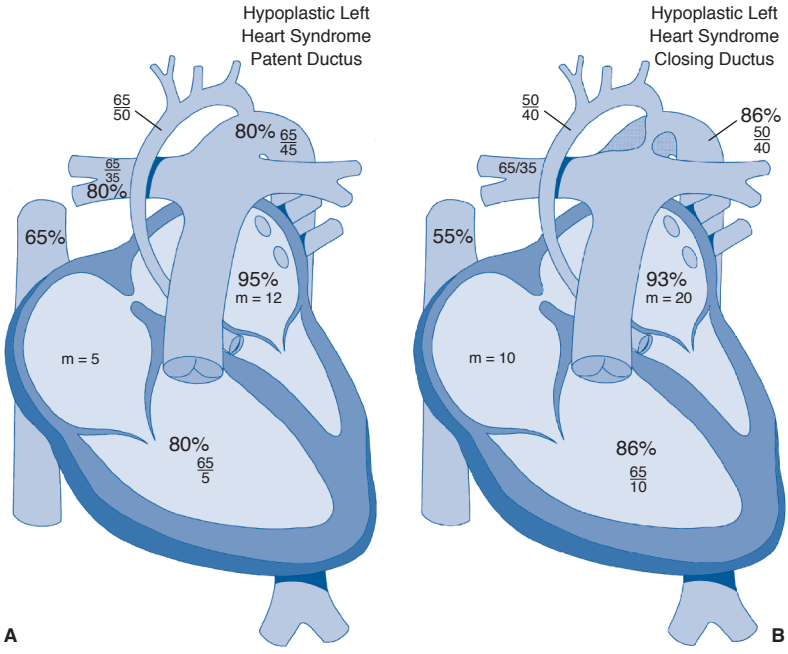

Figure 41.7. **A:** Hypoplastic left heart syndrome in a 24-hour-old patient with falling pulmonary vascular resistance and a nonrestrictive ductus arteriosus. Typical anatomic and hemodynamic findings include (i) atresia or hypoplasia of the left ventricle, mitral, and aortic valves; (ii) a diminutive ascending aorta and transverse aortic arch, usually with an associated coarctation; (iii) coronary blood flow is usually ***retrograde*** from the ductus arteriosus through the tiny ascending aorta; (iv) systemic arterial oxygen saturation (in fraction of inspired oxygen [FiO_2] of 0.21) of 80%, reflecting relatively balanced systemic and pulmonary blood flows—the pulmonary artery and aortic saturations are equal (see text); (v) pulmonary hypertension secondary to the nonrestrictive ductus arteriosus; (vi) minimal left atrial hypertension; and (vii) normal systemic cardiac output (note superior vena cava oxygen saturation of 65%) and blood pressure (65/45 mm Hg). **B:** Acute circulatory collapse following constriction of the ductus arteriosus in hypoplastic left heart syndrome. These neonates are typically in shock with poor perfusion, tachycardia, acidosis, and in respiratory distress. The anatomic features are similar to those in Figure 41.7A, with the exception of the narrowed ductus arteriosus. Note (i) the low cardiac output (as evidenced by the low mixed venous oxygen saturation in the superior vena cava of 55%); (ii) narrow pulse pressure; (iii) elevated atrial and ventricular end-diastolic pressure—elevated left atrial pressure may cause pulmonary edema (note left atrial saturation of 93%); and (iv) significantly increased pulmonary blood flow, as reflected in an arterial oxygen saturation (in FiO_2 of 0.21) of 86%. m, mean value.

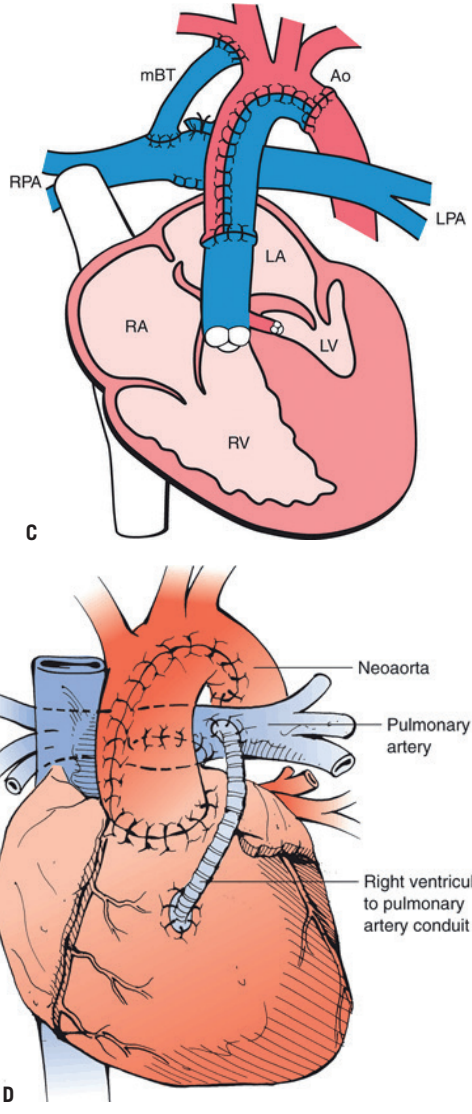

Figure 41.7. Initial palliative strategies for hypoplastic left heart syndrome include, Norwood palliation consisting of anastomosis of the native aorta and pulmonary "neoaortic" valve, homograft augmentation of the aortic arch, atrial septectomy, and a restricted source of pulmonary blood flow via either a modified Blalock-Taussig shunt (**C**) or right ventricle (RV)-pulmonary artery conduit (**D**). (**C**, reprinted with permission from Lee E. *Pediatric Radiology: Practical Imaging Evaluation of Infants and Children*. Philadelphia, PA: Wolters Kluwer; 2017. **D**, reprinted with permission from Rouine-Rapp K, Miller-Hance WC. Transesophageal echocardiography for congenital heart disease in the adult. In: Perrino AC, Reeves ST, eds. *A Practical Approach to Transesophageal Echocardiography*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:395.)

decrease in systemic cardiac output. As the total RV output is limited by heart rate and stroke volume, there is the onset of clinically apparent CHF, RV dilation and dysfunction, progressive tricuspid regurgitation, poor peripheral perfusion with metabolic acidosis, decreased urine output, and pulmonary edema.

Alternatively, a sudden deterioration takes place with rapidly progressive CHF and shock as the ductus arteriosus constricts (see Fig. 41.7B). This scenario is more common in the absence of prenatal diagnosis. There is decreased systemic perfusion and increased pulmonary blood flow, which is largely independent of the pulmonary vascular resistance. The peripheral pulses are weak to absent. Renal, hepatic, coronary, and central nervous system perfusion is compromised. Coronary blood flow (which may be exclusively retrograde via the PDA) may also be compromised leading to further myocardial dysfunction. The arterial blood gas may represent the single best indicator of hemodynamic stability. Low arterial saturation (75% to 80%) with normal pH indicates an acceptable balance of systemic and pulmonary blood flow with adequate peripheral perfusion, whereas elevated oxygen saturation (>90%) with acidosis represents significantly increased pulmonary and decreased systemic flow with probable myocardial dysfunction and secondary effects on other organ systems.

Resuscitation of these neonates involves pharmacologic maintenance of ductal patency with PGE_1 and ventilatory maneuvers to *increase* pulmonary resistance. In general, a mild respiratory acidosis (e.g., pH 7.35) is appropriate for most of these infants. It is important to note that hyperventilation and/or supplemental oxygen is usually of no significant benefit and may be harmful by causing excessive pulmonary vasodilation and pulmonary blood flow at the expense of the systemic blood flow.

Hypotension in these infants is more frequently caused by increased pulmonary blood flow (at the expense of systemic flow) rather than intrinsic myocardial dysfunction. Although small-to-moderate doses of inotropic agents are frequently beneficial, *large doses of inotropic agents may have a deleterious effect*, depending on the relative effects on the systemic and pulmonary vascular beds. Preferential selective elevations of systemic vascular tone will secondarily increase pulmonary blood flow, and careful monitoring of mean arterial blood pressure and arterial oxygen saturation is warranted.

Similar to the patient with critical aortic stenosis, in order for the neonate with hypoplastic left heart syndrome to benefit from a PGE_1 infusion, there must be at least a small PFO to allow for effective systemic blood flow (pulmonary venous return) to cross the atrial septum and ultimately enter the systemic vascular bed through the ductus arteriosus. An infant with hypoplastic left heart syndrome and a severely restrictive or absent PFO will be critically ill with profound cyanosis (oxygen saturation <60% to 65%) and will not improve after the institution of PGE_1. *In these neonates, emergent balloon dilation/stenting of the atrial septum is necessary.*

Medical therapy may be briefly palliative; however, surgical therapy is necessary for survival of infants with hypoplastic left heart syndrome. In the current era, surgical intervention involves staged reconstruction (with a neonatal Norwood procedure as shown in Figures 41.7C and 41.7D, followed by the Glenn and Fontan operations later in infancy and childhood, respectively). A hybrid approach with stenting of the

PDA and placement of bilateral pulmonary artery bands is the preferred approach in some centers or in patients with risk factors such as prematurity or low birth weight. This approach may also be used in high-risk patients as a bridge to heart transplantation. Results from both reconstructive surgery and transplantation have vastly improved the outlook for infants born with this previously 100% fatal condition.

B. Ductal-dependent pulmonary blood flow. This underlying physiology is shared by a diverse group of lesions with the common finding of restricted pulmonary blood flow due to severe pulmonary stenosis or pulmonary atresia. Closure of the ductus arteriosus results in marked cyanosis.

1. **Pulmonary stenosis** (Fig. 41.8) with obstruction to pulmonary blood flow may occur at several levels: (i) within the body of the RV, (ii) at the pulmonary valve (as pictured in Fig. 41.9), and (iii) in the peripheral

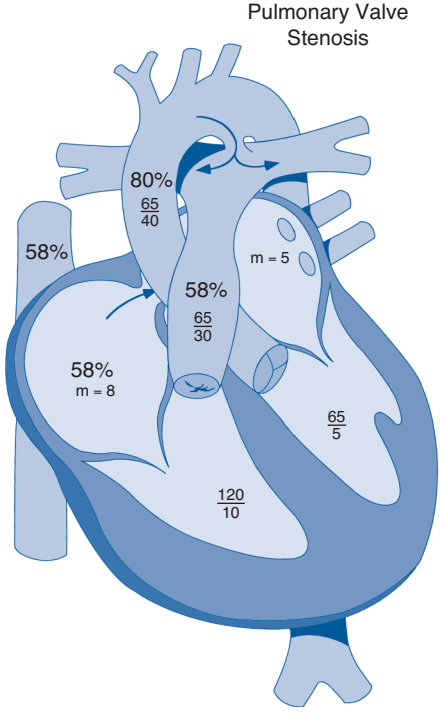

Figure 41.8. Critical pulmonary valve stenosis in a neonate with a nonrestrictive patent ductus arteriosus while receiving prostaglandin E_1 (PGE_1). Typical anatomic and hemodynamic findings include (i) thickened, stenotic pulmonary valve; (ii) poststenotic dilatation of the main pulmonary artery with normal-sized branch pulmonary arteries; (iii) right ventricular (RV) hypertrophy with suprasystemic pressure; (iv) a right-to-left shunt at the atrial level through the patent foramen ovale with systemic desaturation (80%); (v) suprasystemic RV pressure with a 55 mm Hg peak systolic ejection gradient; (vi) systemic pulmonary artery pressure (due to the nonrestrictive patent ductus); and (vii) pulmonary blood flow through the patent ductus arteriosus. m, mean value.

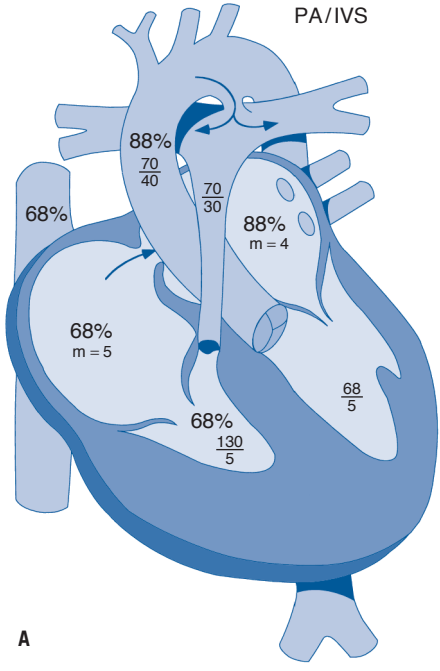

Figure 41.9. **A:** Pulmonary atresia (PA) with intact ventricular septum (IVS) in a neonate with a nonrestrictive patent ductus arteriosus while receiving prostaglandin E_1 (PGE_1). Typical anatomic and hemodynamic findings include (i) hypertrophied, hypoplastic right ventricle; (ii) hypoplastic tricuspid valve and pulmonary annulus; (iii) atresia of the pulmonary valve with no antegrade flow; (iv) suprasystemic right ventricular pressure; (v) pulmonary blood flow through the patent ductus; and (vi) right-to-left shunt at the atrial level with systemic desaturation. Many patients have significant coronary abnormalities with sinusoidal or fistulous connections to the hypertensive right ventricle or significant coronary stenoses (not shown). m, mean value.

pulmonary arteries. Severe pulmonary stenosis is defined as a peak systolic gradient from RV to pulmonary artery of 60 mm Hg or more (see section VI.B.1). By convention, "critical" pulmonary stenosis is defined as severe valvular obstruction with associated hypoxemia due to a right-to-left shunt at the foramen ovale and occurs more rarely. Critical pulmonary stenosis may be associated with hypoplasia of the RV and/or tricuspid valve and significant RV hypertrophy. The pressure in the RV is often higher than the left ventricular pressure (i.e., suprasystemic) in order to eject blood through the severe narrowing. Due to the longstanding (*in utero*) increased RV pressure, there is typically a hypertrophied, noncompliant RV with a resultant increase in right atrial filling pressure. When right atrial pressure exceeds left atrial pressure, a right-to-left shunt at the foramen ovale results in cyanosis and hypoxemia. There may be associated RV dysfunction and/or tricuspid regurgitation.

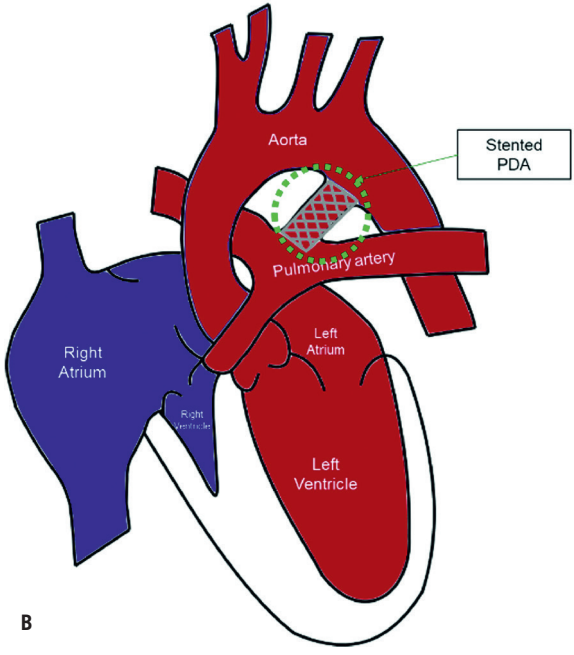

Figure 41.9. **B:** Schematic of ductal stent to maintain patency of the patent ductus arteriosus (PDA) in a patient with PA/IVS. (**B**, reprinted by permission from Springer: Kori MI, Osman K, Khudzari AZM, et al. Computational fluid dynamics application in reducing complications of patent ductus arteriosus stenting. In: Dewi D, Hau Y, Khudzari A, et al, eds. *Cardiovascular Engineering: Technological Advancements, Reviews, and Applications [Series in BioEngineering]*. Singapore: Springer; 2020. Copyright © 2020 Springer Nature.)

After initial stabilization of the patient and definitive diagnosis by echocardiography, transcatheter balloon valvotomy is the treatment of choice for this lesion. Surgical valvotomy is a rare alternative. Despite successful relief of the obstruction during catheterization, cyanosis is usually not completely relieved but rather resolves gradually over the first weeks of life as the RV becomes more compliant, tricuspid regurgitation lessens, and there is less right-to-left shunting at the atrial level. Due to subvalvular outflow tract hypertrophy and persistence of a dynamic obstructive pattern, short-term treatment with a β-blocker is sometimes employed. Successful balloon valvuloplasty is associated with excellent clinical results among patients; the need for repeat procedures is <10%.

2. **Pulmonary atresia with intact ventricular septum** (Fig. 41.9) is comparable to hypoplastic left heart syndrome in that there is atresia of the pulmonary valve with varying degrees of RV and tricuspid valve hypoplasia. Perhaps the most important associated anomaly is the presence of coronary cameral fistulae, which are sinusoidal connections between

the coronary arteries and right ventricular chamber. The coronary arteries may be very abnormal, with areas of stenosis or atresia. Myocardial perfusion therefore may be dependent on the hypertensive RV to supply the distal coronary arteries (RV-dependent coronary arteries). Surgical relief of the pulmonary atresia or decompression of the RV in patients with RV-dependent coronaries can lead to myocardial infarction and death because blood would flow preferentially to the pulmonary arteries instead of the distal coronary segments. Because there is no outlet of the RV, there is typically suprasystemic pressure in the RV and some tricuspid regurgitation. There is an obligatory right-to-left shunt at the atrial level, and pulmonary blood flow is entirely dependent on a PDA.

Although the cornerstone of initial management is PGE_1 infusion to maintain ductal patency, a more durable form of pulmonary blood flow must be created for the infant to survive.

Cardiac catheterization is necessary to define the coronary artery anatomy. In patients without significant coronary abnormalities, pulmonary blood flow is established by perforation of the atretic pulmonary valve followed by balloon pulmonary valvuloplasty. Thus, the atresia is addressed and some patients may avoid neonatal surgical intervention. Alternatively, surgical pulmonary valvotomy and/or right ventricular outflow tract augmentation can be performed. Due to poor RV compliance, pulmonary blood flow may be inadequate and a systemic-to-pulmonary artery shunt (most often a Blalock-Taussig [BT] shunt) or stent implantation in the PDA is necessary to augment pulmonary blood flow. In patients with RV-dependent coronary arteries and in those with a severely hypoplastic tricuspid valve, a systemic-to-pulmonary artery shunt or ductal stent is the typical procedure performed.

3. **Tricuspid atresia** (Fig. 41.10) involves absence of the tricuspid valve and therefore no direct communication from right atrium to RV. The RV may be severely hypoplastic or absent. More than 90% of patients have an associated VSD, allowing blood to pass from the left ventricle to the right ventricular outflow and pulmonary arteries. Most patients have some form of additional pulmonary stenosis. In 70% of cases, the great arteries are normally aligned with the ventricles; however, in the remaining 30%, the great arteries are transposed. An atrial level communication is necessary for blood to travel right to left. In patients with normally related great arteries, pulmonary blood flow depends on the size of the VSD. If the VSD is small, the patient will require an additional source of pulmonary blood flow, such as a BT shunt or ductal stent. More complex cases (e.g., with transposition) may require more extensive palliative procedures. Patients with adequate pulmonary blood flow, with a normal pulmonary valve and adequate pulmonary arteries, may develop hypoxemia in the subsequent weeks to months if the VSD becomes smaller, thus restricting pulmonary blood flow. Patients with unobstructed systemic and pulmonary blood flow will develop symptoms and signs of pulmonary overcirculation in the first few days to weeks of life and will require placement of a pulmonary artery band to limit pulmonary blood flow.

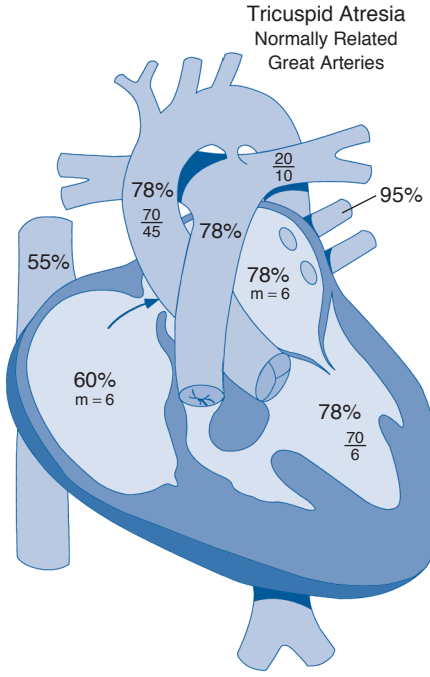

Figure 41.10. Tricuspid atresia with normally related great arteries and a small patent ductus arteriosus. Typical anatomic and hemodynamic findings include (i) atresia of the tricuspid valve; (ii) hypoplasia of the right ventricle; (iii) restriction to pulmonary blood flow at two levels: a (usually) small ventricular septal defect and a stenotic pulmonary valve; (iv) all systemic venous return must pass through the patent foramen ovale to reach the left ventricle; (v) complete mixing at the left atrial level, with systemic oxygen saturation of 78% (in fraction of inspired oxygen [FiO_2] of 0.21), suggesting balanced systemic and pulmonary blood flow ("single ventricle physiology"—see text). m, mean value.

4. **Tetralogy of Fallot** (Fig. 41.11) consists of right ventricular outflow obstruction, a malalignment VSD, "overriding" of the aorta over the ventricular septum, and hypertrophy of the RV. There is a wide spectrum of anatomic variation encompassing these findings, depending particularly on the site and severity of the right ventricular outflow obstruction. The severely cyanotic neonate with tetralogy of Fallot most likely has severe outflow tract obstruction and a large right-to-left shunt at the ventricular level through the large VSD. Pulmonary blood flow may be ductal dependent.

   Immediate medical management involves establishing adequate pulmonary blood flow, usually with PGE_1 infusion. Detailed anatomic definition, particularly regarding coronary artery anatomy, the presence of additional VSDs, and the sources of pulmonary blood flow

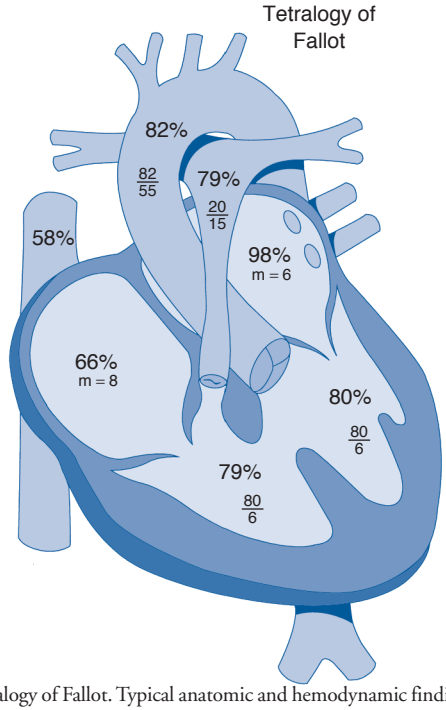

Figure 41.11. Tetralogy of Fallot. Typical anatomic and hemodynamic findings include (i) an anteriorly displaced infundibular septum, resulting in subpulmonary stenosis, a large ventricular septal defect, and overriding of the aorta over the muscular septum; (ii) hypoplasia of the pulmonary valve, main, and branch pulmonary arteries; (iii) equal right and left ventricular pressures; and (iv) a right-to-left shunt at ventricular level, with a systemic oxygen saturation of 82%. m, mean value.

(systemic-to-pulmonary collateral vessels) is necessary before surgical intervention. If echocardiography is not able to fully show these details, then chest computed tomography angiography (CTA), MRI, or diagnostic catheterization is performed. Surgical repair of the asymptomatic child with tetralogy of Fallot is usually recommended within the first 6 months of life. The symptomatic (i.e., severely cyanotic) neonate should have operative neonatal intervention. The decision whether to perform complete repair versus placement of a systemic-to-pulmonary artery shunt is dependent on the institution. In the current era, catheter-based interventions include stenting of the PDA or stenting of the right ventricular outflow tract are frequently used to augment pulmonary blood flow.

5. **Ebstein anomaly** (Figs. 41.12A and 41.12B) is an uncommon and challenging anatomic lesion when it presents in the neonatal period. Anatomically, there is apical displacement of the tricuspid valve into the body of the RV. The tricuspid valve is frequently regurgitant resulting in marked right atrial enlargement and a large right-to-left shunt at the atrial level; there is little forward flow into the pulmonary circulation, often

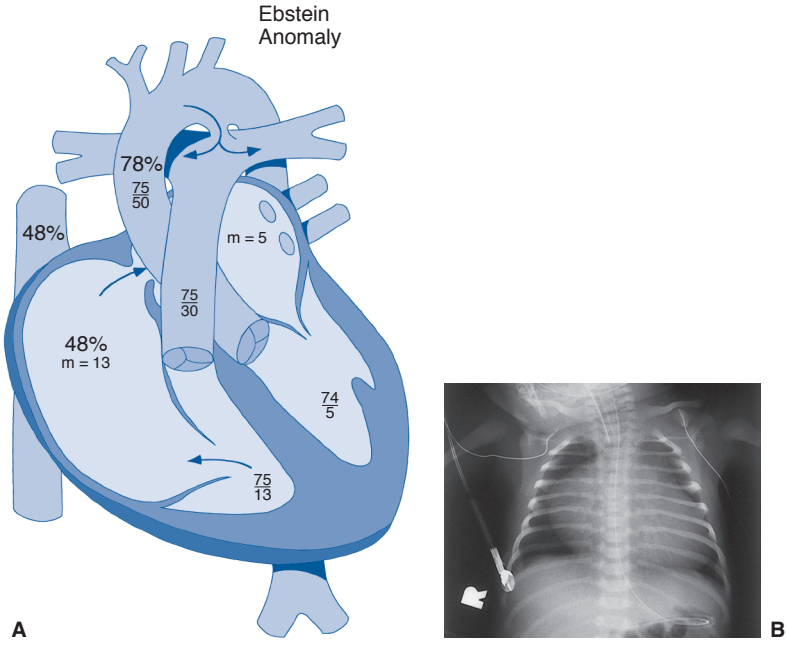

Figure 41.12. **A:** Ebstein anomaly (with large nonrestrictive ductus arteriosus). Typical anatomic and hemodynamic findings include (i) inferior displacement of the tricuspid valve into the right ventricle, which may also cause subpulmonary obstruction; (ii) diminutive muscular right ventricle; (iii) marked enlargement of the right atrium due to "atrialized" portion of right ventricle as well as tricuspid regurgitation; (iv) right-to-left shunting at the atrial level (note arterial oxygen saturation of 78%); (v) a left-to-right shunt and pulmonary hypertension secondary to a large patent ductus arteriosus supplying the pulmonary blood flow; and (vi) low cardiac output (note low mixed venous oxygen saturation in the superior vena cava). **B:** Chest radiograph in a neonate with severe Ebstein anomaly and no significant pulmonary blood flow from the ductus arteriosus. The cardiomegaly is due to marked dilation of the right atrium. The pulmonary vascular markings are diminished due to the decreased pulmonary blood flow. Hypoplasia of the lungs is common due to the large heart causing a "space-occupying lesion." m, mean value.

resulting in functional pulmonary atresia. The prognosis for neonates presenting with profound cyanosis due to Ebstein anomaly is very poor, but outcomes have improved since introduction of the modified Starnes procedure as a palliative strategy. Further complicating the medical condition, Ebstein anomaly is often associated with Wolff-Parkinson-White (WPW) syndrome and supraventricular tachycardia (SVT).

Medical management is aimed at supporting the neonate through the initial period of transitional circulation. Because of elevated pulmonary vascular resistance, pulmonary blood flow may be severely limited with profound hypoxemia and acidosis as a result. Medical treatment includes treatment of pulmonary hypertension with oxygen and inhaled nitric oxide (iNO) (see Chapter 36). If there is pulmonary valve atresia,

PGE_1 is used to maintain patency of the ductus arteriosus. However, the presence of pulmonary regurgitation makes the clinical management more complex. If the RV pressure is high (>20), the goal is to avoid PGE_1 and close the ductus (pharmacologically or surgically) to promote antegrade flow across the pulmonary valve. If the RV pressure is low, then the RV may not be able to eject antegrade. This is the group with the worst prognosis (pulmonary regurgitation and low RV pressure). An important contributor to the high mortality rate in the neonate with severe Ebstein anomaly is the associated pulmonary hypoplasia that is present (due to the massively enlarged right heart *in utero*, see Fig. 41.12B).

C. Parallel circulation/transposition of the great arteries (Fig. 41.13). *Transposition of the great arteries* is defined as an aorta arising from the RV

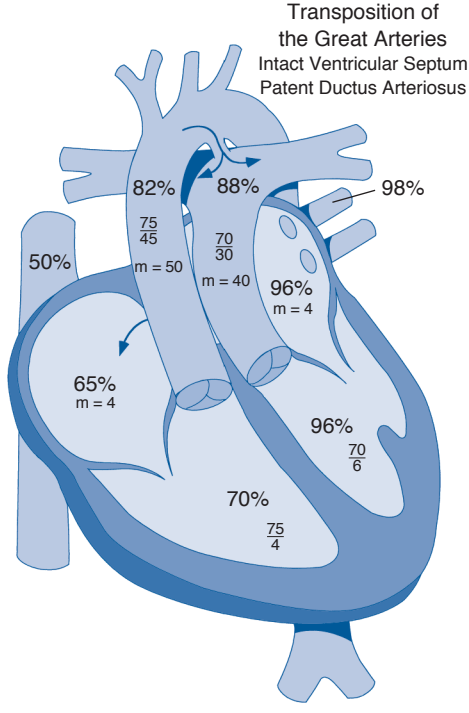

Figure 41.13. Transposition of the great arteries with an intact ventricular septum, a large patent ductus arteriosus (on prostaglandin E_1 [PGE_1]) and atrial septal defect (status postballoon atrial septostomy). Note the following: (i) the aorta arises from the anatomic right ventricle and the pulmonary artery from the anatomic left ventricle; (ii) "transposition physiology," with a higher oxygen saturation in the pulmonary artery than in the aorta; (iii) "mixing" between the parallel circulations (see text) at the atrial (after balloon atrial septostomy) and ductal levels; (iv) shunting from the left atrium to the right atrium through the atrial septal defect (not shown) with equalization of atrial pressures; (v) shunting from the aorta to the pulmonary artery through the ductus arteriosus; (vi) pulmonary hypertension due to a large ductus arteriosus. m, mean value.

and the pulmonary artery from the left ventricle. Approximately one-half of all patients with transposition have an associated VSD.

In the usual arrangement, this creates "parallel circulations" with systemic venous return being pumped through the aorta back to the systemic circulation and pulmonary venous return being pumped through the pulmonary artery to the pulmonary circulation. Following birth, neonates with transposition are dependent on mixing between the parallel systemic and pulmonary circulations to survive. In patients with an intact ventricular septum, mixing occurs primarily at the PFO. These patients are usually clinically cyanotic within the first hours of life leading to their early diagnosis. Those infants with an associated VSD typically have somewhat improved mixing between the systemic and pulmonary circulations and may not be as cyanotic.

In neonates with transposition of the great arteries and an intact ventricular septum, a very low arterial PaO_2 (15 to 20 torr) with high arterial partial pressure of carbon dioxide ($PaCO_2$) (despite adequate chest motion and ventilation) and metabolic acidosis are markers for severely decreased mixing and need urgent attention. The initial management of the severely hypoxemic patient with transposition includes (i) *ensure adequate mixing* between the two parallel circuits and (ii) *maximize mixed venous oxygen saturation.*

In patients with restrictive PFO and severe hypoxemia, *the foramen ovale should be emergently enlarged by balloon atrial septostomy*. Hyperventilation and treatment with sodium bicarbonate are important maneuvers to promote alkalosis, lower pulmonary vascular resistance, and increase pulmonary blood flow (which increases atrial mixing following septostomy). A respiratory acidosis is particularly unfavorable.

In transposition of the great arteries, most of the systemic blood flow is recirculated systemic venous return. In the presence of poor mixing, much can be gained by increasing the mixed venous oxygen saturation, which is the *major determinant of systemic arterial oxygen saturation*. These maneuvers include (i) decreasing the systemic oxygen consumption (sedation, mechanical ventilation, and neuromuscular blockade) and (ii) improving oxygen delivery (increase cardiac output with inotropic agents, increase oxygen-carrying capacity by treating anemia). Coexisting causes of pulmonary venous desaturation (e.g., pneumothorax) should also be sought and treated. Increasing the fraction of inspired oxygen (FiO_2) to 100% will have little effect on the arterial PaO_2, unless it serves to lower pulmonary vascular resistance and increase pulmonary blood flow.

In the current era, definitive management is surgical correction with an arterial switch operation in the early neonatal period. If severe hypoxemia persists despite medical management, mechanical support with extracorporeal membrane oxygenation (ECMO) or an urgent arterial switch operation may be indicated.

D. Lesions with complete intracardiac mixing

1. **Truncus arteriosus** (Fig. 41.14) consists of a single great artery arising from the heart, which gives rise to the coronary arteries, the pulmonary arteries, and the brachiocephalic arteries. The truncal valve is often anatomically abnormal and is frequently thickened, stenotic, and/or regurgitant. A coexisting VSD is present in >98% of cases. The aortic arch is right-sided in approximately one-third of cases. Other arch anomalies

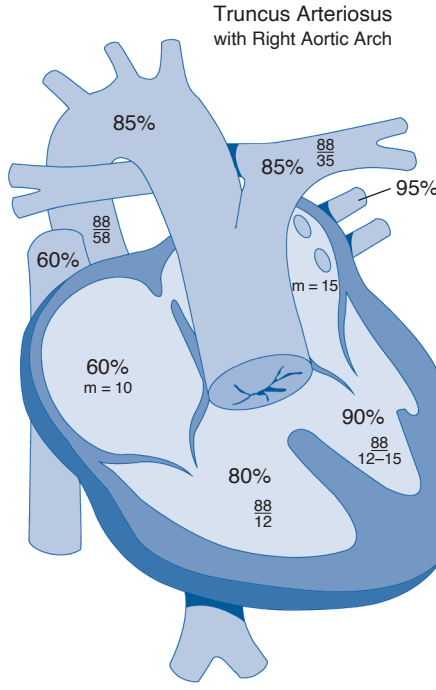

Figure 41.14. Truncus arteriosus (with right aortic arch). Typical anatomic and hemodynamic findings include (i) a single artery arises from the conotruncus giving rise to coronary arteries (not shown), pulmonary arteries, and brachiocephalic vessels; (ii) abnormal truncal valve (quadricuspid shown) with stenosis and/or regurgitation common; (iii) right-sided aortic arch (occurs in ~30% of cases); (iv) large conoventricular ventricular septal defect; (v) pulmonary artery hypertension with a large left-to-right shunt (note superior vena cava oxygen saturation of 60% and pulmonary artery oxygen saturation of 85%); and (vi) complete mixing (of the systemic and pulmonary venous return) occurs at the great vessel level. m, mean value.

such as hypoplasia, coarctation, and interruption are seen in 10% of cases. Extracardiac anomalies are present in 20% to 40% of cases. More than 25% of patients with truncus arteriosus have a chromosome 22q11 deletion.

In the absence of prenatal diagnosis, the overwhelming majority of infants with truncus arteriosus present with symptoms of CHF in the first few days of life. The pulmonary blood flow is increased, with significant pulmonary hypertension common. In the current era, definitive surgery consisting of VSD closure and placement of a conduit from the RV to the pulmonary artery is performed in the neonatal period.

2. **TAPVC** (Figs. 41.15A and 41.15B) occurs when all pulmonary veins drain into the systemic venous system. The anomalous connections of the pulmonary veins may be (i) supracardiac (usually into a vertical vein posterior to the left atrium that connects to the left innominate vein

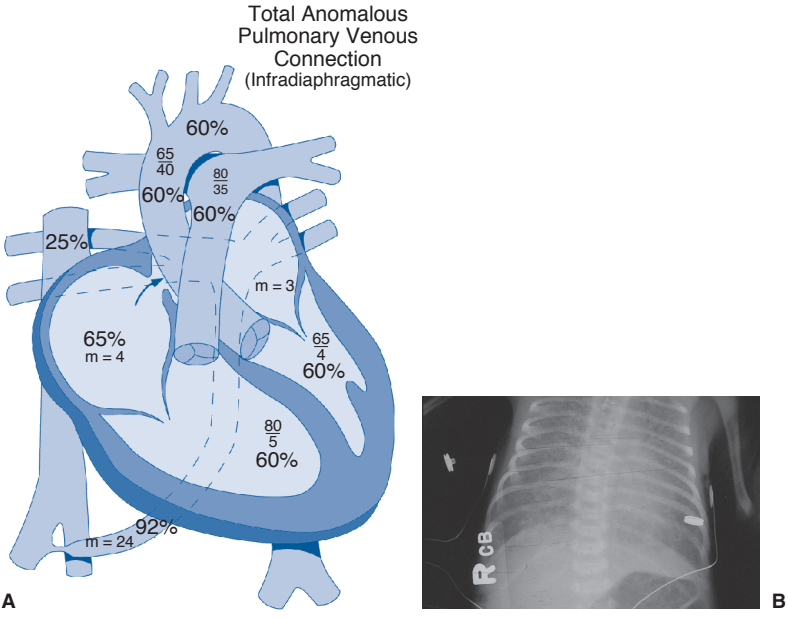

Figure 41.15. **A:** Infradiaphragmatic total anomalous pulmonary venous connection. Note the following: (i) pulmonary venous confluence does not connect with the left atrium but descends to connect with the portal circulation below the diaphragm. This connection is frequently severely obstructed; (ii) obstruction to pulmonary venous return results in significantly elevated pulmonary venous pressures, decreased pulmonary blood flow, pulmonary edema, and pulmonary venous desaturation (92%); (iii) systemic to suprasystemic pressure in the pulmonary artery (in the absence of a patent ductus arteriosus, pulmonary artery pressures may exceed systemic pressures when severe pulmonary venous obstruction is present); (iv) all systemic blood flow must be derived through a right-to-left shunt at the foramen ovale; and (v) nearly equal oxygen saturations in all chambers of the heart (i.e., complete mixing at right atrial level), with severe hypoxemia (systemic oxygen saturation 60%) and low cardiac output (mixed venous oxygen saturation 25%). **B:** Chest radiograph in a 16-hour-old neonate with severe infradiaphragmatic obstruction to pulmonary venous return. Note the pulmonary edema, small heart, and hyperinflated lungs (on mechanical ventilation). Despite high inflating and positive end-expiratory pressures and a fraction of inspired oxygen (FiO_2) of 1, the arterial blood gas revealed a pH of 7.02, arterial carbon dioxide tension ($PaCO_2$) of 84 torr, and an arterial oxygen tension (PaO_2) of 23 torr. Emergent surgical management is indicated. m, mean value.

and the superior vena cava), (ii) cardiac (usually to the right atrium or coronary sinus), (iii) infradiaphragmatic (usually into the portal system), or (iv) mixed drainage.

In patients with total connection below the diaphragm, the pathway is frequently obstructed with severely limited pulmonary blood flow, pulmonary hypertension, and profound cyanosis. This form of TAPVC is a surgical emergency, with minimal beneficial effects from

medical management. Although PGE_1 will maintain ductal patency, the limitation of pulmonary blood flow in these patients is not due to limited antegrade flow into the pulmonary circuit but rather due to outflow obstruction at the pulmonary veins. Obstructed TAPVC represents one of the few remaining neonatal cardiac surgical emergencies. Early recognition of the problem (see Fig. 41.15B) and prompt surgical intervention (surgical anastomosis of the pulmonary venous confluence to the left atrium) are necessary in order for the infant to survive. If missed in the prenatal period, neonates with unobstructed TAPVC are frequently diagnosed by routine neonatal pulse oximetry screening prior to discharge. Patients with a mild degree of obstruction typically have minimal symptoms and may not present until later in infancy when they develop signs and symptoms of CHF.

3. **Complex single ventricles.** There are multiple complex anomalies that share the common physiology of complete mixing of the systemic and pulmonary venous return, frequently with anomalous connections of the systemic and/or pulmonary veins and with obstruction to one of the great vessels (usually the pulmonary artery). In cases with associated polysplenia or asplenia and abnormalities of visceral situs, the term *heterotaxy syndrome* is applied. Physiologically, systemic blood flow and pulmonary blood flow is determined by the balance of anatomic and/or vascular resistance in the systemic and pulmonary circulations. In the well-balanced single ventricle, the oxygen saturation in the pulmonary artery and the aorta will be essentially the same (usually in the high 70% to low 80% range) with a normal pH on arterial blood gas ("single ventricle physiology"). It is beyond the scope of this chapter to define this heterogeneous group of patients further, although all will fail a hyperoxia test, most have significantly abnormal ECGs, and the diagnosis of complex congenital heart disease is rarely in doubt (even before anatomic confirmation with echocardiography). As there is complete mixing of venous return and essentially a single pumping chamber, initial management is similar to that described for hypoplastic left heart syndrome or pulmonary atresia with VSD (see section VI.A.4).

E. Left-to-right shunt lesions. For the most part, infants with left-to-right shunt lesions are not diagnosed because of severe systemic illness but rather due to the finding of a murmur or symptoms of CHF usually occurring in the late neonatal period or beyond. The lesion of this group most likely to require attention in the neonatal nursery is the PDA.

1. **PDA** rarely causes CHF in term newborns. However, the frequency that a premature neonate will develop a hemodynamically significant left-to-right shunt through a PDA is inversely proportional to gestational age and weight (see Chapter 41).

   The typical presentation of a PDA begins with a harsh systolic ejection murmur heard over the entire precordium but loudest at the left upper sternal border and left infraclavicular areas. As the pulmonary vascular resistance decreases, the intensity of the murmur increases and later becomes continuous (i.e., extends through the second heart sound). The peripheral pulses increase in amplitude ("bounding pulses"), the pulse

pressure widens to >25 mm Hg, the precordial impulse becomes hyperdynamic, and the patient's respiratory status deteriorates (manifesting as tachypnea or apnea, carbon dioxide retention, and an increasing mechanical ventilation requirement). Serial chest x-rays show an increase in heart size, and the lungs may appear more radiopaque.

It is important to remember that this typical progression of clinical signs is *not specific* only for a hemodynamically significant PDA. Other lesions may produce bounding pulses, a hyperdynamic precordium, and cardiac enlargement (e.g., an arteriovenous fistula or an aortopulmonary window).

Initial medical management includes increased ventilatory support, fluid restriction, and diuretic therapy. In symptomatic patients, indomethacin, ibuprofen, or acetaminophen may be used for pharmacologic closure of PDA and is effective in approximately 80% of cases. Birth weight does not affect the efficacy of medical therapy, and there is no increase in complications associated with surgery after unsuccessful medical therapy. Adverse reactions to indomethacin and ibuprofen include transient oliguria, electrolyte abnormalities, decreased platelet function, and hypoglycemia. Contraindications to use of indomethacin and ibuprofen as well as dosing information are noted in Appendix A.

Surgical ligation may be considered in neonates in whom one or more courses of pharmacologic therapy fail to close the symptomatic PDA. However, indications for pharmacologic or surgical closure of a PDA in extremely low birth weight (ELBW) infants vary from institution to institution and are controversial. Although presence of a PDA is associated with the development of bronchopulmonary dysplasia (BPD) in ELBW infants, studies show that early or later closure of the PDA does not improve outcomes in these infants (see Chapter 13). Increasingly, transcatheter device PDA closure is possible, even in small infants.

2. **Complete atrioventricular canal** (Fig. 41.16) consists of a combination of defects in the (i) endocardial portion of the atrial septum; (ii) the inlet portion of the ventricular septum; and (iii) a common, single atrioventricular valve annulus. Because of the large net left-to-right shunt, which increases as the pulmonary vascular resistance falls, these infants typically present early in life with symptoms of pulmonary overcirculation. In the absence of associated RV outflow tract obstruction, pulmonary artery pressures are at systemic levels and pulmonary vascular resistance is frequently elevated, particularly in patients with trisomy 21.

   Approximately 70% of infants with complete atrioventricular canal have trisomy 21 (see Table 41.5). Symptoms ensue during the first weeks of life as the pulmonary vascular resistance falls and the patient develops an increasing left-to-right shunt. These patients have a characteristic ECG finding of a "superior axis" (QRS axis from 0 to 180 degrees; Fig. 41.17) which can be a useful clue for the presence of congenital heart disease in an infant with trisomy 21.

   Most patients with complete atrioventricular canal will require medical treatment for symptoms, although prolonged medical therapy in patients with failure to thrive and symptomatic heart failure

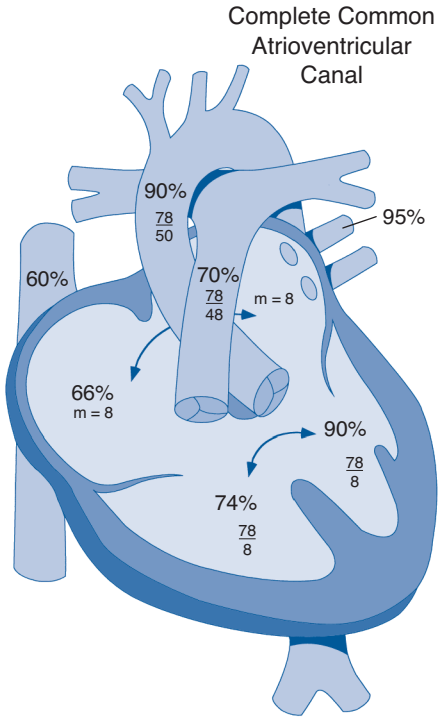

Figure 41.16. Complete common atrioventricular canal. Typical anatomic and hemodynamic findings include (i) large atrial and ventricular septal defects of the endocardial cushion type; (ii) single, atrioventricular valve; (iii) pulmonary artery hypertension (due to large ventricular septal defect); and (iv) bidirectional shunting (with mild hypoxemia) at atrial and ventricular level when pulmonary vascular resistance is elevated in the initial neonatal period. With subsequent fall in pulmonary vascular resistance, the shunt becomes predominantly left-to-right with symptoms of congestive heart failure. m, mean value.

is not warranted. Complete surgical repair is undertaken electively at approximately 4 to 6 months of age, with earlier repair in symptomatic patients.

3. **VSD** is the most common cause of CHF after the initial neonatal period. Moderate-to-large VSDs become hemodynamically significant as the pulmonary vascular resistance decreases and pulmonary blood flow increases via left-to-right shunting across the defect. Because this usually takes 2 to 4 weeks to develop, term neonates with symptomatic VSD should be investigated for coexisting anatomic abnormalities, such as left ventricular outflow tract obstruction, coarctation of the aorta, or PDA. Premature infants, who have a lower initial pulmonary vascular resistance, may develop clinical symptoms of pulmonary overcirculation earlier or require longer mechanical ventilation compared with term infants.

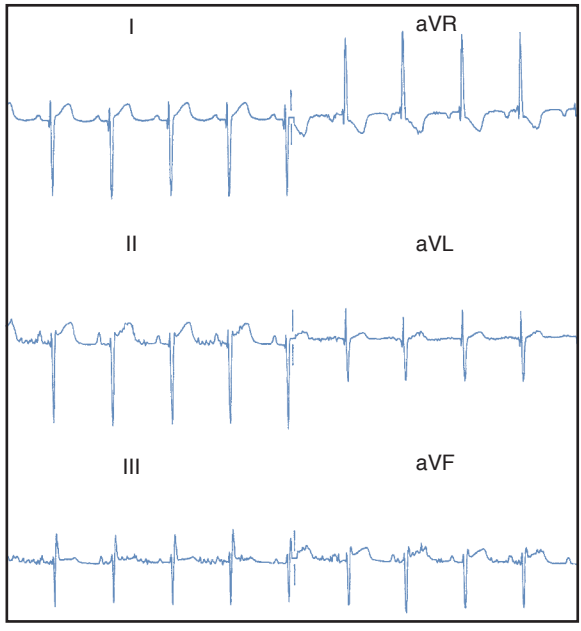

Figure 41.17. Superior ("northwest") axis as seen on the electrocardiogram (only frontal plane leads shown) in a newborn with complete atrioventricular canal. Note the initial upward deflection of the QRS complex (and subsequent predominantly negative deflection) in leads I and aVF. A superior axis (0 to 180 degrees) is present in 95% of patients with endocardial cushion defects.

VSDs may occur anywhere in the ventricular septum and are usually classified by their location (Fig. 41.18). Defects in the membranous septum (also called conoventricular) are the most common type. The diagnosis of VSD is usually initially suspected on physical examination; echocardiography confirms the diagnosis and localizes the defect in the ventricular septum. Because a large number (as many as 90% depending on the anatomic type and size) of VSDs may close spontaneously in the first few months of life, surgery is usually deferred beyond the neonatal period. In large series, only 15% of all patients with VSDs ever become clinically symptomatic. Medical management of symptoms typically includes diuretics and caloric supplementation. Digoxin is used in some institutions. When it occurs, failure to thrive is an indication for surgical repair of the defect.

F. Cardiac surgery in the neonate. Improvements in surgical techniques, cardiopulmonary bypass, and intensive care of the neonate and infant have resulted in significant improvements in surgical mortality and quality of life in the survivors. It is now standard practice to perform definitive repair or palliative procedures in neonates with critical congenital heart defects. It is beyond the scope of this chapter to describe the multiple surgical procedures currently employed in the management of congenital heart disease; the reader is referred to Table 41.9 and general texts of cardiac surgery.

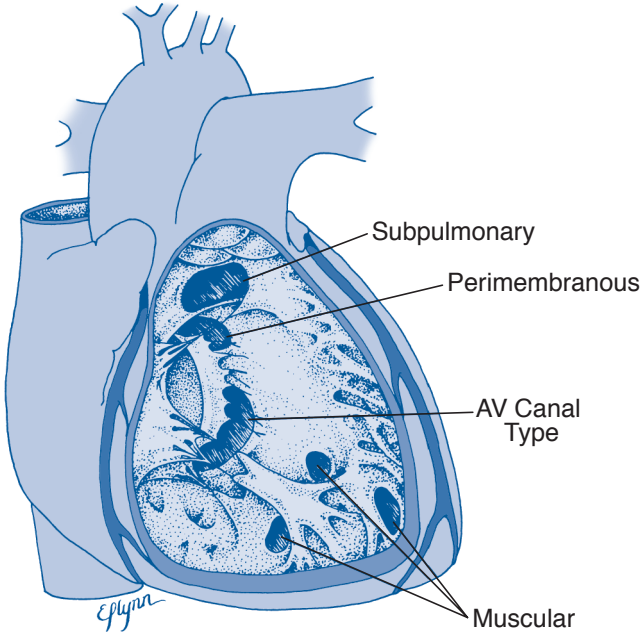

Figure 41.18. Diagram of types of ventricular septal defects as viewed from the right ventricle. AV, arteriovenous. (Reprinted from Fyler DC, ed. *Nadas' Pediatric Cardiology*. St. Louis, MO: Mosby; 1992. Copyright © 1992 Elsevier. With permission.)

Table 41.9. Surgical Repair and Postoperative Complications of Common Lesions

Lesion	Surgical Repair	Postoperative Complications
Aortic coarctation	**1.** Extended end-to-end anastomosis via left thoracotomy, if discrete. **2.** Patch aortic arch augmentation via median sternotomy, if long segment.	Hypertension Vocal cord paralysis Hemidiaphragm paralysis Chylothorax
PDA	Surgical ligation*	Vocal cord paralysis Hemidiaphragm paralysis Chylothorax Aortic or left pulmonary artery injury

(continued)

Table 41.9. Surgical Repair and Postoperative Complications of Common Lesions *(Continued)*

Lesion	Surgical Repair	Postoperative Complications
HLHS	Stage I (Norwood) palliation **1.** Anastomose native aorta to pulmonary artery and reconstruct aortic arch. **2.** Atrial septectomy **3.** Source of restricted pulmonary blood flow (RV-PA conduit or BTT shunt)	Circulatory imbalance due to excessive pulmonary blood flow Vocal cord paralysis Necrotizing enterocolitis Recoarctation Shunt thrombosis (in patients with BTT shunt) Pulmonary artery distortion or stenosis
Tetralogy of Fallot	**1.** VSD closure **2.** Relief of RVOT obstruction with RV muscle bundle resection **3.** One of three options a. RVOT patch and pulmonary valvotomy b. Transannular patch augmentation of the RVOT c. RV-PA conduit if LAD coronary artery crosses RVOT PFO is often left open	Right ventricular systolic and diastolic dysfunction Bidirectional atrial shunting with mild hypoxemia; improves over time Residual VSD Junctional ectopic tachycardiac Residual RVOT obstruction; branch pulmonary artery stenosis Complete heart block
TGA	Arterial switch operation: **1.** Transection of both great arteries above the semilunar valves **2.** Translocation of coronary arteries to the native pulmonary root or neoaortic root **3.** Reanastomosis of the aorta to the LV **4.** Reanastomosis of the pulmonary artery to the RV with or without the LeCompte maneuver (pulmonary artery anterior to aorta) **5.** +/− VSD closure, if applicable	Coronary artery distortion, occlusion, or stenosis Supravalvar PS and branch pulmonary artery stenosis Chylothorax Hemidiaphragm paralysis Complete heart block with VSD closure

(continued)

Table 41.9. *(Continued)*

Lesion	Surgical Repair	Postoperative Complications
Truncus arteriosus	**1.** VSD closure **2.** Separation of pulmonary arteries from the common trunk **3.** RV-PA conduit	Pulmonary hypertension RV systolic or diastolic dysfunction Residual VSD Complete heart block
TAPVR	Opening of left atrium and pulmonary venous confluence and either direct anastomosis of the confluence to the left atrium or left atrium sewn to pericardium surrounding the pulmonary venous confluence (sutureless repair)	Pulmonary hypertension Residual or recurrent pulmonary venous obstruction Sinus node dysfunction Atrial arrhythmias
Palliative strategies for lesions with inadequate or excessive pulmonary blood flow	Inadequate pulmonary blood flow: **1.** PDA stent (transcatheter procedure) **2.** BTT shunt: synthetic shunt between the innominate artery and branch pulmonary artery **3.** Central shunt: anastomotic shunt between the ascending aorta and main pulmonary artery (used to promote growth of small pulmonary arteries, such as in tetralogy of Fallot with pulmonary atresia and MAPCAS) Excessive pulmonary blood flow **1.** Pulmonary artery band placement	Circulatory imbalance due to excessive pulmonary blood flow Shunt or stent thrombosis Vocal cord paralysis Necrotizing enterocolitis Hemidiaphragm paralysis Chylothorax Pulmonary artery distortion

*If device closure via cardiac catheterization is not feasible due to PDA size or anatomy.
PDA, patent ductus arteriosus; HLHS, hypoplastic left heart syndrome; RV-PA, right ventricle to pulmonary artery; BTT, Blalock-Taussig-Thomas; VSD, ventricular septal defect; RVOT, right ventricular outflow tract; LAD, left anterior descending; PFO, patent foramen ovale; TGA, transposition of the great arteries; LV, left ventricle; PS, pulmonary stenosis; TAPVR, total anomalous pulmonary venous repair; MAPCAS, major aortopulmonary collateral arteries.TGA, transposition of the great arteries; PA, pulmonary artery; RV, right ventricle; LV, left ventricle; TOF, tetralogy of Fallot; VSD, ventricular septal defect; RVOT, right ventricular outflow tract; PFO, patent foramen ovale; CoA, coarctation of the aorta; PDA, patent ductus arteriosus; TAPVC, total anomalous pulmonary venous connection; HLHS, hypoplastic left heart syndrome.
Source: Data from Wernovsky G, Erickson LC, Wessel DL. Cardiac emergencies. In: May HL, ed. *Emergency Medicine*. Boston, MA: Little, Brown and Company; 1992.

VII. ACQUIRED HEART DISEASE

A. Myocarditis may occur in the neonate as an isolated illness or as a component of a generalized illness with associated hepatitis and/or encephalitis. Myocarditis is usually the result of a viral infection (enterovirus, adenovirus, and parvovirus are most common), although other infectious agents such as bacteria and fungi as well as noninfectious conditions such as autoimmune diseases also may cause myocarditis. Although the clinical presentation (and in some cases, endomyocardial biopsy) makes the diagnosis, specific identification of the etiologic agent may not be made in most cases.

The infant with acute myocarditis presents with signs and symptoms of CHF (see section IV.B) and/or arrhythmia (see section IX). The course of the illness is frequently fulminant, but, full recovery of ventricular function may occur if the infant can be supported and survive the acute illness. Supportive care includes supplemental oxygen, diuretics, inotropic agents, afterload reduction, and mechanical ventilation. Inotropic agents should be used with caution because ventricular arrhythmias are common. In severe cases, mechanical support of the myocardium with ECMO or ventricular assist devices can be considered.

B. Transient myocardial ischemia with myocardial dysfunction may occur in any neonate with a history of perinatal asphyxia. Myocardial dysfunction may be associated with maternal autoimmune disease such as systemic lupus erythematosus. A tricuspid or mitral regurgitant murmur is often heard. An elevated serum creatine kinase myocardial bound (MB) fraction or cardiac troponin level may be helpful in determining the presence of myocardial damage. Supportive treatment is dictated by the severity of myocardial dysfunction.

C. Hypertrophic and dilated cardiomyopathies represent a rare and multifactorial complex of diseases, complete discussion of which is beyond the scope of this chapter. The differential diagnosis includes primary diseases (e.g., genetic causes as well as metabolic, storage, and neuromuscular disorders) or secondary diseases (e.g., end-stage infection, ischemic, endocrine, nutritional, drugs). The reader is referred to texts of pediatric cardiology for more complete discussion.

The most common hypertrophic cardiomyopathy presenting in neonates is that type seen in **infants born to diabetic mothers**. Echocardiographically and hemodynamically, these infants are indistinguishable from patients with other types of hypertrophic cardiomyopathy. They are different in one important respect: Their cardiomyopathy is expected to completely resolve in 6 to 12 months. Noting a systolic ejection murmur, with or without CHF, in the infant of a diabetic mother, should raise the question of congenital heart disease including hypertrophic cardiomyopathy. Treatment is supportive, addressing the infant's particular CHF symptoms. Propranolol has been used successfully in some patients with severe obstruction. Most patients require no specific care and no long-term cardiac follow-up (see Chapter 2).

VIII. PHARMACOLOGY

A. PGE_1. PGE_1 has been used since the late 1970s to pharmacologically maintain patency of the ductus arteriosus in patients with ductal-dependent

Table 41.10. Catecholamines

Drug	Usual Dose (μg/kg/minute)	Effect
Dopamine	1–5	↑ Urine output, ↑ HR (slightly), ↑ contractility
	6–10	↑ HR, ↑ contractility, ↑ BP
	11–20	↑ HR, ↑ contractility, ↑ SVR, ↓ BP
Dobutamine	1–20	↑ HR, ↑ contractility, ↓ SVR
Epinephrine	0.01–0.50	↑ HR, ↑ contractility, ↑ SVR, ↑ BP
Isoproterenol	0.01–1.00	↑ HR, ↑ contractility, ↓ SVR, ↓ PVR

HR, heart rate; BP, blood pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; ↑, increased; ↓, decreased.

systemic or pulmonary blood flow. It must be administered as a continuous parenteral infusion. The usual starting dose is 0.01 to 0.05 μg/kg/minute. The response to PGE_1 is often immediate if patency of the ductus arteriosus is important for the hemodynamic state of the infant. Failure to respond to PGE_1 may mean that the initial diagnosis was incorrect, the ductus arteriosus is unresponsive to PGE_1 (usually only in an older infant), or the ductus is absent. The infusion site has no significant effect on the ductal response to PGE_1. Adverse reactions to PGE_1 include apnea (10% to 12%), fever (14%), cutaneous flushing (10%), hypotension (<10%), bradycardia (7%), seizures (4%), tachycardia (3%), cardiac arrest (1%), and edema (1%).

B. Catecholamine infusions are the mainstay of pharmacologic therapies aimed at improving cardiac output and are discussed in detail elsewhere in this book (see Chapter 40). Catecholamines, endogenous (dopamine, epinephrine, norepinephrine) or synthetic (dobutamine, isoproterenol), work by stimulating myocardial and vascular adrenergic receptors. These agents must be given as continuous parenteral infusions. They may be given in combination to the critically ill neonate in an effort to maximize the positive effects of each agent while minimizing the negative effects. While receiving catecholamine infusions, patients should be closely monitored, usually with an electrocardiographic monitor and an arterial catheter. Before beginning catecholamine infusions, intravascular volume should be repleted if necessary, although this may further compromise a congenital lesion with coexisting volume overload. Adverse reactions to catecholamine infusions include tachycardia (which increases myocardial oxygen consumption), atrial and ventricular arrhythmias, and increased afterload due to peripheral vasoconstriction (which may decrease cardiac output). See Table 41.10 for recommended dosing of the catecholamines.

C. Afterload-reducing agents

1. **Phosphodiesterase inhibitors** such as *milrinone* selectively inhibit cyclic nucleotide phosphodiesterase. These nonglycosidic and nonsympathomimetic agents exert their effect on cardiac performance by increasing cyclic adenosine monophosphate (cAMP) in the myocardial and vascular muscle, but do so independently of β-receptors. cAMP promotes improved contraction through calcium regulation through two mechanisms: (i) activation of protein kinase (which catalyzes the transfer of phosphate groups from adenosine triphosphate [ATP]) leading to faster calcium entry through calcium channels and (ii) activation of calcium pumps in the sarcoplasmic reticulum resulting in release of calcium.

   There are three major effects of phosphodiesterase inhibitors: (i) increased inotropy; (ii) vasodilatation, with increase in arteriolar and venous capacitance; and (iii) increased lusitropy, or improved relaxation during diastole.

   Indications for use include low cardiac output with myocardial dysfunction and elevated systemic vascular resistance (SVR) not accompanied by severe hypotension. Side effects have been minimal and are typically the need for volume infusions (5 to 10 mL/kg) following loading dose administration. As such, many institutions avoid loading dose administration and start the infusion at the desired dosing. See Appendix A for dosing information.

   The use of milrinone after cardiac surgery in the pediatric patient population has been shown to increase cardiac index and decrease SVR without a significant increase in heart rate. Milrinone is currently the first-line drug in the treatment of low cardiac output in neonates, infants, and children following cardiopulmonary bypass. Caution should be used in patients with renal insufficiency.

2. **Other vasodilators** such as sodium nitroprusside improve low cardiac output principally by decreasing impedance to ventricular ejection; these effects are especially helpful after cardiac surgery in children and in adults when SVR is particularly elevated.

   Many other agents have been used as arterial and venous vasodilators to treat hypertension, reduce ventricular afterload and SVR, and improve cardiac output. A second nitrovasodilator, *nitroglycerine*, principally *a venous dilator,* also has rapid onset of action and a short half-life (~2 minutes). Tolerance may develop after several days of continuous infusion. Nitroglycerine is used extensively in adult cardiac units for patients with ischemic heart disease; experience in pediatric patients is more limited. *Hydralazine* is more typically used for acute hypertension (example: after repair of coarctation); its relatively long half-life limits its use in postoperative patients with labile hemodynamics. *β-Blockers* (e.g., propranolol, esmolol, labetalol), although excellent in reducing blood pressure, may have deleterious effects on ventricular function. *Central-acting calcium channel blockers (e.g., verapamil, diltiazem) are contraindicated in children younger than 1 because they may cause acute and severe hypotension and bradycardia.* However, peripherally acting calcium channel blockers like *nicardipine* have been safely used in neonates after cardiac surgery. All IV vasodilators must be used cautiously in patients

with moderate-to-severe lung disease; their use has been associated with increased intrapulmonary shunting and acute reductions of PaO_2.

D. Digoxin (see Appendix A) remains important for the treatment of CHF and arrhythmia. A "digitalizing dose" (with a total dose of 30 μg/kg in 24 hours for term infants and 20 μg/kg in 24 hours for premature infants) is usually only used for treatment of arrhythmias or severe heart failure. One-half of this total digitalizing dose (TDD) may be given IV, intramuscular (IM), or oral (PO), followed by one-fourth of the TDD every 8 to 12 hours for the remaining two doses. An initial maintenance dose (range 5 to 10 μg/kg/day) may then be adjusted according to the patient's clinical response, renal function, and tolerance for the drug (see Appendix A for further details). The loading dose may be omitted in infants with mild symptoms, primary myocardial disease, renal dysfunction, or the potential for atrioventricular block. The maintenance dose is divided into equal twice-daily doses.

Digoxin toxicity most commonly manifests with gastrointestinal upset, somnolence, and sinus bradycardia. More severe digoxin toxicity may cause high-grade atrioventricular block and ventricular ectopy. Infants suspected of having digoxin toxicity should have a digoxin level drawn and further doses withheld. The therapeutic level is <1.5 ng/mL, with probable toxicity occurring at levels >4.0 ng/mL. In infants particularly, however, digoxin levels do not always correlate well with therapeutic efficacy or with toxicity.

Digoxin toxicity in neonates is usually manageable by withholding further doses until the signs of toxicity resolve and by correcting electrolyte abnormalities (such as hypokalemia), which can potentiate toxic effects. Severe ventricular arrhythmias associated with digoxin toxicity may be managed with phenytoin, 2 to 4 mg/kg over 5 minutes, or lidocaine, 1 mg/kg loading dose, followed by an infusion at 1 to 2 mg/kg/hour. Atrioventricular block is usually unresponsive to atropine. Severe bradycardia may be refractory to these therapies and require temporary cardiac pacing.

The use of digoxin-specific antibody Fab (antigen-binding fragments) preparation (Digibind) is rare and reserved for those patients with evidence of severe digoxin intoxication and clinical symptoms of refractory arrhythmia and/or atrioventricular block.

E. Diuretics (see Appendix A) are frequently used in patients with CHF, often in combination with digoxin. **Furosemide**, 1 mg/kg per dose, usually results in a brisk diuresis within an hour of administration. If no response is noted in an hour, a second dose (double the first dose) may be given. Chronic use of furosemide may produce urinary tract stones as a result of its calciuric effects. A more potent diuretic effect may be achieved using a combination of a thiazide and a "loop" diuretic such as furosemide. Combination diuretic therapy may be complicated by hyponatremia and hypokalemia. PO or IV potassium supplementation or an aldosterone antagonist usually should accompany the use of thiazide and/or "loop" diuretics to avoid excessive potassium wasting. It is important to carefully monitor serum potassium and sodium levels when beginning or changing the dose of diuretic medications. When changing from an effective parenteral to PO dose of furosemide, the dose should be increased by 50% to 80%. Furosemide may increase the nephrotoxicity and ototoxicity of concurrently used aminoglycoside antibiotics. Detailed discussion of alternative diuretics (e.g., chlorothiazide, spironolactone) is found elsewhere in the text (see Appendix A).

IX. ARRHYTHMIAS

A. Initial evaluation. When evaluating any infant with an arrhythmia, it is essential to simultaneously assess the electrophysiology and hemodynamic status. If the baby is poorly perfused and/or hypotensive, reliable IV access should be secured and a level of resuscitation employed appropriate for the degree of illness. As always, emergency treatment of shock should precede definitive diagnosis. It should be emphasized, however, that there is rarely a situation in which it is justified to omit a 12-lead ECG from the evaluation of an infant with an arrhythmia, the exceptions being ventricular fibrillation or torsade de pointes with accompanying hemodynamic instability. These arrhythmias frequently require immediate defibrillation but are extremely rare in neonates and young infants.

Appropriate therapy (short- and long-term) depends on an accurate electrophysiologic diagnosis. Determination of the mechanism of a rhythm disturbance is most often made from a 12-lead ECG in the abnormal rhythm compared to the patient's baseline 12-lead ECG in sinus rhythm. Although rhythm strips generated from a cardiac monitor can be helpful supportive evidence of the final diagnosis, they are typically not diagnostic and should not be the only documentation of arrhythmia if at all possible.

The three broad categories for arrhythmias in neonates are (i) tachyarrhythmias, (ii) bradyarrhythmias, and (iii) irregular rhythms. An algorithm for approaching the differential diagnosis of tachyarrhythmias can be consulted (Fig. 41.19) in most cases. When analyzing the ECG for the mechanism of arrhythmia, a stepwise approach should be taken in three main areas: (i) *rate* (variable, too fast, or too slow), (ii) *rhythm* (regular or irregular, paroxysmal or gradual), and (iii) *QRS morphology*.

B. Differential diagnosis and initial management in the hemodynamically stable patient

1. Narrow QRS complex tachycardias

a. SVT is the most common symptomatic arrhythmias in all children, including neonates. SVTs usually have (i) a rate >220 beats per minute, frequently "fixed" with no beat-to-beat variation in rate; (ii) rapid onset and termination (in reentrant rhythms); and (iii) normal ventricular complexes on the surface ECG. The infant may initially be asymptomatic but may become irritable, fussy, and refuse feedings. CHF usually does not develop before 24 hours of continuous SVT; however, heart failure is seen in 20% of patients after 36 hours and in 50% after 48 hours.

SVT in the neonate is almost always "reentrant," involving either an accessory atrioventricular pathway and the atrioventricular node or due to atrial flutter. Approximately half of these patients will manifest preexcitation (delta wave) on the ECG when not in tachycardia (WPW syndrome; Fig. 41.20). Evaluation for structural heart disease should be considered in all neonates with SVT and is present in 10% to 15%. Another rare cause of SVTs in a neonate is ectopic atrial tachycardia in which the distinguishing features are an abnormal P wave axis, normal QRS axis, and gradual onset.

Long-term medical therapy for SVT in the neonate is based on the underlying electrophysiologic diagnosis. *β-Blocker therapy* is the initial

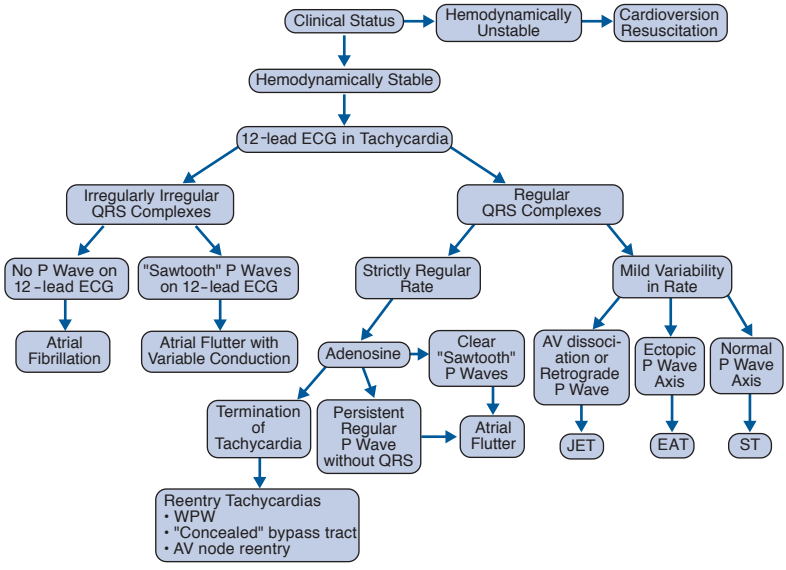

Figure 41.19. Algorithm for bedside differential diagnosis of narrow complex tachycardias, the most common type of arrhythmia in neonates. Note that, regardless of the mechanism of tachycardia, if the patient is hemodynamically unstable, immediate measures to resuscitate the infant including cardioversion are required. Also, treatment with adenosine is helpful therapeutically as well as diagnostically. In general, tachycardias that terminate (even briefly) after adenosine are of the reentry type. ECG, electrocardiogram; AV, atrioventricular; JET, junctional ectopic tachycardia; EAT, ectopic atrial tachycardia; ST, sinus tachycardia; WPW, Wolff-Parkinson-White syndrome.

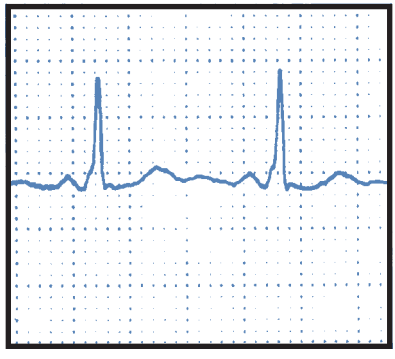

Figure 41.20. Wolff-Parkinson-White syndrome. Note the characteristic "slurred" initial QRS deflection and short PR interval that can occur in any lead; lead I only pictured here.

therapy of choice. *Propranolol* is used as the initial and chronic drug therapy for patients with SVT due to WPW syndrome. Treatment with propranolol may be associated with apnea and hypoglycemia; therefore, neonates started on propranolol should be observed on a continuous cardiac monitor and have serial serum glucose evaluated for 1 to 2 days. If the patient is successfully maintained in sinus rhythm, therapy is continued for 6 to 12 months.

Digoxin is also commonly used in non-WPW syndrome SVT without CHF. Digoxin is avoided in WPW syndrome because of its potential for enhancing antegrade conduction across the accessory pathway. Vagal maneuvers (ice in a plastic bag applied to the face to elicit the "diving reflex") may be tried in stable neonates. Direct pressure over the eyes should be avoided.

The addition or substitution of other antiarrhythmic drugs such as amiodarone alone or in combination may be necessary and should be done only in consultation with a pediatric cardiologist. *Verapamil should not be used* in neonates because it carries a risk of bradycardic, hypotensive cardiac arrest.

In utero SVT may be suspected when a very rapid fetal heart rate is noted by the obstetrician during prenatal care. The diagnosis is confirmed by fetal echocardiography. At that time, an initial search for congenital heart disease and fetal hydrops may be made. *In utero* treatment of the immature fetus with SVT may be accomplished by treatment of the mother with antiarrhythmic drugs that cross the placenta. Digoxin, flecainide, and other antiarrhythmic drugs have been successful therapies. Failure to control the fetal SVT in the presence of fetal hydrops is an indication for delivery. Cesarean delivery of an infant in persistent SVT may be necessary because the fetal heart rate will not be a reliable indicator of fetal distress.

b. Sinus tachycardia in the neonate is defined as persistent heart rate >2 standard deviations above the mean for age with normal ECG complexes including a normal P-wave morphology and axis. Sinus tachycardia is common and occurs particularly in response to systemic events such as anemia, stress, fever, high levels of circulating catecholamines, and hypovolemia. Sinus tachycardia is common in the postoperative period and causes include hypovolemia, tamponade, and low cardiac output. An important clue to the existence of sinus tachycardia, in addition to its normal ECG morphology, is that the rate is not fixed but rather will vary by 10% to 20% over time. Medical management consists of identifying and treating the underlying cause.

2. Wide-complex tachycardia

a. Ventricular tachycardia in the neonate is relatively rare and is usually associated with severe medical illnesses including hypoxemia, shock, electrolyte disturbances, digoxin toxicity, and catecholamine toxicity. It may rarely be due to an abnormality of the electrical conducting system of the heart such as prolonged QTc syndrome and intramyocardial tumors. This ECG pattern may be simulated by SVT in patients with WPW syndrome in whom there is antegrade conduction through the anomalous pathway (SVT with "aberrancy"). Ventricular tachycardia is a potentially unstable rhythm. The underlying cause should be rapidly sought

and treated. The hemodynamically stable patient should be treated with amiodarone or lidocaine. Direct current cardioversion (starting dose to 1 to 2 J/kg) should be used if the patient is hemodynamically compromised, although will frequently be ineffective in the presence of acidosis. If a severe acidosis (pH <7.2) is present, it should be treated with hyperventilation and/or sodium bicarbonate before cardioversion.

b. Ventricular fibrillation in the neonate is almost always an agonal arrhythmia. There is a coarse, irregular pattern on ECG with no identifiable QRS complexes. There are no peripheral pulses or heart sounds on examination. Cardiopulmonary resuscitation should be instituted and defibrillation (starting dose 1 to 2 J/kg) performed. Antiarrhythmics and evaluation for underlying causes should be initiated.

3. Bradycardia

a. Sinus bradycardia in the neonate is not uncommon especially during sleep or during vagal maneuvers, such as bowel movements. If the infant's perfusion and blood pressure are normal, transient bradycardia is not of major concern. Persistent sinus bradycardia may be secondary to hypoxemia, acidosis, and elevated intracranial pressure. Finally, a stable sinus bradycardia may occur with digoxin toxicity, hypothyroidism, or sinus node dysfunction (usually a complication of cardiac surgery).

b. Heart block

i. First-degree atrioventricular block occurs when the PR interval is >0.16 seconds. In the neonate, first-degree atrioventricular block may be due to a nonspecific conduction disturbance, medications (e.g., digoxin), myocarditis, hypothyroidism, or associated with certain types of congenital heart disease (e.g., complete atrioventricular canal or ventricular inversion). No specific treatment is generally indicated.

ii. Second-degree atrioventricular block. Second-degree atrioventricular block refers to intermittent failure of conduction of the atrial impulse to the ventricles. Two types have been described: (i) Mobitz I (Wenckebach phenomenon) and (ii) Mobitz II (intermittent failure to conduct P waves, with a constant PR interval). Second-degree atrioventricular block may occur with atrial flutter, digitalis toxicity, or a nonspecific conduction disturbance. No specific treatment is usually necessary other than diagnosis and treatment of the underlying cause.

iii. Complete heart block (CHB) refers to complete absence of conduction of any atrial activity to the ventricles. CHB typically has a slow, constant ventricular rate that is independent of the atrial rate. CHB is frequently detected *in utero* as fetal bradycardia. Although CHB may be secondary to surgical trauma, congenital CHB falls into two main categories. The most common causes include (i) anatomic defects (ventricular inversion or L-transposition of great artery and heterotaxy syndrome) and (ii) fetal exposure to maternal antibodies related to systemic rheumatologic disease such as lupus erythematosus. The presence of CHB without structural heart disease should alert the clinician to investigate the mother for rheumatologic disease. Although generally well tolerated, fetal CHB may

progress to fetal distress or hydrops fetalis, for which early delivery may be required. Patients with inadequate hemodynamics after delivery may benefit from cardiac pacing immediately after birth.

4. **Irregular rhythms**

a. Premature atrial contractions (PACs; Fig. 41.21) are common in neonates, are usually benign, and do not require specific therapy. Most PACs result in a normal QRS morphology (see Fig. 41.21A),

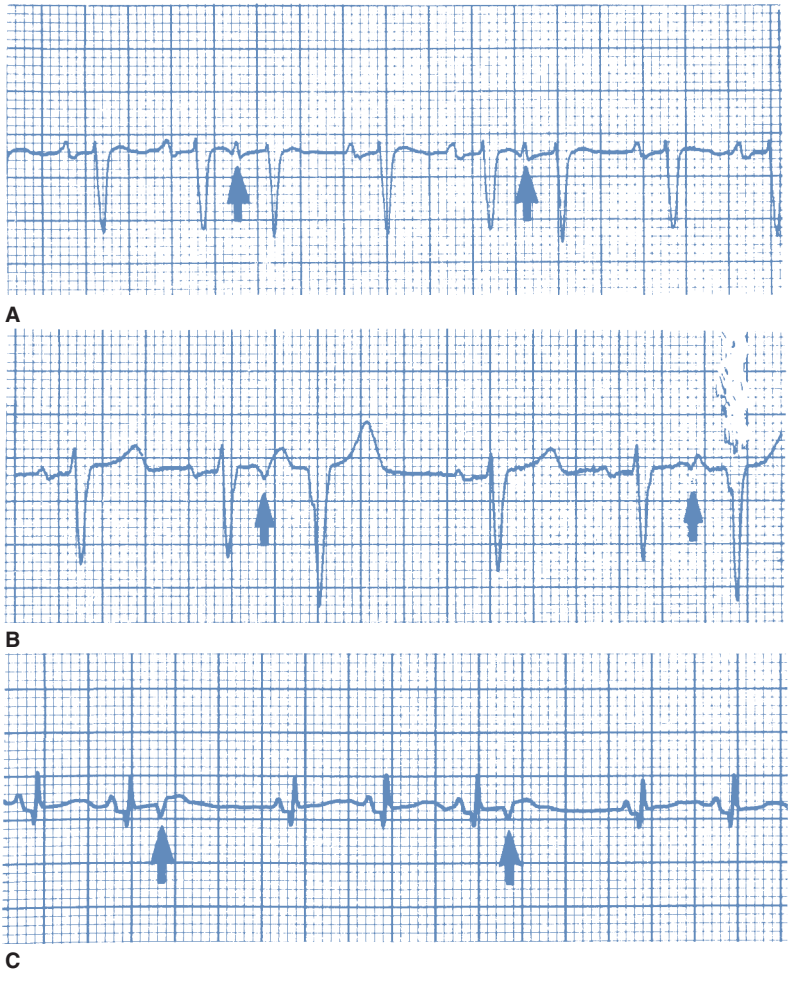

Figure 41.21. Premature atrial contractions (*arrows*) causing (**A**) early ventricular depolarization with a normal QRS complex. **B:** Early ventricular depolarization with "aberration" of the QRS complex. **C:** Block at the atrioventricular node. (Reprinted from Fyler DC, ed. *Nadas' Pediatric Cardiology*. St. Louis, MO: Mosby; 1992. Copyright © 1992 Elsevier. With permission.)

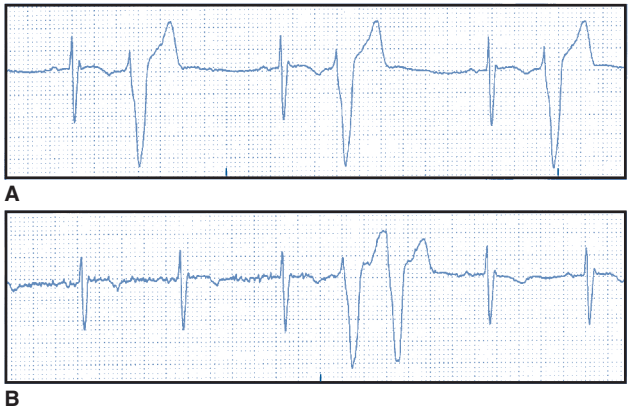

Figure 41.22. Premature ventricular contractions (PVCs). **A:** PVCs alternating with normal sinus beats (ventricular bigeminy) are usually not indicative of significant pathology. **B:** Paired PVCs ("couplet") are a potentially more serious rhythm and require further investigation.

distinguishing them from premature ventricular contractions (PVCs). If the PAC occurs while the atrioventricular node is partially repolarized, an aberrantly conducted ventricular depolarization pattern may be observed on the surface ECG (see Fig. 41.21B). If the premature beat occurs when the atrioventricular node is refractory (i.e., early in the cardiac cycle, occurring soon after the normal sinus beat), the impulse will not be conducted to the ventricle ("blocked") and may therefore give the appearance of sinus bradycardia (see Fig. 41.21C).

b. PVCs (Fig. 41.22) are "wide QRS complex" beats that occur when a ventricular focus stimulates a spontaneous beat before the normally conducted sinus beat. Isolated PVCs are not uncommon in the normal neonate and do not generally require treatment. Although PVCs frequently occur sporadically, they occasionally are grouped, such as every other beat (bigeminy; see Fig. 41.22A), every third beat (trigeminy), and so on. These more frequent PVCs are typically no more worrisome than isolated PVCs, although their greater frequency usually prompts a more extensive diagnostic workup. PVCs may be caused by digoxin toxicity, hypoxemia, electrolyte disturbances, catecholamine, or xanthine toxicity. PVCs occurring in groups of two or more (i.e., couplets, triplets, etc.; see Fig. 41.22B) are pathologic and may be a marker for myocarditis or myocardial dysfunction.

C. Emergency arrhythmia management. It is important to have easily accessible resuscitation equipment available before proceeding with any antiarrhythmic interventions. When possible, an ECG machine should be attached to the patient to document the conversion to sinus rhythm.

1. Tachycardia

a. Adenosine. Adenosine has become the drug of choice for acute management of stable SVT which is unresponsive to vagal maneuvers.

Adenosine transiently blocks AV nodal conduction, allowing termination of rapid reentrant rhythms involving the AV node. It must be given by very rapid IV push because its half-life is 10 seconds or less. Due to this short half-life, adenosine is a relatively safe medication. Adenosine, by virtue of its acute action on the AV node, is frequently diagnostic as well. Patients who respond with abrupt termination of the SVT have reentrant tachycardias involving the AV node; those with SVT due to atrial flutter will have acute AV block and easily visible flutter waves with reappearance of SVT in 10 to 15 seconds.

b. Cardioversion. In the hemodynamically unstable patient, first-line therapy is synchronized direct current cardioversion. The energy should start at 0.5 J/kg and be increased by a factor of 2 if unsuccessful. Pad position should be anterior–posterior, if possible.

D. Bradycardia. Therapeutic options for treating symptomatic bradycardia are more limited. Transcutaneous or transvenous pacing is a temporary measure in severely symptomatic neonates while preparing for placement of permanent epicardial pacemaker leads; however, transvenous pacing in a small neonate is technically difficult and frequently requires fluoroscopy. A number of transcutaneous pacemakers (Zoll) are available, but long-term use must be avoided due to cutaneous burns. An isoproterenol infusion may temporarily increase the ventricular rate and cardiac output. For the infant with transient bradycardia (due to increased vagal tone), IV atropine may be used.

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42 Blood Products Used in the Newborn

Steven R. Sloan

KEY POINTS

- Blood components should be transfused when clinically indicated to promote oxygen delivery and coagulation.
- Immunocompromised patients such as those with congenital immune deficiencies or very low weight infants are at risk for transfusion-associated graft-versus-host disease (TA-GVHD) and require red blood cell (RBC) and platelet units that have been irradiated or pathogen reduced.
- Neonates at risk for cytomegalovirus (CMV) should receive blood components that are CMV safe. Blood from donors lacking antibodies to CMV and leukoreduced blood components are CMV safe.
- Risks of transfusion-transmitted infections are very low. Recent interventions have reduced the risk of bacterial contamination of platelets.

I. WHOLE BLOOD AND BLOOD COMPONENT TRANSFUSIONS

A. General principles. There are six types of blood components including packed red blood cells (RBCs), platelets, frozen plasma, fresh frozen plasma (FFP), cryoprecipitate (CRYO), and granulocytes. In some cases, such as neonatal exchange transfusions, whole blood, usually in the form of reconstituted whole blood, is used. However, in most other cases, blood components are preferred because each component is condition-specific, has unique optimal storage conditions, and component therapy maximizes the use of blood donations. Other blood products include those used for hematopoietic stem cell transplants, such as umbilical cord blood (UCB), and derivatives purified from blood, such as intravenous immunoglobulin (IVIG).

B. Side effects

1. Infectious diseases. A variety of infectious diseases can be transmitted by blood transfusion. In the United States, HIV, hepatitis B virus, hepatitis C virus, syphilis, human T-lymphotropic virus types I or II (HTLV I/II), Chagas disease, and West Nile virus are screened for by donor history questionnaires and laboratory tests. Blood collected in states endemic for babesiosis is tested for that disease. Donated blood has also been tested for Zika virus, but this testing is being discontinued

Table 42.1. Current Infectious Disease Risks from Blood Transfusions

Pathogen	Risk per Unit
Human immunodeficiency virus (HIV)	1 in 2,135,000
Hepatitis C virus (HCV)	1 in 1,935,000
Hepatitis A virus	1 in 1,000,000
Hepatitis B virus (HBV)	1 in 205,000–488,000
West Nile virus (WNV)	none
Parvovirus B19	1 in 10,000

Source: Modified from Stramer SL. Current risks of transfusion-transmitted agents: a review. *Arch Pathol Lab Med* 2007;131(5):702–707; Reprinted with permission from *Archives of Pathology & Laboratory Medicine*. Copyright 2007. College of American Pathologists.

because the risk of transfusion-transmitted Zika virus is negligible in the United States. Medical history questionnaires alone are used to screen for other diseases such as malaria and Creutzfeldt-Jakob disease. The risk of acquiring a transfusion-transmitted infectious disease is very low and too low to accurately measure but has been calculated in the United States and are shown in Table 42.1. The risks vary depending on the prevalence of the disease and the testing performed and thus differ in other countries. Of note, SARS-CoV-2 has not been reported to be transmitted by blood transfusion.

Cytomegalovirus (CMV) can also be transmitted by blood, but this is rare if the blood is leukoreduced or it tests negative for antibodies to CMV. Animal studies suggest that variant Creutzfeldt-Jakob disease (vCJD) can also be transmitted by blood transfusion, and a few probable cases of transfusion-transmitted vCJD in humans have been reported.

C. Special considerations

1. **Directed or designated donor blood.** Blood donated by family members or friends for specific patients is commonly known as directed or designated donor blood. Directed donations have a small increase in rate of infectious disease transmission. Additionally, in a case of hemolytic disease of the newborn or neonatal alloimmune thrombocytopenia, the neonate's blood contains maternal antibodies that are directed against paternally inherited antigens on blood cells. In these cases, paternal relatives' blood may carry the same antigens rendering their blood incompatible with the baby. Finally, directed donor blood from relatives can induce an immune response against human leukocyte antigen (HLA) and other antigens against those relatives. This would complicate future therapy if the relatives were to be considered as donors of other tissue for the patient later in life. For these reasons, some medical centers do not offer directed donor blood.

2. **Medically indicated directed donor blood.** Blood may be collected from the mother for a neonate born with neonatal alloimmune thrombocytopenia or rarely neonatal alloimmune neutropenia. In these cases, neonatal plasma contains antibodies against paternally inherited antigens on platelets or neutrophils. Maternal platelets or neutrophils lack the corresponding antigen and would survive in the patient's bloodstream longer.
3. **Leukoreduction.** Leukoreduction filters remove approximately 99.9% of the white blood cells from RBCs and platelets. In addition, most platelets collected by apheresis are leukoreduced even without additional filtration. Benefits of leukoreduction include the following:
   a. Decreased rate of febrile transfusion reactions
   b. Decreased rate of CMV transmission to a negligible rate
   c. Potential to reduce a possible immunomodulatory effect of blood transfusions
   d. Decreased immunization to antigens on leukocytes such as HLA. This has only been shown for some oncology patients, and its importance for neonates is unknown.
4. **Irradiation.** Transfusion-associated graft-versus-host disease (TA-GVHD) occurs when transfused lymphocytes mount an immune response against the patient and the patient's immune system is unable to destroy the transfused lymphocytes. Irradiation of the blood component prevents proliferation of lymphocytes and thus prevents TA-GVHD. Some premature infants and children with certain congenital immunodeficiencies are at risk for TA-GVHD. Additionally, recipients of blood from first-degree relatives are at risk for TA-GVHD. Hence, these directed donor units must be irradiated.
5. **Pathogen reduction.** Pathogen-reduced platelets that have been treated with a psoralen and two types of pathogen-reduced plasma components are available in the United States. Other pathogen reduction technologies are available in other countries. These components have not undergone extensive testing in neonates, but initial reports show no significant reactions and generally good efficacy.

II. PACKED RED BLOOD CELLS

A. General principles

1. **Mechanism.** RBCs provide oxygen-carrying capacity for patients whose blood lacks sufficient oxygen-carrying capacity due to anemia, hemorrhage, or a hemoglobinopathy. Transfusion for hemoglobinopathies is unusual in the neonatal period when most patients will have significant amounts of fetal hemoglobin.

   Several types of RBC units are available that vary in the preservatives added. Chemical additives delay storage damage to RBCs allowing for extended storage times. The types of units that are currently available in the United States are as follows:

   a. Anticoagulant-preservative solution units. These units contain approximately 250 mL of a concentrated solution of RBCs. The hematocrit of these units is usually 70% to 80%. In addition, these units contain 62 mg

Table 42.2. Glucose (Dextrose) Concentrations in Red Blood Cell Additive Solutions (mM)

AS-1*	AS-3*	AS-5*	AS-7*	SAGM	MAP	PAGGSM
111	55	45	80	45	40	47

*U.S. Food and Drug Administration (FDA) approved for use in the United States.
AS, additive solution; SAGM, saline-adenine-glucose-mannitol; MAP, mitogen-activated protein; PAGGSM, phosphate-adenine-glucose-guanosine-saline-mannitol.

of sodium, 222 mg of citrate, and 46 mg of phosphate. Three types of units are currently approved for use in the United States. These are as follows:

i. **Citrate-phosphate-dextrose.** This contains 773 mg of dextrose and has a 21-day shelf life.

ii. **Citrate Phosphate Double Dextrose.** This contains 1,546 mg of dextrose and has a 21-day shelf life.

iii. **Citrate-phosphate-dextrose adenine.** This contains 965 mg of dextrose and 8.2 mg of adenine and has a 35-day shelf life. This is the most widely used of the anticoagulant-preservative solution units but is infrequently used because most RBC units are stored in additives.

b. Additive solution units. Most RBC units used in the United States are additive units. Four additive solutions are currently approved for use in the United States. Each of these units contains approximately 350 mL, has an average hematocrit of 50% to 60%, and has a 42-day shelf life. Neonatologists should be aware of the glucose concentrations in these units (Table 42.2) because this can significantly impact neonatal glucose homeostasis.

2. **Several changes occur in RBCs during storage:**

a. The pH decreases from 7.4 to 7.55 to pH 6.5 to 6.6 at the time of expiration.

b. Potassium is released from the RBCs. The initial plasma K^+ concentration is approximately 4.2 mM and increases to 78.5 mM in CPDA-1 units at day 35 and 45 to 50 mM in additive solution units on day 42. CPDA-1 units contain about one-third the supernatant volume as additive units, so the total amount of extracellular potassium is similar in all units of the same age.

c. 2,3-Diphosphoglycerol (2,3-DPG) levels drop rapidly during the first 2 weeks of storage. This increases the affinity of the hemoglobin for oxygen and decreases its efficiency in delivering oxygen to tissue. The 2,3-DPG levels replenish over several hours after being transfused.

3. **Toxicity.** The concentrations of all the elements in additives are low enough to be safe for neonates. This has been confirmed by case reports and case series. However, some blood banks reduce the additive concentrations in RBC units to be transfused to neonates.

B. Indications/contraindications. RBC transfusions are indicated for neonates who have signs or symptoms of hypoxia or who require an exchange

transfusion (see Chapter 45). Results are expected to soon be published on the long-term neurologic effects of different RBC transfusion strategies. At this point, RBC transfusion triggers for premature infants should be based on illness severity and may range from 8 to 10 g/dL hemoglobin for healthy infants to as high as 15 g/dL for premature infants requiring substantial oxygen support.

C. Dosing and administration. The usual dose for a simple transfusion is 5 to 15 mL/kg transfused at a rate of up to 5 mL/kg/hour. Unless the patient is actively bleeding the rate should not be increased but may need to be decreased for some patients.

D. Side effects

1. Acute transfusion reactions

a. Volume overload. Blood components have high oncotic pressure, and rapid infusion can cause excessive intravascular volume. This can cause a sudden deterioration of vital signs. Chronically anemic neonates can be especially susceptible to volume overload from transfusions. This is probably the most common type of reaction in neonates.

b. Acute hemolytic transfusion reactions. These reactions are usually due to incompatibility of donor RBCs with antibodies in the patient's plasma. The antibodies usually responsible for acute hemolytic transfusion reactions are isohemagglutinins (anti-A, anti-B). These reactions are rare in neonates who do not make isohemagglutinins until they are 4 to 6 months old. However, maternal isohemagglutinins can be present in the neonatal circulation.

- **i. Symptoms.** Possible symptoms include hypotension, fever, tachycardia, infusion site pain, and hematuria.
- **ii. Treatment.** Administer fluids and furosemide to protect kidneys. If necessary, treat hypotension with pressors and use hemostatic agents for bleeding; may need to transfuse compatible RBCs

c. Allergic transfusion reactions. These are unusual in neonates. Allergic reactions are due to antibodies in the patient's plasma that react with proteins in donor plasma.

- **i. Symptoms.** Mild allergic reactions are characterized by hives and possibly wheezing. More severe reactions can present as anaphylaxis.
- **ii. Treatment.** These reactions can be treated with antihistamines, bronchodilators, and corticosteroids as needed. These reactions are usually specific to individual donors. If they are serious or reoccur, RBCs and platelets can be washed.

d. Hypocalcemia. Rapid infusion of components, especially FFP, can cause transient hypocalcemia secondary to transfusion of citrate. This can cause hypotension.

e. Hypothermia. Cool blood can cause hypothermia. Transfusion through blood warmers can prevent this, but care must be taken to ensure the blood does not recool between the blood warmer and the patient.

f. Transfusion-associated acute lung injury (TRALI). This is most frequently due to antibodies in donor plasma that react with the patient's histocompatibility (HLA) antigens. These reactions present as respiratory

compromise and are more likely to occur with blood components containing significant amounts of plasma such as platelets or FFP. Blood centers now minimize collections of these products from female donors who developed anti-HLA antibodies during pregnancies which has substantially decreased the incidence of these reactions.

g. Hyperkalemia. Extracellular potassium concentrations are insignificant for simple transfusions of 5 to 20 mL/kg. However, transfusion-associated hyperkalemia has been reported secondary to large transfusions such as exchange transfusions or transfusions for major surgery. Either fresher or washed RBC units can be provided for these transfusions.

h. Febrile nonhemolytic transfusion reactions are usually due to cytokines released from leukocytes in the donor unit. These occur less frequently from transfusions of leukoreduced units.

i. Bacterial contamination can occur but is rare with RBC transfusions.

j. TA-GVHD. Lymphocytes from donor blood components can mount an immune response against the patient. Patients are at risk if they are unable to mount immune responses against the transfused lymphocytes. Such patients include premature infants, infants with congenital immune deficiencies, and patients sharing HLA types with blood donors as often occurs when people donate blood for relatives. Irradiating blood components prior to transfusion prevents TA-GVHD. Leukoreduction filters do not remove enough lymphocytes to prevent TA-GVHD.

k. Necrotizing enterocolitis is likely NOT due to transfusions despite multiple reports of a temporal association. Anemia itself, not transfusions, likely contributes to the risk of developing necrotizing enterocolitis.

E. Special considerations. Donor exposures can be minimized by reserving a fresh unit of RBCs for a neonate at their first transfusion. Subsequent transfusions can utilize aliquots of that unit until it is depleted or expires. This is useful for premature infants who are expected to require multiple simple transfusions for anemia of prematurity.

III. FRESH FROZEN PLASMA, THAWED PLASMA

A. General principles. Two frozen plasma products that are most frequently available are FFP and thawed plasma. Other products are pathogen reduced. Each of these components is used to administer all clotting factors. The contents are as follows:

1. Each component has approximately 1 unit/mL of each coagulation factor except that thawed plasma may have approximately two-thirds the levels of the least stable factors: factors V and VIII.
2. 160 to 170 mEq/L sodium and 3.5 to 5.5 mEq/L potassium
3. All plasma proteins including albumin and antibodies
4. 1,440 g sodium citrate

B. Indications. Plasma is indicated to correct coagulopathies due to factor deficiencies. Although plasma contains proteins and albumins, these components are not indicated for intravascular volume expansion or for antibody replacement because other components are safer for those indications (see Chapter 43).

C. Dosing and administration. Ten to 20 mL/kg is usually an adequate dose, and this may need to be repeated every 8 to 12 hours depending on the clinical situation. Plasma should be transfused no faster than 5 mL/kg/hour in a nonbleeding patient.

D. Side effects. Many of the side effects of RBC transfusion can also occur with plasma transfusions, with some differences in the risk profile for plasma:

1. Hyperkalemia will not occur.
2. Acute hemolytic reactions involving hemolysis of transfused RBCs is extremely unlikely. However, if the plasma contains incompatible antibodies (e.g., group O plasma transfused to a group A patient), an acute hemolytic reaction could theoretically occur. For this reason, transfused plasma should be compatible with the patient's blood group.
3. **Citrate-induced hypocalcemia** is a risk with plasma infusions. The amount of citrate is unlikely to cause transient hypocalcemia in most situations, but this can happen with rapid infusions of large amounts of plasma.

IV. PLATELETS

A. General principles. Platelets can be prepared from whole blood donations or collected by apheresis. If they are collected by apheresis, an aliquot is obtained for a neonatal transfusion. Often, only a portion of a whole blood–derived platelet unit is transfused to neonates, but most blood banks do not aliquot whole blood–derived platelets. Platelets can be stored in plasma or a platelet additive solution (PAS). Some platelets stored in PAS can be treated to reduce the risk of pathogens.

B. Contents. Each unit of whole blood–derived platelets contains at least 5×10^{10} platelets in approximately 50 mL of anticoagulated plasma including proteins and electrolytes. Because platelets are stored at room temperature for up to 7 days, there may be relatively low levels of the least stable coagulation factors V and VIII. Apheresis platelets may be stored in PAS, in which case minimal concentrations of plasma proteins are present and the liquid phase will consist of a buffered isotonic solution.

C. Indications. See Chapter 47.

D. Dosing and administration. A dose of approximately 5 mL/kg should raise the platelet count by approximately 30,000/mm. Platelets, like other blood components should be transfused at a rate no higher than 5 mL/kg/hour.

E. Side effects. The side effects of FFP transfusions can also occur with platelet transfusions. Additionally:

1. Platelets are more likely to be contaminated with bacteria causing septic reactions because platelets are stored at room temperature. For this reason, blood banks in the United States test units for bacteria or treat platelet units to inactivate bacteria.
2. **Inventory issues can limit the ability to match ABO types of platelets and patients.** ABO-incompatible plasma in a platelet unit can rarely cause a hemolytic transfusion reaction. For this reason, some blood banks remove plasma from platelet units containing antibodies

that are incompatible with the patient or avoid platelets with high titers of these antibodies.

F. Special considerations. Platelets can be concentrated by centrifugation resulting in a volume of 15 to 20 mL and then need to be resuspended. Some units are not successfully resuspended, and even if the platelet product appears acceptable, the platelets may have been activated and may not properly function in the patient.

V. GRANULOCYTES

A. Indications (see Chapter 49). Granulocyte transfusions are a controversial therapy that may benefit patients with severe neutropenia or dysfunctional neutrophils and a bacterial or fungal infection not responding to antimicrobial therapy. Most granulocytes are given to patients who are neutropenic secondary to hematopoietic progenitor cell (HPC) transplants. However, septic infants with chronic granulomatous disease also may benefit from granulocyte transfusions. Granulocyte transfusions are a temporary therapy until the patient starts producing neutrophils or until another curative therapy can be instituted.

B. Dosing and administration. 10 to 15 mL/kg. This may need to be repeated every 12 to 24 hours.

C. Side effects. In addition to all the potential adverse effects associated with RBC transfusions, granulocyte transfusions can cause pulmonary symptoms and must be administered slowly to minimize the chances of severe reactions. Additionally, granulocytes can transmit CMV. Hence, donors should be serologically negative for CMV if the patient is at risk for CMV disease.

D. Special considerations. Granulocyte collections need to be specially scheduled, and the granulocytes should be transfused as soon as possible after collection and no later than 24 hours after the collection.

VI. WHOLE BLOOD

A. General principles. Whole blood contains RBCs and plasma clotting factors. Some blood banks store a few units as whole blood but that is usually to support trauma patients. Whole blood can be reconstituted from a unit of RBCs and FFP.

B. Indications. Whole blood is usually used for neonatal exchange transfusions. It also may be used as a substitute for blood components in priming circuits for extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass, but this may cause increased fluid retention and longer postoperative recovery times. Whole blood may be useful for neonates immediately following disconnection from a cardiopulmonary bypass circuit for cardiac surgery.

C. Side effects. All of the adverse effects of individual blood components can occur with whole blood.

D. Special considerations. Whole blood should be transfused when it is relatively fresh because whole blood is stored at 1° to 6°C and coagulation

factors decay at this temperature. When used just after cardiopulmonary bypass, the blood should be no more than 2 to 3 days old. When used in other situations, the whole blood should be no more than 5 to 7 days old.

Platelets in whole blood will be cleared rapidly following transfusion, and reconstituted whole blood lacks significant quantities of platelets.

VII. INTRAVENOUS IMMUNOGLOBULIN

A. General principles. IVIG is a concentrated purified solution of immunoglobulins with stabilizers such as sucrose. Most products contain >90% immunoglobulin G (IgG) with small amounts of immunoglobulin M (IgM) and immunoglobulin A (IgA). Several brands of IVIG are available.

B. Indications. IVIG can have an immunosuppressive effect that is useful for alloimmune disorders such as neonatal alloimmune thrombocytopenia and possibly alloimmune hemolytic anemia. Both of these disorders are due to maternal antibodies to antigens on the neonate's cells (see Chapters 26 and 47).

IVIG can also be used to replace immunoglobulins for patients who are deficient in immunoglobulins as occurs with some congenital immunodeficiency syndromes.

Some studies have attempted to determine whether IVIG is useful as a prophylaxis or treatment for neonatal sepsis. Results from these studies are mixed, and not enough evidence exists for routine use of IVIG for general sepsis (see Chapter 49).

1. **Hyperimmune immunoglobulins.** High titer disease-specific immunoglobulins are available for several infectious agents including varicella zoster virus and respiratory syncytial virus. These immunoglobulins may be useful for infants at high risk for these infections.

C. Dosing and administration. IVIG (non–disease-specific) is usually given at a dose of 500 to 1,000 mg/kg. Doses for the disease-specific immunoglobulins should follow manufacturer's recommendations.

D. Side effects. Rare complications include transient tachycardia or hypertension. Because of the purification processes, current IVIG has a negligible risk of transmitting infectious diseases.

VIII. UMBILICAL CORD BLOOD

A. General principles. UCB is the only blood that is derived from neonatal blood. UCB contains HPCs and is used for HPC transplants. UCB can be used for autologous transplants in which the patient receives the same blood that he or she donated or can be used for allogeneic transplants in which the UCB is infused into an individual who did not donate the UCB.

B. UCB donations. UCB is collected from the placenta and umbilical cord immediately following delivery and clamping of the umbilical cord. If the mother and baby are healthy, the cord blood can be collected without any impact on the neonate.

UCB can be collected for processing, freezing, and storage by private UCB banks which charge families for this service. A UCB unit stored in a private bank may be used by the neonate that donated the UCB or by

other people designated by the family. The UCB has a very low chance of being needed by the neonate because he or she would only be able to use the UCB if he or she were to develop a malignancy for which an autologous transplant is indicated when he or she is a child. A single UCB unit has an insufficient dose for transplants for adolescents or adults, although approaches to expand the cells in the cord blood are under investigation.

UCB can be processed, frozen, and stored by a public UCB bank. Such banks do not charge for this service. A UCB unit in a public bank is available for any patient who could use it and can be a valuable source of stem cells for a child with a malignancy or for a child with some congenital hematologic diseases.

C. Dosing and administration. An entire cord blood is used for younger children. Cord bloods are usually infused into central veins as part of a hematopoietic cell transplant protocol.

D. Side effects. All of the side effects for other blood components can occur for UCB transplants. However, the plasma content is low and TRALI is unlikely. Because UCB cannot be leukoreduced, febrile reactions are more common than with other blood components. Because UCB cannot be irradiated and patients are immunosuppressed, the risk of GVHD is significant.

Suggested Readings

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43 Bleeding

Stacy E. Croteau

KEY POINTS

- Normal levels of procoagulant and anticoagulant proteins are age-dependent, termed *developmental hemostasis*. The physiologic balance of procoagulant and anticoagulant proteins and platelet function differs in the neonate compared to the older child or adult. Despite this, the *healthy* neonate is not predisposed to hemorrhage or thrombosis.
- Cord blood samples may be sent for coagulation testing; venipuncture blood draw is the method of choice if cord blood samples are not obtained. Heel sticks and arterial draws should be avoided.
- One-third of patients with severe hemophilia have *de novo* mutations, so absence of family history does not exclude the diagnosis.
- Vitamin K is essential for normal production of several coagulation factors. Vitamin K deficiency bleeding (VKDB) can be seen at birth due to maternal ingestion of certain medications or in the first several days to weeks of life in breastfed infants without administration of vitamin K prophylaxis at birth.

I. ETIOLOGY

A. Acquired clotting factor deficiency

1. Vitamin K deficiency bleeding (VKDB, hemorrhagic disease of the newborn). Vitamin K deficiency impacts both procoagulant clotting factors II, VII, IX, and X and anticoagulant proteins C and S.
   a. Early VKDB. Within 24 hours, etiologies: maternal medications (e.g., warfarin and anticonvulsants including phenytoin, primidone, phenobarbital)
   b. Classic VKDB. Within 1 week after birth, etiologies: idiopathic, maternal medications, and breastfeeding
   c. Late VKDB. 2 weeks to 6 months of age, etiologies: generally secondary to underlying diseases (e.g., biliary atresia, cystic fibrosis, and other liver diseases with cholestasis), total parenteral alimentation, chronic diarrhea, antibiotic therapy
2. Liver disease
3. Disseminated intravascular coagulation (DIC)
   a. May be due to infection, shock, anoxia, necrotizing enterocolitis (NEC), renal vein thrombosis (RVT), or the use of vascular catheters

b. Extracorporeal membrane oxygenation (ECMO) in neonates with critical cardiopulmonary disease is a special case of coagulopathy related to consumption of clotting factors in the bypass circuit plus therapeutic anticoagulation (see Chapter 39).

B. Congenital (inherited) clotting factor deficiencies

1. **X-linked** (manifests predominantly in males, mild deficiencies can occur in females, severely affected females should raise concern of compound heterozygosity, Turner syndrome, partial X deletions, or nonrandom X chromosome inactivation). **One-third of patients with severe hemophilia have de novo variants; family history alone cannot exclude the diagnosis.**
   a. Hemophilia A, factor VIII deficiency, incidence 1 in 5,000 live male births
   b. Hemophilia B (also known as Christmas disease), factor IX deficiency, incidence 1 in 25,000 live male births
2. **Autosomal dominant**
   a. von Willebrand disease (VWD) is caused by decreased levels (deficiency) or functional activity (qualitative defects) of von Willebrand factor (VWF). VWD, type 1 is the most common inherited coagulation defect, ~1 in 1,000 may experience clinically significant bleeding. VWF is an acute phase reactant and can be elevated in normal neonates compared to older children and nonpregnant adults because of maternal estrogen.
   b. Dysfibrinogenemia (rare) is due to structural variants of fibrinogen.
3. **Autosomal recessive**
   a. Rare bleeding disorders in order of frequency: factors XI, VII, V, X, II, fibrinogen (hypofibrinogenemia), and factor XIII. Factor levels do not correlate well with bleeding symptoms; heterozygous states can result in symptomatic, mild deficiency.
   b. Factor XII deficiency prolongs the partial thromboplastin time (PTT) but is not associated with bleeding.
   c. Combined deficiency of factors V and VIII is caused by a transport gene variant, not mutations of the factor V and VIII genes.
   d. Severe factor VII or XIII deficiency can present as intracranial hemorrhage in neonates. Bleeding from the umbilical stump is also a feature of factor XIII deficiency.
   e. VWD type 3 is the rare, complete absence of VWF.
   f. Vitamin K–dependent clotting factor deficiency (VKCFD) is the rare inherited form of defective gamma-carboxylation, *GGCX* and *VKOR*.

C. Platelet-related bleeding (see Chapter 47)

1. **Qualitative disorders** include congenital (hereditary) conditions (e.g., storage pool defects, Glanzmann thrombasthenia, Bernard-Soulier syndrome, platelet-type VWD) and acquired disorders that result from medications or maternal use of antiplatelet agents.
2. **Quantitative disorders** may also be congenital or acquired:
   a. Immune thrombocytopenia (maternal idiopathic thrombocytopenic purpura [ITP] or neonatal alloimmune thrombocytopenia [NAIT])
   b. Maternal preeclampsia or hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome (see Chapter 3) or severe uteroplacental vascular insufficiency

c. DIC
d. Inherited marrow failure syndromes, including Fanconi anemia and congenital amegakaryocytic thrombocytopenia
e. Congenital leukemia
f. Inherited thrombocytopenia syndromes, including gray-platelet syndrome and the macrothrombocytopenias (e.g., MYH9-related disorders, May-Hegglin syndrome)
g. Consumption of platelets, i.e., catheter-related thrombosis, RVT, NEC, or vascular anomalies, such as Kasabach-Merritt phenomenon (KMP) with kaposiform hemangioendothelioma (KHE) or tufted angioma (TA)
h. Heparin-induced thrombocytopenia (HIT) results from antibody development to the complex of heparin with platelet factor 4, extremely rare in neonates.

D. Other potential causes of bleeding

1. **Vascular anomalies** may cause central nervous system (CNS), gastrointestinal (GI), or pulmonary hemorrhage.
2. **Trauma** (see Chapter 6)
   a. Rupture of spleen or liver associated with breech delivery
   b. Retroperitoneal or intraperitoneal bleeding may present as scrotal ecchymosis.
   c. Subdural hematoma, cephalohematoma, or subgaleal hemorrhage (the latter may be associated with vacuum extraction)

II. DIAGNOSTIC WORKUP OF THE BLEEDING NEONATE/INFANT

A. History

1. Family history of abnormal bleeding or clotting
2. Maternal medications (e.g., aspirin, phenytoin)
3. Pregnancy and birth history
4. Maternal history of personal or a prior infant with a bleeding disorder
5. Illness, medication, anomalies, or procedures performed on the infant

B. Examination

The crucial decision in diagnosing and managing the bleeding infant is determining whether the infant is sick or well (Table 43.1).

1. **Sick infant.** Consider DIC, viral or bacterial infection, or liver disease. Hypoxic/ischemic injury may lead to DIC.
2. **Well infant.** Consider vitamin K deficiency, isolated clotting factor deficiencies, or immune thrombocytopenia. Maternal blood in the infant's GI tract will not cause symptoms in the infant.
3. **Petechiae, small superficial ecchymosis, or mucosal bleeding** suggests a platelet problem or VWD.
4. **Large bruises** can be seen with platelet, VWF, or clotting factor abnormalities.
5. **Enlarged spleen** suggests possible congenital infection or erythroblastosis.
6. **Jaundice** suggests infection, liver disease, or resorption of a large hematoma.
7. **Abnormal retinal findings** suggest infection (see Chapter 48).

Table 43.1. Differential Diagnosis of Bleeding in the Neonate

Clinical Evaluation	Laboratory Studies			Likely Diagnosis
	Platelets	PT	PTT	Diagnosis
"Sick"	D−	I+	I+	DIC
	D−	N	N	Platelet consumption (infection, necrotizing enterocolitis, venous thromboembolism, KMP)
	N	I+	I+	Liver disease, hereditary clotting factor deficiencies, heparin contamination
	N	N	N	Compromised vascular integrity associated with hypoxia, prematurity, acidosis, hyperosmolality, hereditary clotting factor deficiencies
"Healthy"	D−	N	N	Immune thrombocytopenia, occult infection, venous thromboembolism, bone marrow hypoplasia (rare), or bone marrow infiltrative disease
	N	I+	I+	Vitamin K deficiency bleeding, hereditary clotting factor deficiencies
	N	N	I+	Hereditary clotting factor deficiencies
	N	I+	N	Hereditary clotting factor deficiencies
	N	N	N	Bleeding due to local factors (trauma, anatomic abnormalities), qualitative platelet abnormalities (rare), hereditary clotting factor deficiencies

PT, prothrombin time; PTT, partial thromboplastin time; D−, decreased; I+, increased; DIC, disseminated intravascular coagulation; N, normal; KMP, Kasabach-Merritt phenomenon.

Source: Modified from Glader BE, Amylon MO. Bleeding disorders in the newborn infant. In: Taeusch HW, Ballard RA, Avery ME, eds. *Diseases of the Newborn*. Philadelphia, PA: WB Saunders; 1991.

Table 43.2. Normal Values for Laboratory Screening Tests in the Neonate

Laboratory Test	Premature Infant Having Received Vitamin K	Term Infant Having Received Vitamin K	Child 1–2 Months of Age
Platelet count/μL	150,000–400,000	150,000–400,000	150,000–400,000
PT (seconds)*	14–22	13–20	12–14
PTT (seconds)*	35–55	30–45	25–35
Fibrinogen (mg/dL)	150–300	150–300	150–300

*Normal values may vary from laboratory to laboratory, depending on the particular assay reagents used. In full-term infants who have received vitamin K, the PT and PTT values generally fall within the normal "adult" range by several days (PT) to several weeks (PTT) of age. Small premature infants (<1,500 g) tend to have longer PT and PTT than larger babies. In infants with hematocrit levels >60%, the ratio of blood to anticoagulant (sodium citrate 3.8%) in tubes should be 19:1 rather than the usual ratio of 9:1; otherwise, spurious results will be obtained because the amount of anticoagulant solution is calculated for a specific volume of plasma. Blood drawn from heparinized catheters should not be used. The best results are obtained when blood from a clean venipuncture is allowed to drip directly into the tube from the needle or scalp vein set. Factor levels II, VII, IX, and X are decreased. Three-day-old full-term baby not receiving vitamin K has levels similar to a premature baby. Fibrinogen, factor V, and factor VIII are normal in premature and term infants. Factor XIII is variable.

PT, prothrombin time; PTT, partial thromboplastin time.

Source: Data from normal laboratory values at the Hematology Laboratory, The Children's Hospital, Boston; Alpers JB, Lafonet MT, eds. *Laboratory Handbook*. Boston, MA: The Children's Hospital; 1984.

C. Laboratory tests

Cord blood samples may be sent for coagulation testing if there is a suspicion for an inherited bleeding disorder at birth. Heel sticks and arterial draws should be avoided in patients at risk for a severe bleeding diathesis; venipuncture blood draw is the method of choice if cord blood samples are not obtained (Table 43.2).

1. **The Apt test** is used to rule out maternal blood. If the neonate is well and only "GI bleeding" is noted, an Apt test is performed on gastric aspirate or stool to rule out the presence of maternal blood swallowed during labor or delivery or from a bleeding breast. A breast pump can be used to collect milk to confirm the presence of blood in the milk, or the infant's stomach can be aspirated before and after breastfeeding.
   a. Procedure. Mix one part bloody stool or vomitus with five parts water; centrifuge it and separate the clear pink supernatant (hemolysate); add 1 mL of sodium hydroxide 1% (0.25 M) to 4 mL of hemolysate.

b. Result. Hemoglobin A (HbA) changes from pink to yellow brown (maternal blood); hemoglobin F (HbF) stays pink (fetal blood).

2. **Peripheral blood smear** is used to assess the number, size, and granulation of platelets and the presence of fragmented red blood cells (RBCs) as seen in DIC. Large platelets reflect either a congenital macrothrombocytopenia or young platelets, suggesting an immune-mediated or destructive thrombocytopenia.
3. **Platelet count. Significant bleeding** from thrombocytopenia **is a greater risk with platelet counts ≤20,000 to 30,000/mm^3**; however, bleeding with platelet counts up to 50,000 platelets/mm^3 may be seen with NAIT. These alloantibodies against the platelet antigen HPA1 (also known as PLA1) interfere with platelet surface fibrinogen receptor, glycoprotein IIb to IIIa causing functional impairment (see Chapter 47).
4. **Prothrombin time (PT)** is a test of the "extrinsic" clotting system, integrating activation of factor X by factor VII and tissue factor. Factor Xa, with factor Va as a cofactor, activates prothrombin (factor II) to form thrombin. Thrombin cleaves fibrinogen to fibrin (clot).
5. **PTT** is a test of the "intrinsic" clotting system and of the activation of factor X by factors XII, XI, IX, and VIII as well as the downstream factors of the common coagulation pathway (factor V, prothrombin, and fibrinogen).
6. **Fibrinogen** can be measured on the same sample used for PT and PTT (light blue top/sodium citrate tube). It may be decreased in liver disease and consumptive states. The typical clinical laboratory is a functional assay.
7. **D-Dimers** measure degradation products of fibrin, derivatives of cross-linked fibrin generated by the action of plasmin on fibrin, found in the plasma. Normal range is methodology/hospital-lab dependent. Levels are increased in patients with liver disease who have problems clearing fibrin split products, thromboembolism, and DIC. False-positive elevation in D-dimers is common in the intensive care unit setting because trivial clotting from catheter tips and other causes give positive results in this sensitive assay.
8. **Factor activity assays and VWD panel** for patients with positive family history **can be measured in cord blood or by venipuncture after birth.** Age-specific norms must be referenced.
9. **Bleeding time test is discouraged in all patients but especially in neonates.** This test measures response to a standardized razor blade cut. The apparatus is not well suited to infants and should never be used. Prolongation is not predictive of surgical bleeding.
10. Platelet function analysis using instruments such as the PFA100 may be useful as a screening test for VWD or platelet dysfunction in some settings, but confirmatory assays are required for positive tests. Because functional platelet assays are best drawn through large bore needles, if possible, assessment later in late infancy or in affected family members is preferable to testing neonates.

III. TREATMENT OF NEONATES WITH ABNORMAL COAGULATION LABS WITHOUT CLINICAL BLEEDING.

In general, we treat *clinically ill* infants or infants weighing <1,500 g with fresh frozen plasma (FFP; 10 mL/kg) if the PT or PTT or both are ≥2 times normal for age and with platelets (10 to 15 mL/kg) (see section IV.A.3) if the platelet count is ≤25,000/mm^3 (see Chapter 47). This will vary with the clinical situations, trend of the laboratory values, impending surgery, and so forth. Some neonates will receive platelets if their platelet count is ≤100,000/mm^3, particularly in NAIT. In rare cases such as KMP, attempt at correction of the platelet count in the absence of bleeding can actually cause enlargement of the underlying vascular anomaly and worsening of symptoms.

IV. TREATMENT OF BLEEDING

A. Replacement therapies

1. **Vitamin K_1 (phytonadione).** An intravenous (IV) or intramuscular (IM) dose of 1 mg is administered in case the infant was not given vitamin K at birth. Infants receiving total parenteral nutrition and infants receiving antibiotics for more than 2 weeks should be given at least 0.5 mg of vitamin K_1 (IM or IV) weekly to prevent vitamin K depletion. If bleeding is minimal, vitamin K (rather than FFP) should be given for prolonged PT and PTT due to vitamin K deficiency. FFP should be reserved for significant or emergent bleeding; correction using vitamin K can take 12 to 48 hours.
2. **FFP and cryoprecipitate** (see Chapter 42). FFP (10 mL/kg) is given intravenously for active bleeding and may be repeated every 8 to 12 hours as needed. A drip of 1 mL/kg/hour is an alternative, particularly if fluid balance is an issue. FFP replaces all the clotting factors; however, 10 mL/kg of FFP will transiently raise the factor levels only to approximately 20% of adult normal, which depending on the baseline factor may or may not achieve an adequate hemostatic level. Specific factor deficiencies (factor VIII, factor IX, and VWF in particular) should be treated with factor concentrate when available. Cryoprecipitate contains only factor VIII, VWF, fibrinogen, and factor XIII. Specific concentrates are available for each of these once a specific diagnosis is made.
3. **Platelets** (see Chapter 47). Transfuse 10 mL/kg of irradiated, CMV-safe platelets over 2 hours. In the absence of platelet consumption or destruction (such as DIC, immune destruction, or sepsis), 1 unit of random donor platelets should raise the platelet count by 50,000 to 100,000/mm^3 in a neonate. The platelet count will drop over 3 to 5 days unless platelet production increases. For alloimmune platelet destruction, either maternal platelets or platelets from a known platelet-compatible donor should be used if available. In the setting of bleeding, random donor platelets can be used.
4. **Fresh whole blood** (see Chapters 42 and 45). Whole blood is no longer available at most institutions. Initial transfusion may be 10 mL/kg but should be tailored to the clinical situation. Reconstituted components (FFP, packed red blood cell [PRBC], cryoprecipitate, and platelets) are more flexible and readily dosed than fresh whole blood.

5. **Clotting factor concentrates** (see Chapter 42). Factor concentrates are available for fibrinogen, factors VIII, IX, VII, X, XIII, and VWF. In the setting of serious bleeding, if deficiency of factor VIII or IX, activity levels should be raised to normal adult levels (50% to 100%). Factor VIII or IX concentrates should be used if the diagnosis of hemophilia has been made. If severe VWD is considered, a VWF-containing, plasma-derived factor VIII concentrate should be used. Recombinant VWF concentrate was recently licensed in the United States but has not been investigated in the neonatal setting and is not approved in children.

B. Treatment of specific disorders

1. **DIC.** The infant typically appears ill and may have petechiae, GI hemorrhage, oozing from venipuncture sites, signs of infection, asphyxia, or hypoxia. The platelet count is decreased; PT and PTT are increased. Fibrinogen is decreased, and D-dimers are increased. Fragmented RBCs are seen on the blood smear. Treatment involves the following steps:
   a. Identify and treat the underlying cause (e.g., sepsis, NEC, herpes). This is **always** the most important factor in treatment of DIC.
   b. Confirm that vitamin K_1 has been given.
   c. Administer platelets and FFP as needed to keep the platelet count ≥50,000/mL and to control bleeding. FFP contains anticoagulant proteins, which may slow down or stop ongoing consumption.
   d. For persistent bleeding consider the following:
      i. Exchange transfusion with fresh citrated whole blood or reconstituted whole blood (PRBCs, platelets, FFP)
      ii. Continued transfusion with platelets, PRBCs, and FFP as needed particularly if exchange is not possible.
      iii. Administer cryoprecipitate (1 to 2 units per 10 kg) for hypofibrinogenemia.
   e. For consumptive coagulopathy secondary to large vessel thrombosis without concurrent bleeding, consider treatment with unfractionated heparin (UFH) infusion **without a bolus** (e.g., 20 to 25 units/kg/hour as a continuous infusion) to maintain a UFH level of 0.35 to 0.7 units/mL. Check levels 4 hours after initiation and 4 hours after each infusion rate change. Administer platelets and FFP after heparin initiation to maintain platelet counts ≥50,000/mL and provide antithrombin and anticoagulant proteins essential to heparin function. When DIC manifests as both bleeding and thrombosis concurrently, heparinization is complicated; consult an expert hematologist immediately (see Chapter 44).

2. **VKDB**
   a. Non–life-threatening bleeding: Treat with phytonadione (vitamin K_1) single IV dose of 250 to 300 μg/kg.
   b. Severe bleeding episodes: Infusion of FFP (10 to 15 mL/kg) or prothrombin complex concentrate (PCC) (50 to 100 units/kg) may be indicated.
   c. If the mother has been treated with phenytoin (Dilantin), primidone (Mysoline), methsuximide (Celontin), or phenobarbital, the infant may be vitamin K deficient and bleed during the first 24 hours. The mother should receive vitamin K_1 10 mg IM 24 hours before delivery. The usual dose of vitamin K_1 (1 mg) should be given to the infant postpartum and repeated in 24 hours.

Suggested Readings

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44 Neonatal Thrombosis

Stacy E. Croteau

KEY POINTS

- Neonatal thrombosis is significant cause of neonatal morbidity and mortality.
- The presence of an intravascular catheter is the single most important risk factor for neonatal thrombosis and is associated with >90% of thrombotic events. Renal vein thrombosis is the most common cause of non–catheter-associated thrombosis in neonates and can result in long-term renal impairment.
- The frequency and contribution of inherited and acquired prothrombotic states to thromboembolic events in neonates remains poorly understood.
- Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) (e.g., enoxaparin) are first-line prophylactic and therapeutic anticoagulants for neonates.
- Thrombolysis with tissue plasminogen activator (tPA) can be considered for organ-, limb-, or life-threatening thrombosis, although associated risks must be carefully weighed.

I. PHYSIOLOGY

A. Physiology of thrombosis

1. **Thrombin is the primary procoagulant protein**, converting fibrinogen into a fibrin clot. The intrinsic and extrinsic coagulation pathways lead to activation of prothrombin to thrombin (factor II).
2. **Inhibitors of coagulation** include antithrombin, heparin cofactors, protein C, protein S, α2-macroglobulin, and tissue factor pathway inhibitor. Antithrombin activity is potentiated by endothelial surface heparan sulfate as well as exogenous heparin.
3. **Plasmin is the primary fibrinolytic enzyme**, degrading fibrin in a reaction that produces fibrin degradation products and D-dimers. Plasmin is formed from plasminogen by numerous enzymes, most important of which is tissue plasminogen activator (tPA).
4. In neonates, factors affecting blood flow, blood composition (leading to hypercoagulability), and vascular endothelial integrity can all contribute to thrombus formation.

B. Unique physiologic characteristics of coagulation in neonates

1. *In utero*, coagulation proteins are synthesized by the fetus as early as 10 weeks' gestational age and do not cross the placenta.
2. Levels of both procoagulant and anticoagulant proteins are in a different balance in the neonate compared to the older child and adult. Healthy neonates do not demonstrate hypercoagulable or bleeding tendencies; however, they are vulnerable to hemorrhage and thrombosis in the sick state.
3. Compared to adults, neonates have a decreased ability to generate thrombin, and values for the prothrombin time (PT) and the activated partial thromboplastin time (PTT) are prolonged.
4. Concentrations of most antithrombotic and fibrinolytic proteins are also reduced, including protein C, protein S, plasminogen, and antithrombin, although α2-macroglobulin concentration is increased. Thrombin inhibition by plasmin is diminished compared with adult plasma.
5. Platelet number and lifespan appear to be similar to that of adults; however, neonatal platelets are less reactive.

II. EPIDEMIOLOGY AND RISK FACTORS

A. Epidemiology

1. Thrombosis occurs more frequently in the neonatal period than at any other age in childhood.
2. Reported incidence of clinically significant thrombosis among infants in neonatal intensive care unit (NICU) was 24 per 10,000 NICU admissions.
3. Significant mortality associated with neonatal thrombosis; ~2% to 4% of infants with thrombosis die as a direct result of thrombosis.
4. The presence of an **indwelling vascular catheter** is the single greatest risk factor for arterial or venous thrombosis. Catheter-related thrombi are often asymptomatic, rates as high as 20% to 30% among all neonates with catheters.
5. Umbilical arterial catheterization (UAC) appears to result in severe symptomatic vessel obstruction requiring intervention in approximately 1% of patients.
6. **Multiple maternal, perinatal, and neonatal risk factors have been associated with thrombosis in newborns.** Maternal factors include infertility, oligohydramnios, preeclampsia, diabetes, intrauterine growth restriction (IUGR), prolonged rupture of membranes, chorioamnionitis, and autoimmune and prothrombotic disorders. Perinatal risk factors include emergent cesarean section or instrumented delivery and fetal heart rate abnormalities. Neonatal risk factors include congenital heart disease, sepsis, birth asphyxia, respiratory distress syndrome, dehydration, polycythemia, congenital nephritic/nephrotic syndrome, necrotizing enterocolitis, pulmonary hypertension, and prothrombotic disorders.

7. Infants undergoing surgery involving the vascular system, including repair of congenital heart disease, are at increased risk for thrombotic complications. Diagnostic or interventional catheterizations also increase the risk of thrombosis.
8. **Renal vein thrombosis** is the most common type of non–catheter-related pathologic thrombosis in newborns accounting for about 10% of neonatal thromboses.

B. Inherited hypercoagulable states

1. The magnitude of risk inherited thrombophilias contribute to neonatal thrombosis is unclear. The absolute risk of thrombosis in the neonatal period in all patients with an inherited nonhomozygous thrombophilia is low.
2. Inherited thrombophilia can be associated with a positive family history of venous thromboembolism (VTE), early age at first VTE, recurrent VTE, and atypical locations of VTE.
3. **Deficiencies of anticoagulant proteins (protein C, protein S, and antithrombin)** are associated with increased risk of VTE. Patients who are homozygous for a single defect or double heterozygotes for different defects can present in the neonatal period, often with significant illness due to thrombosis. **Purpura fulminans** is the characteristic presentation of homozygous protein C or S deficiency, which presents within hours or days of birth, often with evidence of *in utero* cerebral damage.
4. **Factor V Leiden (activated protein C resistance) and prothrombin gene mutation (*PT* G20210A)** have a high prevalence (2% to 10%), particularly in certain ethnic populations, but appear to have low risk of thrombosis in neonates.
5. **Hyperhomocysteinemia and increased lipoprotein (a) levels** significance in neonatal thrombosis is still poorly understood.

C. Acquired hypercoagulable states

1. Maternal antiphospholipid antibodies, including lupus anticoagulant and anticardiolipin antibodies, cross the placenta and can results in clinically significant hypercoagulable state in newborns. Neonates can present with significant thrombosis, including purpura fulminans.
2. Mothers should be screened for the presence of autoimmune antibodies as part of a thrombophilia evaluation for neonates presenting with clinically significant non–catheter-associated thrombosis.

III. SPECIFIC CLINICAL CONDITIONS

A. VTE

1. General considerations

a. VTE usually occurs in the presence of one or more clinical risk factors. Less than 1% of clinically significant venous thromboembolic events in neonates are idiopathic. Spontaneous (i.e., non–catheter-related) venous thrombosis can occur in renal veins, adrenal veins, superior or inferior vena cava, portal vein, hepatic veins, and the venous system of the brain.

b. Most VTE are **central venous catheters (CVCs)** associated. Short-term complications of CVC-VTE include loss of access, pulmonary embolism, superior vena cava syndrome, and specific organ impairment.

c. Cerebral sinus venous thrombosis (CSVT) can result in cerebral infarction and hemorrhage.

d. Surgical repair of complex congenital heart disease has been associated with an increased risk of thrombosis, particularly of the superior vena cava.

e. Frequency of pulmonary embolism in sick neonates may be underestimated because signs and symptoms are similar to common neonatal pulmonary diseases.

f. Long-term complications of VTE are poorly understood. Inferior vena cava thrombosis, if extensive, can be associated with a high rate of persistent partial obstruction and symptoms such as leg edema, abdominal pain, lower extremity thrombophlebitis, varicose veins, and leg ulcers. Other complications can include chylothorax, portal hypertension, and embolism.

2. Catheter-associated venous thrombosis

a. Signs and symptoms

i. The most common initial sign of catheter-related thrombosis is usually difficulty infusing through or withdrawing from the line.

ii. Additional signs of venous obstruction include swelling of the extremities, head and neck, or distended superficial veins.

iii. The onset of thrombocytopenia in the presence of a CVC also raises the suspicion of thrombosis.

b. Diagnosis

i. Ultrasound with Doppler is the primary diagnostic for VTE. There are limitations with intervariation between operators, difficulty to test in patients with edema, upper limb deep vein thrombosis (DVT), intrathoracic vessels, and bowel gas obscuring abdominal findings.

ii. Venography and pulmonary angiography remain the gold standards for VTE/pulmonary embolism diagnosis; however, technical experience, cost, contrast media–related side effects, exposure to radiation, and improving U.S. technology limits use.

c. Prevention of catheter-associated venous thrombosis

i. Unfractionated heparin (UFH) 0.5 U/mL is added to all compatible infusions through CVCs.

ii. Umbilical venous catheters (UVCs) should be removed as soon as clinically feasible and should not remain in place for longer than 10 to 14 days. A peripherally inserted central catheter (PICC) line is typically placed if the anticipated need for central access is >7 days.

d. Management of catheter-associated venous thrombosis

i. Nonfunctioning CVC. If fluid can no longer be easily infused through the catheter, clearance of the blockage with thrombolytic agents (e.g., tPA) can be considered. If line-associated VTE is identified removal the nonfunctioning CVC is appropriate. Recommendations vary as to timing of removal after initiation of anticoagulation therapy.

ii. **Line-associated VTE with functioning line.** It is currently recommended that UVCs and CVCs be removed if not necessary for care. Recommendations vary as to timing of removal after initiation of anticoagulation therapy. If line is required, it may be left in place with initiation of therapeutic anticoagulation and VTE monitored for progression.

3. Renal vein thrombosis

a. Renal vein thrombosis is most common in newborns and young infants and typically presents in the first week of life. A significant proportion of cases appear to result from *in utero* thrombus formation. Renal vein thrombosis occurs more often in preterm infants, left kidney, and male infants.

b. Additional risk factors include perinatal asphyxia, hypotension, polycythemia, increased blood viscosity, and cyanotic congenital heart disease.

c. Presenting symptoms in the neonatal period include flank mass, hematuria, proteinuria, thrombocytopenia, and renal dysfunction. The diagnosis is made by ultrasound with Doppler.

d. Complications can include hypertension, renal failure, adrenal hemorrhage, extension of the thrombus into the inferior vena cava, and death.

e. Retrospective studies have demonstrated that 43% to 67% of neonates with renal vein thrombosis had at least one or more prothrombotic risk factors.

f. Management is generally based on the extent of thrombosis.

i. Unilateral renal vein thrombosis without significant renal dysfunction or extension into the inferior vena cava is often managed with supportive care and close radiologic monitoring.

ii. Unilateral renal vein thrombosis with renal dysfunction or extension into the inferior vena cava and bilateral renal vein thrombosis should be considered for therapeutic anticoagulation with UFH or low molecular weight heparin (LMWH) for a total duration of 6 weeks to 3 months. Note that dosing of LMWH may need to be reduced in patients with renal insufficiency.

iii. Bilateral renal vein thrombosis with significant renal dysfunction should be considered for thrombolysis with tPA followed by anticoagulation with UFH or LMWH.

4. Portal vein thrombosis

a. Portal vein thrombosis is primarily associated with sepsis, omphalitis, exchange transfusion, and the presence of a UVC.

b. Diagnosis is made by ultrasound with Doppler; reversal of portal flow is an indication of severity.

c. Spontaneous resolution is common (30% to 70% of cases); however, portal vein thrombosis can be associated with later development of portal hypertension.

d. There are currently no data to suggest that anticoagulation decreases the time to resolution or the risk of developing portal hypertension.

5. CSVT

a. CSVT is an important cause of neonatal cerebral infarction and is associated with significant morbidity including epilepsy, cerebral palsy, and cognitive impairment in 10% to 80% of cases. Reported mortality rates range between 2% and 24%.

b. Major presenting clinical features of CSVT in neonates include seizures, lethargy, irritability, and poor feeding. The majority of cases present within the first day to week of life.

c. The superior sagittal sinus, transverse sinuses, and straight sinus are most commonly affected.

d. Hemorrhagic infarction is a frequent complication of CSVT noted in 50% to 60% of cases on initial imaging.

e. The majority of cases of neonatal CSVT are associated with maternal conditions including preeclampsia, diabetes, and chorioamnionitis as well as acute systemic illness in the neonate.

f. Ultrasound and computed tomography (CT) can identify CSVT, but magnetic resonance imaging (MRI) with venography is the imaging modality of choice for optimal detection of CSVT and associated cerebral injury.

g. No randomized studies have evaluated anticoagulation therapy in neonatal CSVT. Anticoagulation may reduce thrombus propagation; no clear increase morbidity or mortality due to anticoagulation. UFH or LMWH anticoagulation for CSVT without associated hemorrhage for 6 weeks to 3 months. If significant hemorrhage is present, anticoagulate or provide supportive care with radiologic monitoring and add anticoagulation if clot extends (collaborative decision making depends on clinical context).

B. Aortic or clinically significant arterial thrombosis

1. General considerations

a. Spontaneous arterial thrombi in the absence of a vascular catheter are unusual but may occur in ill neonates. Potential locations include the aortic arch, descending aorta, left pulmonary artery, and iliac arteries.

b. Acute complications of CVC-related and spontaneous arterial thrombi depend on location and can include renal failure, hypertension, intestinal necrosis, peripheral gangrene, other organ failure, and death.

c. Thrombosis of cerebral arteries is an important cause of neonatal cerebral infarction.

d. Long-term effects of symptomatic and asymptomatic arterial thrombi are not well studied but may include increased risk for atherosclerosis and chronic renal hypertension.

2. Aortic thrombosis

a. Signs and symptoms

i. An initial sign is often isolated dysfunction of the UAC.

ii. Mild clinical signs include microscopic or gross hematuria in absence of transfusions or hemolysis, hypertension, and intermittent decreased perfusion or color change of the lower extremities.

iii. Strong clinical signs include persistent lower extremity color change or decreased perfusion, blood pressure differential between upper and lower extremities, decrease or loss of lower extremity pulses, oliguria despite adequate intravascular volume, signs of necrotizing enterocolitis, or congestive heart failure.

b. Diagnosis

i. **Ultrasound** with Doppler flow imaging should be performed in cases of suspected aortic thrombosis particularly if signs do note resolve promptly after removal of the arterial catheter.

ii. **Echocardiogram** should be considered if there is concern for the presence of thrombus within the heart, aortic arch, or proximal aorta or if there is evidence of congestive heart failure.

c. Prevention of catheter-associated arterial thrombosis

i. UFH 0.5 to 1 U/mL is added to all compatible infusions through arterial catheters to prolong patency. This has not been shown to decrease the risk of associated thrombosis.

ii. A review of the literature suggests **"high" umbilical arterial lines** (tip in descending aorta below left subclavian artery and above diaphragm) are preferable to "low" lines (tip below renal arteries and above aortic bifurcation), with fewer clinically evident ischemic complications and trend toward a decreased incidence of associated thrombi. No difference was noted in the incidence of serious complications including necrotizing enterocolitis and renal dysfunction.

iii. Consider placing a **peripheral arterial line** rather than an umbilical arterial line in infants weighing >1,500 g.

iv. Monitor carefully for clinical evidence of thrombus formation when a UAC is present, including serial evaluations of lower extremity color, pulses, and perfusion; concordance of upper and lower extremity blood pressures; hypertension; decreased urine output; urine for microscopic or gross hematuria; and waveform dampening with difficulty flushing or withdrawing blood.

v. UACs should be removed as soon as clinically feasible. It is generally recommended that UACs remain in place for no longer than 5 to 7 days. If necessary, a peripheral arterial line should be placed if continued arterial access is needed.

d. Management of aortic and clinically significant arterial thrombosis

i. **Minor aortic thrombi** with mild symptoms can often be managed with prompt removal of the UAC, resulting in rapid resolution of symptoms.

ii. For **large but nonocclusive thrombi** that are not accompanied by signs of significant clinical compromise, the arterial catheter should be removed and anticoagulation with UFH or LMWH considered. Close follow-up with serial ultrasound imaging is indicated.

iii. **Large occlusive aortic thrombi or thrombi accompanied by signs of significant clinical compromise** should be managed aggressively. If the catheter is still present and patent, consider local thrombolytic therapy through the catheter. If the catheter has already been removed or is obstructed, consider systemic thrombolytic therapy. The catheter should be removed if still in place and obstructed.

iv. Surgical thrombectomy may be indicated in the setting of life- or limb-threatening thrombosis. Limited experience suggests thrombectomy and subsequent vascular reconstruction may have utility in significant peripheral arterial thrombosis.

3. Peripheral arterial thrombosis

a. Although rare, congenital occlusions of large peripheral arteries can present with a range of signs from a poorly perfused pulseless extremity to a black necrotic limb, depending on the duration and timing of the occlusion. Common symptoms include decreased perfusion, decreased pulses, and pallor. Embolic phenomena may manifest as skin lesions or petechiae. The diagnosis is confirmed with Doppler flow ultrasound.

b. Peripheral arterial catheters are rarely associated with significant thrombosis. Poor perfusion to the distal extremity is frequently seen and usually resolves with prompt removal of the arterial line. UFH 0.5 to 1 U/mL at 1 to 2 mL/hour is generally infused continuously through all peripheral arterial lines. Treatment of significant thrombosis or persistently compromised extremity perfusion associated with a peripheral catheter should consist of anticoagulation and consideration of systemic thrombolysis for extensive lesions. Close follow-up with serial ultrasound imaging is indicated.

IV. DIAGNOSTIC CONSIDERATIONS

A. Ultrasound with Doppler flow analysis is the most used diagnostic modality. Advantages include relative ease of performance, noninvasiveness, and ability to perform sequential scans to assess progression of thrombosis or response to treatment.

B. Although uncommonly used, **radiographic line study and venography** can aid in diagnosis. Imaging after injection of contrast material through a central catheter can be diagnostic for catheter-associated thrombi, although a line study will not provide information on thrombosis proximal to catheter tip. Venography with injection of contrast through peripheral vessels may be necessary when other diagnostic methods fail to demonstrate the extent and severity of thrombosis; upper extremity and upper chest venous thromboses can be particularly difficult to visualize by ultrasound.

V. MANAGEMENT

A. General considerations

1. Precautions

a. It is important to note that recommendations and dosing regimens for anticoagulant and thrombolytic therapies in neonates are largely based on findings from adult and pediatric studies. Small neonatal cohort studies and case series have further informed expert consensus.

b. In some cases, watchful waiting is a reasonable option for thrombotic events that are not organ-, limb-, and life-threatening. Clinicians must carefully weigh the risks and benefits of anticoagulation and thrombolytic therapies for clinically significant thrombotic events in a high-risk neonatal population.

c. Practically, it is important to avoid procedures such as intramuscular injections and arterial punctures and limit physical manipulation of the patient (i.e., no physical therapy) during anticoagulant or

thrombolytic therapy. It is similarly important to avoid indomethacin or other antiplatelet drugs during therapy.

d. Monitor clinical status carefully for signs of hemorrhage, particularly internal and intracranial hemorrhage.

2. Guidelines for choice of therapy

a. Small asymptomatic nonocclusive arterial or venous thrombi related to catheters can often be treated with catheter removal and supportive care alone.

b. Large or occlusive arterial or venous thrombi can be treated with anticoagulation with UFH or LMWH. Usually, relatively short courses of anticoagulation are sufficient, but occasionally, long-term treatment may be necessary.

c. In cases of massive arterial or venous thrombi with significant clinical compromise, treatment with local or systemic thrombolysis may be considered.

3. Contraindications to anticoagulation and thrombolytic therapy

a. In general, **absolute contraindications** include central nervous system surgery or ischemia within past 10 days, invasive procedures within past 3 days, seizures within past 48 hours, and severe active bleeding.

b. In general, **relative contraindications** include platelet count $<50{,}000/\mu L$ or $<100{,}000/\mu L$ in critically ill neonates, fibrinogen level <100 mg/dL, international normalized ratio (INR) >2, severe coagulopathy, and hypertension.

B. UFH

1. General considerations

a. Term newborns generally have faster clearance of heparin and lower antithrombin levels compared with adults resulting in a relative increase in the heparin dose required to achieve therapeutic levels in neonates. There is also significant interpatient variability in heparin dosage requirements. Preterm infants may have a higher dose requirement than term infants and older children.

b. If possible, UFH should be infused through a dedicated intravenous (IV) line not used for any other medications or fluids.

c. Prior to starting UFH or LMWH, a baseline complete blood count (CBC), PT, and PTT should be obtained and monitored serially during the course of treatment. Heparin-induced thrombocytopenia (HIT), secondary to heparin-associated antiplatelet antibodies, is an extremely rare complication of heparin therapy in neonates.

d. Adjustment of the UFH infusion rate is based on clinical response, serial evaluation of thrombus (usually by ultrasound), and monitoring of laboratory parameters, ideally antifactor Xa level. Use of PTT to monitor UFH effect is problematic in neonates due to significant variability of coagulation factor concentrations and baseline prolongation of the PTT.

e. Heparin activity level is a more reliable marker of therapeutic heparin activity. Typical target therapeutic range is an antifactor Xa level of 0.35 to 0.7 U/mL.

f. Heparin activity is dependent on the presence of antithrombin. Consider administration of fresh frozen plasma (10 mL/kg) when effective

anticoagulation with UFH is difficult to achieve. Administration of antithrombin concentrate can also be considered, although evidence for its use in neonates is limited.

i. Antithrombin levels can be measured directly to aid in therapy, although administration of exogenous antithrombin can increase sensitivity to heparin even in patients with near-normal antithrombin levels.

2. **Dosing guidelines**

a. Standard UFH is initiated with a bolus of 75 U/kg IV, followed by a continuous infusion starting at 28 U/kg/hour and titrated by levels and clinical effect. For premature infants <37 weeks' gestation, lower dosing of 25 to 50 U/kg bolus followed by 15 to 20 U/kg/hour can be considered.

b. Heparin activity levels and/or PTT should be measured 4 hours after initial bolus and 4 hours after each change in infusion dose and every 24 hours once a therapeutic infusion dose has been achieved (Table 44.1).

3. **Duration of therapy.** Anticoagulation with UFH may continue up to 10 to 14 days. Oral anticoagulants are generally not recommended in neonates, but studies are ongoing. If long-term anticoagulation is needed, consult hematology and consider transitioning to LMWH.

4. **Reversal of anticoagulation**

a. Termination of the UFH infusion will quickly reverse anticoagulation effects of heparin therapy and is usually sufficient.

b. If rapid reversal is necessary, protamine sulfate may be given IV. Protamine can be given in a concentration of 10 mg/mL at a rate not to

Table 44.1. Unfractionated Heparin Dosage Monitoring and Adjustment

PTT (second)*	Heparin Activity (U/mL)	Bolus (U/kg)	Hold	Rate	Recheck
<50	0–0.2	50	—	+10%	4 hours
50–59	0.21–0.34	0	—	+10%	4 hours
60–85	0.35–0.7	0	—	—	24 hours
86–95	0.71–0.8	0	—	−10%	4 hours
96–120	0.81–1.0	0	30 minutes	−10%	4 hours
>120	>1	0	60 minutes	−15%	4 hours

*Partial thromboplastin time (PTT) values may vary by laboratory depending on reagents used. Generally, PTT values of 1.5 to 2.5 × the baseline normal for a given laboratory correspond to heparin activity levels of 0.35 to 0.7 U/mL.

Source: Adapted from Monagle P, Chan AK, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(2 suppl):e737S–e801S.

Table 44.2. Protamine Dosage to Reverse Heparin Therapy (Based on Total Amount of Unfractionated Heparin Received in Prior 2 Hours)

Time since Last Heparin Dose (minutes)	Protamine Dose (mg/100 U Heparin Received)
<30	1.0
30–60	0.5–0.75
60–120	0.375–0.5
>120	0.25–0.375

Maximum dosage is 50 mg. Maximum infusion rate is 5 mg/minute of 10 mg/mL solution.

Source: Adapted from Monagle P, Chan AK, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(2 suppl):e737S–e801S. Copyright © 2012 The American College of Chest Physicians. With permission.

exceed 5 mg/minute. Hypersensitivity can occur in patients who have received protamine-containing insulin or previous protamine therapy.

c. Dosing. Based on total amount of heparin received in last 2 hours as shown in Table 44.2.

C. LMWH

1. General considerations

a. In recent years, **LMWH**, specifically enoxaparin (Lovenox), has become the **anticoagulant of choice for neonates** based on growing experience as well as evidence of safety and efficacy in this patient population.

b. Several **advantages of LMWH** over standard UFH exist: more predictable pharmacokinetics, decreased need for laboratory monitoring, decreased need for dedicated venous access, subcutaneous twice daily (BID) dosing, reduced risk of HIT, and possible reduced risk of bleeding at recommended dosages.

c. Therapeutic LMWH antifactor Xa levels are 0.50 to 1.0 U/mL, measured 4 to 6 hours after at least two doses. After therapeutic levels have been achieved weekly monitoring of anti-Xa level, platelet count, and creatinine are recommended while hospitalized.

d. Several different LMWHs are available, and the dosages are not interchangeable. **Enoxaparin (Lovenox)** has the most widespread pediatric usage.

e. Cases of severe bleeding, including hematoma formation at injection sites, gastrointestinal bleeding, and intracranial hemorrhage have been reported in rare cases in association with LMWH usage in neonates and should be monitored for closely.

2. Dosing guidelines (Tables 44.3 and 44.4)

Table 44.3. Initial Dosing of Enoxaparin, Age Dependent

Age	Initial Treatment Dose	Initial Prophylactic Dose
Premature neonates	2 mg/kg per dose SQ q12h	0.75 mg/kg per dose SQ q12h
Full-term neonates	1.7 mg/kg per dose SQ q12h	
1–<2 months	1.5 mg/kg per dose SQ q12h	
>2 months	1.0 mg/kg per dose SQ q12h	0.5 mg/kg per dose SQ q12h

SQ, subcutaneous.

Source: Reprinted from Monagle P, Chan AK, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(2 suppl):e737S–e801S. Copyright © 2012 The American College of Chest Physicians. With permission; and Malowany JI, Monagle P, Knoppert DC, et al; for Canadian Paediatric Thrombosis and Hemostasis Network. Enoxaparin for neonatal thrombosis: a call for a higher dose for neonates. *Thromb Res* 2008;122(6):826–830. Copyright © 2007 Elsevier. With permission.

3. **Reversal of anticoagulation**
   - **a.** Termination of subcutaneous injections usually is sufficient to reverse anticoagulation when clinically necessary.
   - **b.** If rapid reversal is needed, protamine sulfate can be given within 3 to 4 hours of last injection, although protamine may not completely reverse anticoagulant effects. Administer 1 mg protamine sulfate per 1 mg LMWH given in last injection.

Table 44.4. Monitoring and Dosage Adjustment of Enoxaparin Based on Antifactor Xa Level Measured 4 Hours after Dose of Enoxaparin

Antifactor Xa Level (U/mL)	Dose Titration	Repeat Anti-Xa Level
<0.35	Increase dose by 25%.	4 hours after next dose
0.35–0.49	Increase dose by 10%.	4 hours after next dose
0.5–1.0	No change in dose	24 hours
1.1–1.5	Decrease dose by 20%.	Before next dose
1.6–2.0	Hold dose for 3 hours and decrease dose by 30%.	Before next dose and then 4 hours after next dose
>2.0	Hold all doses until anti-Xa is 0.5 U/mL; decrease dose by 40%.	Before next dose and q12h until anti-Xa <0.5 U/mL

Source: Adapted from Monagle P, Michelson AD, Bovill E, et al. Antithrombotic therapy in children. *Chest* 2001;119(suppl 1):344S–370S. Copyright © 2001 The American College of Chest Physicians. With permission.

D. Thrombolysis

1. General considerations

a. Thrombolytic agents convert endogenous plasminogen to plasmin. Plasminogen levels in neonates are reduced compared with adult values, and thus, effectiveness of thrombolytic agents may be diminished. Administration of fresh frozen plasma can increase thrombolytic effect of these agents.

b. Indications include massive arterial or venous thrombosis with evidence of organ dysfunction, compromised limb viability, or life-threatening thrombosis. Thrombolytic agents can also be used to restore patency of occluded central vascular catheters. Local infusions of low-dose thrombolytic agents can also be used for small to moderate occlusive thrombosis near a central catheter.

c. Minimal data exist in newborn populations regarding all aspects of thrombolytic therapy, including appropriate indications, safety, efficacy, choice of agent, duration of therapy, use of heparin, and monitoring guidelines. Recommendations for use are generally based on small series, case reports, and expert consensus which overall suggest that thrombolytic therapy in neonates can be effective with limited significant complications.

d. Consider evaluating all patients for intraventricular hemorrhage prior to initiating thrombolytic therapy.

2. Treatment guidelines

a. Preparation for thrombolytic therapy

i. Place sign at head of bed indicating thrombolytic therapy.
ii. Have topical thrombin available in unit refrigerator.
iii. Notify blood bank to ensure availability of cryoprecipitate.
iv. Notify pharmacy to ensure availability of antifibrinolytic therapy.
v. Obtain good venous access. Consider need for mode of access to allow frequent blood draws to minimize need for phlebotomy.
vi. Consider hematology consult.

b. Thrombolysis can be achieved by local, site-directed administration of thrombolytic agents in low doses directly onto or near a thrombosis via a central catheter or by **systemic** administration of thrombolytic agents in higher doses. Local therapy is generally limited to small or moderate-sized thromboses. Minimal data exist supporting one method over the other.

c. Recombinant tPA is the thrombolytic agent of choice for neonates. Streptokinase and urokinase have also been used in newborns, but tPA is preferred (although significantly more expensive) due to better clot lysis, less risk for allergic reactions, and shortest half-life.

d. Obtain a baseline CBC, PT, PTT, and fibrinogen level prior to initiating therapy.

e. Monitor PT, PTT, and fibrinogen every 4 hours initially and then at least every 12 to 24 hours. Monitor hematocrit and platelet count every 12 to 24 hours. Monitor thrombosis by imaging every 6 to 24 hours.

f. Expect fibrinogen to decrease by 20% to 50%. If no decrease in fibrinogen is seen, obtain D-dimers or fibrinogen split products to show evidence that a thrombolytic state has been achieved.

g. Maintain fibrinogen level >100 mg/dL and platelet count >50,000 to 100,000 to minimize the risks of clinical bleeding. Administer cryoprecipitate 10 mL/kg (or 1 U/5 kg) or platelets 10 mL/kg as needed. If fibrinogen level drops <100, decrease the dose of thrombolytic agent by 25%.

h. If no improvement in clinical condition or thrombosis size is seen after initiating therapy, and if fibrinogen levels remain high, **consider giving fresh frozen plasma 10 mL/kg**, which may correct deficiencies of plasminogen and other thrombolytic factors.

i. Duration of therapy. Thrombolytic therapy is usually provided for a brief period, (i.e., 6 to 12 hours), but longer durations can be used for refractory thromboses with appropriate monitoring. Overall, therapy should balance resolution of the thrombus and improvement in clinical status against signs of clinical bleeding.

j. Concomitant UFH therapy, usually without the loading bolus dose, should be initiated during or immediately after completion of thrombolytic therapy.

3. **Dosing** (Tables 44.5 and 44.6)

4. **Treatment of bleeding during thrombolytic therapy**

a. For localized bleeding, apply pressure, administer topical thrombin, and provide supportive care. Thrombolytic therapy does not necessarily need to be stopped if bleeding is controlled.

b. For severe bleeding, stop the infusion and administer cryoprecipitate (1 U/5 kg).

c. In the setting of life-threatening bleeding, stop the infusion, give cryoprecipitate, and infuse an antifibrinolytic agent after consulting hematology.

5. **Postthrombolytic therapy.** Consider initiating UFH without the initial loading dose or LMWH. Consider discontinuing anticoagulation if no reaccumulation of the thrombus occurs after 24 to 48 hours.

E. Treatment of CVC obstruction

1. **Treatment guidelines**

a. Central catheters may become occluded because of thrombus or chemical precipitate often secondary to parenteral nutrition.

Table 44.5. Systemic Thrombolytic Therapy

Agent	Load	Infusion	Notes
tPA	None	0.1–0.6 mg/kg/hour for 6 hours	Duration usually 6 hours; can continue for 12 hours or repeat after 24 hours, although lysis of clot will continue for hours after infusion stops. Lower dose appears to be as effective as higher dose.

Consider concomitant unfractionated heparin therapy at 5 to 20 U/kg/hour without bolus dose. Optimal duration of therapy is uncertain and can be individualized based on clinical response.

tPA, tissue plasminogen activator.

Table 44.6. Local Site-Directed Thrombolytic Therapy

Agent	Infusion	Notes
tPA	0.01–0.05 mg/kg/hour	Duration of therapy is based on clinical response. Systemic thrombolysis has been reported at doses of 0.05 mg/kg/hour.

Monitor laboratory studies similar to systemic treatment.

tPA, tissue plasminogen activator.

b. tPA may be used for thrombosis, and hydrochloric acid (HCl) may be attempted for chemical blockage.

c. General procedure

i. Instill chosen agent at volume needed to fill catheter (up to 1 to 2 mL) with gentle pressure. Agent should not be forced if resistance is too high. If instillation is difficult, a three-way stopcock can be used to create a vacuum in the catheter: Attach catheter, 10-mL empty syringe, and 1-mL syringe containing agent to the stopcock. Create vacuum by gently drawing back several milliliters in the 10-mL syringe while the stopcock is off to the 1-mL syringe. While holding pressure, turn stopcock off to the 10-mL syringe and allow vacuum in catheter to draw in infusate from the 1-mL syringe.

ii. Use of HCl for central catheter clearance in neonates is based on limited clinical data and experience and should be performed with caution. Suggested volumes to use range from 0.1 mL to 1 mL of 0.1 molar solution. Because severe tissue damage may result from peripheral administration or extravasation of HCl, consultation with a surgeon prior to HCl use should be considered.

iii. Wait 1 to 2 hours for tPA agents and 30 to 60 minutes for HCl and attempt to withdraw fluid through the catheter.

iv. If unsuccessful, previous steps can be repeated once.

v. If clearance of catheter is not successful after two attempts, the catheter should be removed.

2. Dosing guidelines (Table 44.7)

Table 44.7. Local Instillation of Agents for Catheter Blockage

Agent	Dosing
tPA	0.5 mg per lumen diluted in NS to volume needed to fill line, to max 3 mL
HCl	0.1 M, 0.1–1 mL per lumen

tPA, tissue plasminogen activator; NS, normal saline; HCl, hydrochloric acid.

Suggested Readings

Grizante-Lopes P, Garanito MP, Celeste DM, et al. Thrombolytic therapy in preterm infants: fifteen-year experience. *Pediatr Blood Cancer* 2020;67(10):e28544. doi:10.1002/pbc.28544.

Kenet G, Cohen O, Bajorat T, et al. Insights into neonatal thrombosis. *Thromb Res* 2019;181(suppl 1):S33–S36. doi:10.1016/S0049-3848(19)30364-0.

Monagle P, Chan AK, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(2 suppl):e737S–e801S.

Monagle P, Cuello CA, Augustine C, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism. *Blood Adv* 2018;2:3292–3316.

Robinson V, Achey MA, Nag UP, et al. Thrombosis in infants in the neonatal intensive care unit: analysis of a large national database. *J Thromb Haemost* 2020;19(2):400–407. doi:10.1111/jth.15144.

45 Anemia

Ravi M. Patel and Cassandra D. Josephson

KEY POINTS

- A term newborn with a hematocrit (Hct) of <42% should raise concern about the presence of anemia and prompt consideration and evaluation of the etiology.
- Infants have progressive declines in hemoglobin over the first weeks of life. This decline is exaggerated in very preterm infants, with anemia compounded by bleeding, phlebotomy, and immature erythropoiesis, and recent studies support more conservative thresholds for transfusion in this population. For more mature preterm and term infants, optimal transfusion thresholds are less certain.
- Delayed umbilical cord clamping improves iron stores and may reduce the need for red blood cell (RBC) transfusion and mortality in preterm infants. Umbilical cord milking should be avoided in extremely preterm infants, as it might increase the risk of intracranial hemorrhage.
- All preterm infants should have at least 2 mg/kg/day of enteral iron intake, with human milk–fed infants receiving iron supplementation by 1 month of age. For term infants who are breastfeeding, enteral iron supplementation of 1 mg/kg/day should begin at 4 months of age. Formula-fed infants do not need routine supplementation.
- Use of erythropoiesis-stimulating agents are not currently recommended, given the lack of benefit in important clinical outcomes in recent trials, although additional trials are ongoing.

I. HEMATOLOGIC PHYSIOLOGY OF THE NEWBORN.

Significant changes occur in the red blood cell (RBC) mass of an infant during the neonatal period and ensuing months. The evaluation of anemia must consider this developmental process as well as the infant's physiologic needs.

A. The physiologic anemia of infancy

1. *In utero*, the fetal aortic oxygen saturation is 45%, erythropoietin (Epo) levels are high, and RBC production is rapid. The fetal liver is the major site of Epo production.
2. After birth, with the abrupt transition from relative hypoxia *in utero* to the relatively oxygen-rich extrauterine environment, Epo is above normal adult reference range levels but declines rapidly in the first few days of life as oxygen delivery to tissues significantly increases. The Epo

Table 45.1. Hemoglobin Nadir

Characteristic	Hemoglobin Level		
	Healthy Term Infants	Very Low Birth Weight Infants (1,000–1,500 g)	Extremely Low Birth Weight Infants (<1,000 g)
Hemoglobin nadir	10 g/dL	8 g/dL	7 g/dL
Postnatal age	10–12 weeks	4–6 weeks	4–6 weeks

Source: Reprinted from Strauss RG. Anemia of prematurity: pathophysiology and treatment. *Blood Rev* 2010;24(6):221–225. Copyright © 2010 Elsevier. With permission.

concentrations then remain low throughout the first month of life. RBC production quickly decreases following the decline in Epo production.

3. A combination of shortened survival and decreased production of RBCs coupled with increased somatic growth with rapid blood volume expansion underpins the progressive decrease in hemoglobin levels (Table 45.1).
4. Despite dropping hemoglobin levels, the ratio of hemoglobin A to hemoglobin F increases, and the levels of 2,3-diphosphoglycerate (2,3-DPG) (which interacts with hemoglobin A to decrease its affinity for oxygen, thereby enhancing oxygen release to the tissues) are high. As a result, oxygen delivery to tissues increases. This physiologic "anemia" is not a functional anemia in that oxygen delivery to the tissues may be adequate. Iron from degraded RBCs is stored.
5. At 8 to 12 weeks, hemoglobin levels reach their nadiring, 9 to 11 g/dL by approximately 2 months, renal Epo production is stimulated, and RBC production increases (see Table 45.1).
6. Signs of recovery from physiologic anemia can be detected around 4 to 8 weeks of life, with increases in reticulocyte counts. The hemoglobin subsequently increases to a mean level of 12.5 g/dL.
7. Infants who have received transfusions in the neonatal period have lower nadirs than normal because of their higher percentage of hemoglobin A.
8. During this period of active erythropoiesis, iron stores are rapidly used. Iron stores are sufficient for 15 to 20 weeks in term infants. After this time, hemoglobin decreases if iron is not supplemented.

B. Anemia of prematurity is nearly universal in very low birth weight infants (see Table 45.1).

1. Multiple factors influence the development and severity of anemia of prematurity.
   a. Incomplete iron stores due to preterm birth
   b. Phlebotomy-related blood loss from laboratory testing

c. Low Epo levels and incomplete fetal erythropoiesis (why preterm infants typically have a lower hemoglobin than infants born at term)
d. Bleeding, including from intraventricular hemorrhage

2. The hemoglobin nadir is reached at an earlier postnatal age than in a term infant because of the following:
a. Shorter RBC survival
b. More rapid growth. For example, a premature infant gaining 150 g/week requires approximately a 12-mL/week increase in total blood volume.
c. Lower red cell mass and iron stores because of phlebotomy-related blood loss
d. The hemoglobin nadir in preterm infants is lower than in term infants because Epo is produced by the term infant at a hemoglobin level of 10 to 11 g/dL but is produced by the premature infant at a hemoglobin level of 7 to 9 g/dL.

II. ETIOLOGY OF ANEMIA IN THE NEONATE.

Anemia should be considered in any term infant with a hematocrit (Hct) of <42% on the day of birth. Causes of anemia can be thought of in one of three broad categories:

- Blood loss, which may be antenatal (fetomaternal hemorrhage) or perinatal (e.g., intracranial hemorrhage)
- Increased RBC destruction (e.g., hemolysis)
- Decreased RBC production (e.g., congenital infection)

A. Blood loss may present acutely or chronically. In acute blood loss, the infant might demonstrate compromise such as respiratory depression or shock. The Hct may be low or normal, if blood loss very recent, as equilibration of physiologic mechanisms to increase blood volume, such as retention of water, can take time. In chronic blood loss, the Hct may be low with increased reticulocytes, without evidence of shock or hypovolemia. In severe chronic intrauterine anemia, there may be hydrops fetalis, and caution should be exercised with volume bolus administration.

1. **Obstetric causes of blood loss**, including the following malformations of placenta and cord:
a. Abruptio placentae
b. Placenta previa
c. Incision of placenta at cesarean section
d. Rupture of anomalous vessels (e.g., vasa previa, velamentous insertion of cord, or rupture of communicating vessels in a multilobed placenta). Bleeding during rupture of membranes should raise suspicion of this.
e. Hematoma of cord caused by varices or aneurysm
f. Rupture of cord (more common in short cords and in dysmature cords)

2. **Occult blood loss**
a. Fetomaternal bleeding may be chronic or acute. It occurs in 8% of all pregnancies. The diagnosis is by a Kleihauer-Betke stain of maternal smear for fetal cells, which can yield the percentage of RBCs in maternal circulation that are fetal in origin. This is then multiplied by 5,000 mL to estimate volume of fetal hemorrhage (e.g., 1% on stain would be equal to 50 mL of blood loss, which can then be divided by the estimated infant blood volume [e.g., 80 mL/kg] to determine magnitude of hemorrhage).

Chronic fetal-to-maternal transfusion is suggested by a reticulocyte count >10%. Many conditions may predispose to this type of bleeding:

i. Placental malformations—chorioangioma or choriocarcinoma
ii. Obstetric procedures—traumatic amniocentesis, external cephalic version, internal cephalic version, breech delivery
iii. Spontaneous fetomaternal bleeding

b. Fetoplacental bleeding

i. Chorioangioma or choriocarcinoma with placental hematoma
ii. Cesarean section, with infant held above the placenta
iii. Tight nuchal cord or occult cord prolapse

c. Twin-to-twin transfusion

d. Twin anemia polycythemia sequence (TAPS), an uncommon form of chronic intertwin transfusion between monochorionic twins characterized by large intertwin hemoglobin differences in the absence of amniotic fluid discordance.

3. **Postnatal bleeding** in the neonate may be due to the following:

a. Intracranial bleeding associated with the following:

i. Trauma
ii. Prematurity, particularly extreme prematurity
iii. Hypoxia
iv. Bleeding disorders, such as hemophilia and neonatal alloimmune thrombocytopenia (NAIT)

b. Massive cephalohematoma, subgaleal hemorrhage, or hemorrhagic caput succedaneum

i. If a subgaleal hemorrhage is suspected, recommend intensive care unit admission given the large potential space for hemorrhage; may have fluid wave and bleeding can extend to orbits or lead to forward displacement of ears.

c. Retroperitoneal bleeding

d. Ruptured liver or spleen

e. Adrenal or renal hemorrhage

f. Gastrointestinal bleeding (maternal blood swallowed from delivery or breast should be ruled out by the Apt test) (see Chapter 43)

i. Gastric bleeding from ulceration or irritation from gastric tube, particularly if placed on suction
ii. Necrotizing enterocolitis (NEC)

g. Bleeding from umbilicus

h. Iatrogenic causes. Excessive blood loss may result from blood sampling with inadequate replacement.

B. Hemolysis should be suspected with presence of a low Hct in a term newborn (<42%) with increased reticulocyte count or with jaundice presenting in the first 24 hours of life.

1. **Immune hemolysis** (see Chapter 26)

a. Rh incompatibility

b. ABO incompatibility

c. Minor blood group incompatibility (e.g., c, E, Kell, Duffy)

d. Maternal disease (e.g., lupus), autoimmune hemolytic disease, rheumatoid arthritis (positive direct Coombs test in mother and newborn, no antibody to common red cell antigen Rh, AB, etc.), or drugs

2. **Hereditary RBC disorders**
   - **a. RBC membrane defects** such as spherocytosis, elliptocytosis, or stomatocytosis
   - **b. Metabolic defects**—glucose-6-phosphate dehydrogenase (G6PD) deficiency (significant neonatal hemolysis due to G6PD deficiency is mostly commonly seen in Mediterranean or Asian males but can occur in other populations); pyruvate kinase deficiency, 5′-nucleotidase deficiency, and glucose-phosphate isomerase deficiency
   - **c. Hemoglobinopathies**
     - **i.** α- and γ-Thalassemia syndromes
     - **ii.** α- and γ-Chain structural abnormalities
3. **Acquired hemolysis**
   - **a. Infection**—bacterial or viral
   - **b. Disseminated intravascular coagulation**
   - **c. Vitamin E deficiency** and other nutritional anemias
   - **d. Microangiopathic hemolytic anemia**, hemangioma, renal artery stenosis, and severe coarctation of the aorta

C. Diminished RBC production is manifested by a decreased Hct, decreased reticulocyte count, and normal bilirubin level. These are uncommon in term infants.

1. **Diamond-Blackfan syndrome**
2. **Congenital leukemia** or other malignancy
3. **Infections**, especially rubella and parvovirus (see Chapters 48 and 49)
4. **Osteopetrosis**, leading to inadequate erythropoiesis
5. **Drug-induced suppression of RBC production**
6. **Physiologic anemia or anemia of prematurity** (see sections I.A and I.B)

III. DIAGNOSTIC APPROACH TO ANEMIA IN THE NEWBORN

A. The **family history** should include questions about anemia, jaundice, gallstones, and splenectomy.

B. The **obstetric history** should be evaluated.

C. The **physical examination** may reveal an associated abnormality and provide clues to the origin of the anemia.

D. Acute blood loss leads to shock, with cyanosis, poor perfusion, and acidosis.

E. Chronic blood loss produces pallor, but the infant may exhibit only mild symptoms of respiratory distress or irritability.

F. Chronic hemolysis is associated with pallor, jaundice, and hepatosplenomegaly.

G. Complete blood cell count. Of note, a capillary blood Hct is 3.7% to 2.7% higher than a venous Hct. Warming the foot reduced the difference.

H. Reticulocyte count (elevated with chronic blood loss and hemolysis, depressed with infection and production defect)

I. Blood smear (Table 45.2)

J. Coombs test and bilirubin level

Table 45.2. Classification of Anemia in the Newborn

Reticulocytes	Bilirubin	Coombs Test	RBC Morphology	Diagnostic Possibilities
Normal or ↓	Normal	Negative	Normal	Physiologic anemia of infancy or prematurity; congenital hypoplastic anemia; other causes of decreased production
Normal or ↑	Normal	Negative	Normal	Acute hemorrhage (fetomaternal, placental, umbilical cord, or internal hemorrhage)
↑	↑	Positive	Hypochromic microcytes	Chronic fetomaternal hemorrhage
			Spherocytes	Immune hemolysis (blood group incompatibility or maternal autoantibody)
Normal or ↑	↑	Negative	Spherocytes	Hereditary spherocytosis
			Elliptocytes	Hereditary elliptocytosis
			Hypochromic microcytes	α- or γ-Thalassemia syndrome
			Spiculated RBCs	Pyruvate kinase deficiency
			Schistocytes and RBC fragments	Disseminated intravascular coagulation; other microangiopathic processes
			Bite cells (Heinz bodies with supravital stain)	Glucose-6-phosphate dehydrogenase deficiency
			Normal	Infections; enclosed hemorrhage (cephalohematoma)

RBC, red blood cell; ↓, decreased; ↑, increased.

Source: Adapted with permission from the work of Dr. Glader Bertil, Director of Division of Hematology-Oncology, Children's Hospital at Stanford, California, 1991.

K. Apt test (see Chapter 43) on gastrointestinal blood of uncertain origin

L. Kleihauer-Betke preparation of the mother's blood. Of note, a large volume (e.g., 50 mL) of fetal blood hemorrhage into the maternal circulation will show up as relatively small percentage (e.g., 1%) of fetal cells in the maternal circulation on the test.

M. Ultrasound of abdomen and head

N. Parental testing. Complete blood cell count, smear, and RBC indices are useful screening studies. Osmotic fragility testing and RBC enzyme levels (e.g., G6PD, pyruvate kinase) may be helpful in selected cases.

O. Studies for infection (toxoplasmosis, other, rubella, cytomegalovirus, and herpes simplex [TORCH]; see Chapters 48 and 49)

P. Bone marrow (rarely used except in cases of bone marrow failure from hypoplasia or tumor)

IV. THERAPY

A. Transfusion (see Chapter 42). Recent randomized trials have informed neonatal transfusion practices, with newer studies supporting the use of more restrictive transfusion thresholds, including the Transfusion of Prematures (TOP) and Effects of Transfusion Thresholds on Neurocognitive Outcomes (ETTNO) trials, that compared higher and lower hemoglobin transfusion thresholds for extremely preterm infants (e.g., birth weight <1,000 g or gestational age <29 weeks) (Table 45.3).

1. Indications for transfusion (Tables 45.4 and 45.5). The decision to transfuse should consider both a hemoglobin or Hct as well as the infants' condition. Importantly, clinicians should be aware that oxygen delivery to tissues depends on other factors beyond hemoglobin concentration, including oxygen saturation targets and cardiac output.

a. Transfusion guidelines for extremely preterm infants are shown in Table 45.4. These are informed by the lower thresholds in the TOP trial.

b. For non–extremely preterm infants, suggest transfusion of asymptomatic infants on minimal or no respiratory support at an Hct ≤20% to 22% in most circumstances, as this is the lowest threshold studied in

Table 45.3. Hemoglobin Threshold Ranges Used in Trials of Transfusion for Preterm Infants

Thresholds	Iowa Trial	PINT Trial	TOP Trial	ETTNO Trial
Liberal	10.0–15.3	8.5–13.5	10.0–13.0	9.3–13.7
Restrictive	7.3–11.3	7.5–11.5	7.0–11.0	7.0–11.3

Thresholds are hemoglobin values in grams per deciliter, and ranges reflect variation based on an infant's respiratory illness severity and postnatal age.

PINT, Premature Infants in Need of Transfusion (Study); TOP, Transfusion of Prematures; ETTNO, Effects of Transfusion Thresholds on Neurocognitive Outcomes (Trial).

Table 45.4. Evidence-Based Hematocrit Thresholds for Transfusing Extremely Preterm Infants with Anemia

Postnatal Age	Respiratory Support	No Respiratory Support
Week 1	≤32%	≤29%
Week 2	≤29%	≤25%
Week 3 and older	≤25%	≤21%

To obtain hemoglobin, divide hematocrit (%) by 2.941. Respiratory support is mechanical ventilation, continuous positive-airway pressure, nasal cannula ≥1 L/minute or fraction of inspired oxygen (FiO_2) >0.35.

Source: Based on lower thresholds of Transfusion of Prematures trial (Kirpalani H, Bell EF, Hintz SR, et al. Higher or lower hemoglobin transfusion thresholds for preterm infants. *N Engl J Med* 2020;383[27]:2639–2651.).

most randomized trials in neonates (see Table 45.5); may use clinical judgment based on underlying cause, considering reticulocyte response and other factors, and decide to monitor and not transfuse.

c. Moderate or late-preterm or term infants may be transfused at thresholds as in Table 45.4, although these were evaluated in extremely preterm infants. Some studies suggest term and late-preterm infants are transfused at slightly higher thresholds than more moderate or extremely preterm infants.

Table 45.5. Suggested Transfusion Guidelines for Selected Infants

1. **Suggest transfusion of asymptomatic infants on minimal or no respiratory support** at Hct ≤20%–22%. Moderate or late-preterm or term infants may be transfused at thresholds as in Table 45.4.
2. **Infants with major surgery** (preoperative or immediately postoperative): Transfuse if Hct ≤30%; consider if <32%–35%.
3. **Infant pre-ECMO or ECMO, with severe cardiopulmonary disease or shock**: Transfuse if Hct ≤35%.
4. **Chronic intrauterine anemia**: If hydropic, consider isovolumetric exchange. Otherwise, consider serial small volume (5–7.5 mL/kg) transfusions to avoid volume overload.
5. **Severe hemorrhage or hemorrhagic shock**: Aim to administer RBC:plasma/cryo:platelets rapidly in a 2:1:1 or 1:1:1 ratio.

Weak recommendations based on author opinion and current transfusion practices at U.S. centers, along with selected studies noted.

Hct, hematocrit; ECMO, extracorporeal membrane oxygenation.

d. Infants with major surgery (preoperative or immediately postoperative)—Transfuse if Hct ≤30%; consider if <32% to 35%. Oxygen delivery and demands may be impact by surgery. One study showed preoperative anemia is associated with postoperative mortality.

e. Infants that are pre-extracorporeal membrane oxygenation (pre-ECMO) or ECMO, with severe cardiopulmonary disease or shock—Transfuse if Hct ≤35%. Data suggests lower threshold associated with reduction in RBC transfusion volume without increasing complication rates and increased transfusion rates associated with higher mortality.

f. Chronic intrauterine anemia. If hydropic, consider isovolumetric exchange transfusion, in which packed RBCs are transfused while blood is withdrawn in infants, similar to the process in exchange transfusion.

- **i.** For an isovolumetric exchange transfusion, packed RBCs are infused into a vein (e.g., peripheral or umbilical) while blood is withdrawn (usually from a peripheral or umbilical artery). If no arterial access is available, a push–pull method can be done using the umbilical vein with a stopcock designed for an exchange transfusion that allows withdrawal and infusion of blood easily through the same catheter.
- **ii.** To raise Hct, the volume to exchange can be calculated as [(weight in kilogram × estimated infant blood volume) (e.g., 85 mL/kg) × (desired Hct – observed Hct)] / Hct of packed RBCs (this will depend on the type of units [e.g., citrate-phosphate-dextrose-adenine (CPDA-1) or Additive Solution Formula 3 (AS3)]). Of note, CPDA-1 units will have a higher Hct than AS3 units. You may want to contact the blood bank for an estimated Hct for the unit allocated to the infant. Otherwise, consider serial small volume (5 to 7.5 mL/kg) transfusions to avoid volume overload.

g. Severe hemorrhage or hemorrhagic shock. Transfuse RBCs rapidly and notify blood bank about need for product. Aim to administer RBC:plasma/cryo:platelets in a 2:1:1 or 1:1:1 ratio (10 to 15 mL/kg aliquot). Reassess and obtain repeat labs. Repeat transfusion in ratio until bleeding is no longer life-threatening. Ratios based on Transfusion and Anemia Expertise Initiative (TAXI) guidelines for older infants and children.

h. Infants with ABO incompatibility who do not have an exchange transfusion may have protracted hemolysis and may require a transfusion several weeks after birth. This may be ameliorated with the use of intravenous immunoglobulin (IVIG). If they do not have enough hemolysis to require treatment with phototherapy, they will usually not become anemic enough to need a transfusion (see Chapter 26).

2. **Blood products and methods of transfusion** (see Chapter 42)

a. Packed RBCs. The volume of transfusion is typically 10 to 20 mL/kg, with the most common transfusion volume being 15 mL/kg.

b. The average newborn blood volume is 80 mL/kg (lower for term and higher for preterm infants); the Hct of packed RBCs differs by storage unit and is 60% to 80% for CPDA-1 and lower for AS units.

c. Irradiated RBCs are recommended in premature infants weighing <1,500 g.

d. Leukocyte reduction reduces the risk of cytomegalovirus (CMV) transfusion. However, the use of CMV-seronegative donors for neonatal transfusion in conjunction with leukocyte reduction is preferable if the infant is ≤1,500 g, given studies have shown a very low risk of postnatal CMV infection with the combined strategy. If CMV-negative RBCs are unavailable, transfusion should not be delayed and CMV untested, leukoreduced RBCs are acceptable.

e. Directed-donor transfusion is requested by many families. Irradiation of directed-donor cells is especially important, given the human leukocyte antigen (HLA) compatibility among first-degree relatives and the enhanced potential for foreign lymphocyte engraftment.

f. Reducing donor exposure may reduce risks of transfusion-transmitted infection. Because of concern for multiple exposure risk associated with repeated transfusions in ELBW infants, we recommend transfusing stored RBCs from a single unit reserved for an infant.

g. There is no benefit of using fresh RBCs for transfusion, as one multicenter trial showed no differences in outcomes with fresh versus stored RBCs**.**

B. Prevention of anemia

1. **Enteral iron supplementation**

   a. Term infants. According to the 2010 American Academy of Pediatrics (AAP) recommendation, breastfed infants should be started on iron supplementation with 1 mg/kg/day at the age of 4 months. Nonbreastfed infants should be sent home from the hospital on iron-fortified formula.

   b. Premature infants. According to the 2010 AAP recommendation, all preterm infants should have at least 2 mg/kg/day of enteral iron intake, with human milk–fed infants receiving iron supplementation by 1 month of age (see Chapter 21). Higher doses of iron may be associated with improved neurodevelopment, although data from randomized trials are lacking.

2. **Delayed cord clamping** can help reduce iron deficiency and prevent anemia in both term and preterm infants.

3. **Erythropoiesis stimulating agents**, such as Epo, may help prevent anemia and reduce the need for RBC transfusion but do not improve important clinical outcomes and therefore are not recommended by the authors. Additional trials of other erythropoiesis stimulating agents such as darbepoetin are ongoing.

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46 Polycythemia

Matthew A. Saxonhouse and Ashley Hinson

KEY POINTS

- Polycythemia of the newborn is a hematocrit level >65%.
- Hyperviscosity represents a value of more than two standard deviations greater than the mean.
- Most neonates with polycythemia are asymptomatic and do not require any treatment.
- Many of the symptoms associated with hyperviscosity in the newborn are due to the underlying disorder and not the elevated hematocrit value.
- Partial volume exchange transfusion (PVET) should be reserved for those cases in which the infant's symptoms are attributed to hyperviscosity.

Many newborns, either in the newborn nursery or neonatal intensive care unit (NICU), may be born with polycythemia, defined simply as a hematocrit >65%. With delayed cord clamping becoming standard, more and more newborns will meet criteria for polycythemia. Most newborns with polycythemia are asymptomatic without resultant hyperviscosity. As blood viscosity increases, so does the risk for end-organ dysfunction. Thus, the clinician is often forced to make the decision on when it is appropriate to intervene. The majority of neonatal studies evaluating the management of polycythemia have not identified an optimal treatment strategy.

I. DEFINITIONS

A. Polycythemia refers to a hematocrit value in a newborn >65%. It may occur due to an increase in red blood cell production (active polycythemia) or a passive red blood cell transfusion (passive polycythemia). Capillary hematocrit samples may be as high as 20% more than venous samples and should not be used to make a diagnosis of polycythemia. Therefore, only hematocrit values >65% from a free-flowing peripheral vein or umbilical vein should be used when referring to polycythemic neonates. Hematocrit values for term newborns rise after birth and peak by 6 to 12 hours of age postpartum. The values then decrease and plateau by 18 to 24 hours of age postpartum.

Table 46.1. Blood Components and Their Effect on Blood Viscosity

Blood Component	Effect on Blood Viscosity
Hematocrit	Primary determinant of blood viscosity in the newborn. Has a logarithmic relationship with viscosity at shear rates. Biggest changes are observed at lower shear rates when the hematocrit values are >65%.
White blood cells	Extremely high values may influence blood viscosity in the newborn.
Platelets	Does not affect blood viscosity in the newborn
Plasma proteins	Does not affect blood viscosity in the newborn

B. Hyperviscosity of the newborn is a value more than two standard deviations greater than the mean. Poiseuille described blood viscosity as the ratio of shear stress to shear rate and is demonstrated by the formula:

$$n = \frac{(p - p')r^4\pi \text{ (shear stress)}}{8lQ \text{ (shear rate)}}$$

n = blood viscosity

p − p′ = pressure gradient along the blood vessel

r = radius of the blood vessel

l = length of the blood vessel

Q = blood flow

The relationship between hematocrit values and blood viscosity is linear when hematocrit values are <60% but then increase exponentially when the hematocrit is >70%. The viscosity of a fluid is constant but only when that fluid is homogenous. Blood is not homogenous as it is composed of many different particles. Factors affecting blood viscosity are displayed in Table 46.1.

In neonates, larger blood vessels have higher shear rates and thus lower viscosity. Smaller blood vessels have lower shear rates and are affected the most by higher hematocrit values. However, the viscosity of blood decreases with diminishing size of capillaries and viscosity of blood does not affect capillaries as much as the smaller arterioles and venules.

II. INCIDENCE.

Polycythemia affects approximately 1% to 5% of term newborns.

III. CAUSES OF POLYCYTHEMIA.

Risk factors for the development of polycythemia of the newborn are listed in Table 46.2.

Following birth, hematocrit values will rise from 6 to 12 hours and become stable by 24 hours of age. Significant delayed cord clamping will not result in severe hyperviscosity as demonstrated by a recent review of 73 newborns. Delays of up to 5 minutes after birth did not prompt an occurrence of severe polycythemia compared with standard cord clamping.

Table 46.2. Risk Factors Associated with Polycythemia of the Newborn

Mechanism	Cause	Description
Passive red blood cell transfusion	Delayed cord clamping	Standard therapy: If clamped within 1 minute, blood volume is 80 mL/kg; if clamped within 2 minutes, blood volume is 90 mL/kg.
	Cord stripping	If forceful
	Maternal-to-fetal transfusion	Diagnosed by Kleihauer-Betke stain in newborn
	Twin-to-twin transfusion	Recipient affected
Increased red blood cell production (chronic fetal hypoxia leads to elevated Epo levels and thus increased production of red blood cells)	Fetal growth restriction	Restricted placental blood flow resulting in chronic hypoxic state
	Maternal hypertension	Chronic hypertension, preeclampsia, HELLP
	Postterm infants	
	Maternal chronic hypoxia	Heart disease/pulmonary disease in mother
	High altitude	
	Infants of diabetic mothers	Increased erythropoiesis
	Maternal smoking	
	Other maternal conditions	Advanced maternal age, maternal renal disease
	Placental disorders	Placental previa, placental infarctions
Other conditions	Large for gestational age	
	Genetic syndromes	Congenital adrenal hyperplasia, Beckwith-Wiedemann syndrome, neonatal thyrotoxicosis, congenital hypothyroidism, trisomy 21, trisomy 13, trisomy 18
	Maternal medications	Propranolol
	Sepsis/dehydration/perinatal asphyxia	Lower RBC deformability

Epo, erythropoietin; HELLP, hemolysis, elevated liver enzymes, low platelets; RBC, red blood cell.

IV. SYMPTOMS. Most neonates with polycythemia are asymptomatic. Polycythemia leads to symptoms when hyperviscosity develops, leading to altered blood flow dynamics and compromising blood flow to vital organs, leading to end-organ damage. Most symptoms associated with polycythemia are due to the underlying cause of polycythemia and not hyperviscosity. A complete list of symptoms associated with polycythemia and hyperviscosity are listed in Table 46.3.

Regarding necrotizing enterocolitis (NEC), there is no clear association between polycythemia and NEC but rather due to fetal growth restriction and partial volume exchange transfusions (PVET; see following text).

V. SCREENING/DIAGNOSIS. Even with risk factors present, term or late preterm asymptomatic neonates do not need routine screening complete blood counts to evaluate for polycythemia. If symptoms are present and a blood sample is warranted, it is acceptable to obtain a warmed, capillary sample from the heel. If the hematocrit is >65%, the value should be repeated from a free-flowing venous sample. Blood viscosity values may be obtained from laboratory equipment, but many central hospital laboratories do not have them and are therefore not recommended. If the equipment is present at your institution, the value may help determine a true hyperviscosity syndrome in an affected neonate and may be of clinical value.

VI. MANAGEMENT. The most important management in any neonate with symptoms of polycythemia is to determine if there is another underlying cause and to treat that effectively. If after a thorough evaluation is performed, the neonate is determined to have symptoms specifically related to polycythemia and hyperviscosity, then a PVET should be performed. There is no data to support the use of IV fluid boluses instead of PVET for symptomatic infants. The management of the polycythemic neonate, based on hematocrit value and/or symptoms, is displayed in Table 46.4.

VII. PVET. When the decision is made to perform a PVET, the following formula should be used:

$$\frac{(\text{Observed Hct} - \text{Desired Hct}) \times (\text{Blood volume/kg} \times \text{Weight in kg})}{\text{Observed Hct}}$$

Hct = hematocrit

Either 5% albumin or normal saline (NS) should be used with most institutions using NS. The goal hematocrit should be 50% to 60%. Blood volume varies inversely with birth weight as demonstrated in Figure 46.1. Blood may be removed via an umbilical arterial catheter, umbilical venous catheter, or peripheral arterial catheter (depending on what may already be inserted). If the infant does not have any of the aforementioned, insertion of an umbilical venous catheter should be done with the intention of removal of the catheter as soon as the procedure is completed. NS may be infused via a peripheral or central venous catheter.

Providing a PVET will improve the symptoms associated with hyperviscosity. However, there are complications (0.5% to 3%) associated with PVET

Table 46.3. Signs and Symptoms Associated with Polycythemia and Hyperviscosity

Organ System	Sign/Symptom	Clinical Relevance
Cardiorespiratory	Cyanosis, tachypnea, tachycardia, heart murmur, cardiomegaly, heart failure, increased pulmonary vascular resistance, pulmonary hemorrhage, pleural effusions, increased pulmonary markings on CXR	Decreased cardiac output due to reduced stroke volume or heart rate but no change in oxygen transport or consumption
Gastrointestinal	Poor feeding	Enterohepatic circulation of bile acids and exocrine pancreatic function may be affected but rarely demonstrate clinical symptoms.
Renal	Decreased GFR, decreased sodium excretion, hematuria, proteinuria, oliguria, renal vein thrombosis	Infants with normovolemic polycythemia will have a reduction in renal function while increased blood volume will have normal renal function.
Skeletal muscle	None	Does not affect skeletal muscle
CNS	Poor feeding, tremulous, jitteriness, seizures, lethargy, apnea, hypotonia, cerebral sinovenous thrombosis	Significant reduction in cerebral blood flow velocity due to increase in arterial oxygen content but autoregulation is preserved. Any reduction in cerebral blood flow that presents in symptoms is usually due to the *in utero* disorder or acute birth complications.
Endocrine	Hypoglycemia, hypocalcemia	
Hematology	Thrombocytopenia, DIC, organ infarctions, jaundice, hyperbilirubinemia, hepatosplenomegaly	Most significant thromboses are due to other associated risk factors and not polycythemia itself.

CXR, chest x-ray; GFR, glomerular filtration rate; CNS, central nervous system; DIC, disseminated intravascular coagulation.

Table 46.4. Management of Polycythemia/Hyperviscosity in the Newborn

Venous Hematocrit Value	Symptoms	Management Plan
60%–70%	None	Hydration* and recheck in 4–6 hours.
>65%	As listed in Table 46.3 and felt to be due to hyperviscosity	PVET
>70%	None	Hydration* and/or PVET
		If choose hydration, recheck hematocrit in 4–6 hours.
>70%	As listed in Table 46.3 and felt to be due to hyperviscosity	PVET

*Hydration: feeding infant as would in normal term newborn and/or *in vitro* fertilization if needed for other symptoms.

PVET, partial volume exchange transfusion.

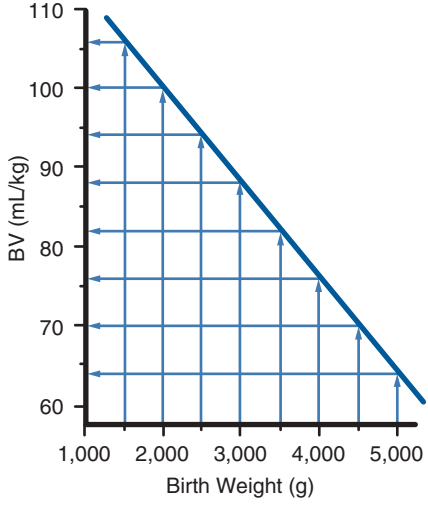

Figure 46.1. Nomogram designed for clinical use, correlating blood volume (BV) per kilogram with birth weight in polycythemic neonates. (Reprinted from Rawlings JS, Pettett G, Wiswell T, et al. Estimated blood volumes in polycythemic neonates as a function of birth weight. *J Pediatr* 1982;101[4]:594–599. Copyright © 1982 Elsevier. With permission.)

such as hypoglycemia (most common), bradycardia, apnea, catheter-related complications, thrombocytopenia, hypocalcemia, and hypokalemia. NEC, cardiovascular collapse, sepsis, and pulmonary hemorrhage have also been reported.

VIII. OUTCOMES. There have been multiple studies evaluating both the short- and long-term outcomes of neonates with both asymptomatic polycythemia and symptomatic hyperviscosity. The studies have concluded that polycythemia appears to be a part of the fetal adaptive process to both acute and chronic hypoxia and that hypoxia may result in irreversible brain injury. However, the optimal treatment strategy for symptomatic neonates remains controversial. Performing a PVET will decrease the hematocrit and blood viscosity and may reverse many of the physiologic abnormalities associated with polycythemia. However, performing a PVET does not appear to change long-term neurologic outcomes.

Data from most patient studies evaluating neurologic outcomes from 8 months to 3 years of life demonstrated similar long-term neurologic outcomes between polycythemic neonates and normal term infants, including those infants treated with PVET.

Studies have demonstrated an increased incidence of NEC when PVETs were done using an umbilical vein.

A more recent review evaluated the use of fluid boluses in neonates that were polycythemic. Neonates >34 weeks' gestation and with a hematocrit of 65% to 75% were eligible for study. One group received a 25-mL/kg NS bolus over 6 to 8 hours in addition to maintenance fluid hydration and were compared to polycythemic and normal neonates receiving normal maintenance fluid hydration. There were no differences noted between all the groups.

IX. CONCLUSION. Polycythemia of the newborn appears to be a fetal adaptive process. Most neonates are asymptomatic, and many of the symptoms associated with hyperviscosity are usually due to the underlying disorder and not polycythemia/hyperviscosity itself. PVET should be reserved for those neonates that are symptomatic with a central hematocrit value >65% and the clinician feels that the symptoms are mainly due to the hyperviscosity resulting in end-organ dysfunction. Although, the symptoms will be improved following the PVET, the long-term neurologic outcome may not be affected. Further randomized clinical trials comparing symptomatic and asymptomatic neonates with polycythemia and/or hyperviscosity need to be performed before any firm clinical suggestions may be made. For now, when dealing with a polycythemic newborn and concerns for hyperviscosity, the clinician should always approach with the intention to first do not harm with the patient's best interests in mind basing this decision on limited long-term data.

Suggested Readings

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47 Neonatal Thrombocytopenia

Patricia Davenport and Martha Sola-Visner

KEY POINTS

- The most common cause of mild-to-moderate, early-onset thrombocytopenia in well-appearing neonates is placental insufficiency, frequently manifesting as small for gestational age at birth. This thrombocytopenia resolves spontaneously, usually within 10 days, and carries a good prognosis. Thrombocytopenia in sick infants is usually associated with sepsis or necrotizing enterocolitis (NEC) and requires prompt intervention.
- Neonates with *severe* thrombocytopenia in the first day of life, particularly if well appearing, should be screened for neonatal alloimmune thrombocytopenia (NAIT). Random donor platelet transfusions (± intravenous immunoglobulin [IVIG]) represent the first line of therapy for these infants, unless human platelet antigen (HPA)-1b1b platelets (formerly known as PLA-1 negative) are maintained in the blood bank inventory and are immediately available for use (as is the case in some European countries or in known affected pregnancies). If available, these platelets are the preferred first-line treatment.
- The risk of bleeding in thrombocytopenic neonates is multifactorial and is not related to the severity of the thrombocytopenia. Current evidence suggests that gestational age <28 weeks, postnatal age <10 days, and a diagnosis of NEC are more important predictors of bleeding than the platelet count itself.
- There has been significant worldwide variability in platelet transfusion thresholds used in the neonatal intensive care unit (NICU). In 2019, the largest trial comparing liberal versus restrictive platelet transfusion thresholds in preterm neonates (Platelets for Neonatal Transfusion—Study 2 [PlaNeT-2]) was published. This study randomized 660 thrombocytopenic infants <34 weeks' gestation to receive platelet transfusions when the platelet count fell $<50 \times 10^3/\mu L$ (high threshold) or $<25 \times 10^3/\mu L$ (low threshold). Surprisingly, it found a significantly *higher* incidence of death or major bleeding in the 28 days following randomization (primary outcome) in neonates randomized to the high-threshold compared to the low-threshold group.
- A subsequent risk stratification analysis of these results revealed that neonates with a high baseline risk of bleeding and mortality benefited from the lower platelet transfusion threshold as much (or more) than neonates with a low baseline risk. Thus, the current evidence supports the use of a restrictive transfusion threshold for most neonates in the NICU.

I. INTRODUCTION.

Neonatal thrombocytopenia is traditionally defined as a platelet count $<150 \times 10^3/\mu L$ and is classified as mild (100 to $149 \times 10^3/\mu L$), moderate (50 to $99 \times 10^3/\mu L$), or severe ($<50 \times 10^3/\mu L$). However, platelet counts in the 100 to $149 \times 10^3/\mu L$ range are somewhat more common among neonates than adults. The most recent and largest study on neonatal platelet counts demonstrated that platelet counts at birth increase with advancing gestational age. Importantly, although the mean platelet count was $\geq 200 \times 10^3/\mu L$ even in the most preterm infants, the 5th percentile was $104 \times 10^3/\mu L$ for those ≤32 weeks' gestation, and $123 \times 10^3/\mu L$ for late-preterm and term neonates. These findings suggest that different definitions of thrombocytopenia may need to be applied to preterm infants. For that reason, careful follow-up and expectant management in an otherwise healthy-appearing neonate with mild, transient thrombocytopenia is an acceptable approach, although lack of quick resolution, worsening of thrombocytopenia, or changes in clinical condition should prompt further evaluation.

The incidence of thrombocytopenia in neonates varies significantly, depending on the population studied. Specifically, although the *overall* incidence of neonatal thrombocytopenia is relatively low (0.7% to 0.9%), the incidence among neonates admitted to the neonatal intensive care unit (NICU) is rather high (18% to 35%). Within the NICU, mean platelet counts are lower among preterm neonates than among neonates born at or near term, and the incidence of thrombocytopenia is inversely correlated to the gestational age, reaching approximately 70% among neonates born with a weight <1,000 g.

II. APPROACH TO THE THROMBOCYTOPENIC NEONATE.

When evaluating a thrombocytopenic neonate, the first step in narrowing the differential diagnosis is to classify the thrombocytopenia as either **early onset (within the first 72 hours of life)** or **late onset (after 72 hours of life)** and to determine whether the infant is clinically ill or well. Importantly, infection/sepsis should always be considered near the top of the differential diagnosis (regardless of the time of presentation and the infant's appearance) because any delay in diagnosis and treatment can have life-threatening consequences.

A. Early-onset thrombocytopenia

(Fig. 47.1). The most frequent cause of mild-to-moderate, early-onset thrombocytopenia in a well-appearing neonate is chronic intrauterine hypoxia, commonly seen in maternal conditions associated with placental insufficiency such as pregnancy-induced hypertension/preeclampsia or diabetes. It manifests in the fetus as intrauterine growth restriction (IUGR) and hematologic abnormalities. This thrombocytopenia is mild to moderate (platelet counts between 50 and $100 \times 10^3/\mu L$), presents immediately or shortly after birth, reaches a nadir on day of life 4, and resolves within 7 to 10 days. If an infant with a prenatal history consistent with placental insufficiency and mild-to-moderate thrombocytopenia remains clinically stable and the platelet count normalizes within 10 days, no further evaluation is necessary. However, if the thrombocytopenia becomes severe and/or persists >10 days, further investigation is indicated.

A second common cause of early-onset neonatal thrombocytopenia is perinatal asphyxia. As with chronic intrauterine hypoxia, the thrombocytopenia associated with asphyxia is self-limited and typically mild to

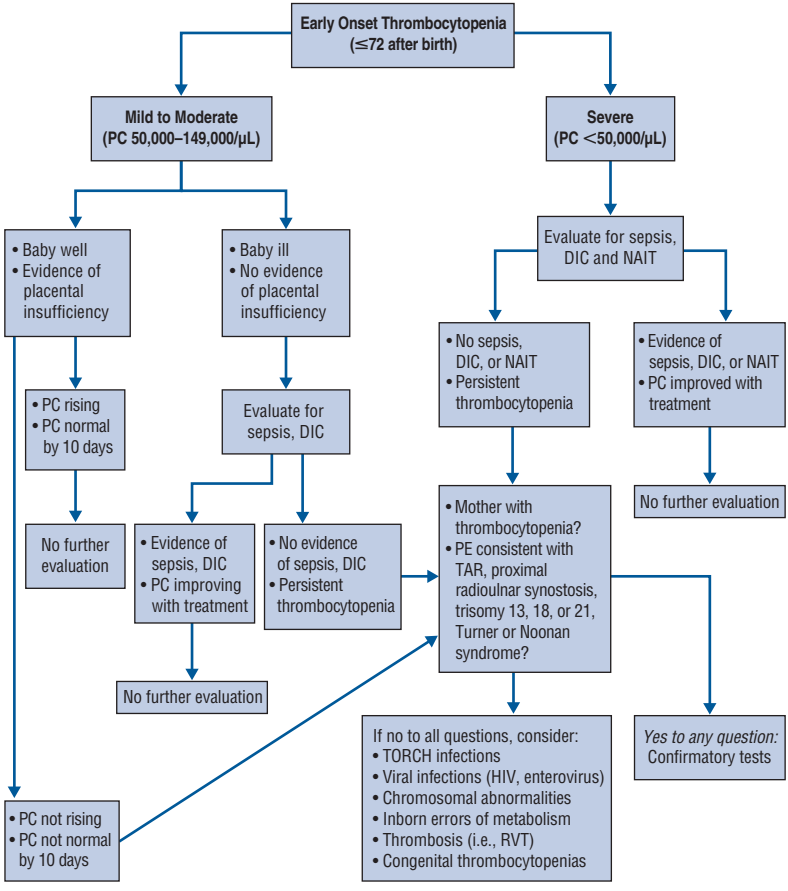

Figure 47.1. Guidelines for the evaluation of neonates with early-onset thrombocytopenia (≤72 hours of life). PC, platelet count; DIC, disseminated intravascular coagulation; NAIT, neonatal alloimmune thrombocytopenia; PE, physical examination; TAR, thrombocytopenia-absent radius; TORCH, toxoplasmosis, other, rubella, cytomegalovirus, and herpes simplex; RVT, renal vein thrombosis.

moderate, with platelet counts between 50 and 100 $\times$ 10^3/μL. In some infants, it is associated with disseminated intravascular coagulation (DIC), but in others, the underlying mechanism of thrombocytopenia is less clear and is thought to be secondary to decreased platelet survival and/or platelet hyporegeneration. Total body cooling (therapeutic hypothermia) has become widely accepted as an intervention to improve the neurodevelopmental outcome of neonates with moderate to severe perinatal asphyxia. Total body cooling of infants with neonatal asphyxia results in an even higher incidence of thrombocytopenia compared to infants with asphyxia only. This is likely due to hypothermia-induced changes in the platelet surface

antigen composition that result in their rapid removal from circulation. Importantly, the thrombocytopenia associated with total body cooling of asphyxiated infants is still mild to moderate and transient, although the nadir platelet count occurs slightly later than in infants with thrombocytopenia of asphyxia alone (day 5 vs. day 3).

Severe early-onset thrombocytopenia in an otherwise healthy infant should trigger suspicion for an immune-mediated thrombocytopenia, either autoimmune (i.e., the mother is also thrombocytopenic) or alloimmune (the mother has a normal platelet count). These varieties of thrombocytopenia are discussed in detail in the following text. Early-onset thrombocytopenia of any severity in an *ill-appearing* term or preterm neonate should prompt evaluation for sepsis, congenital viral or parasitic infections, or DIC. DIC is most frequently associated with sepsis but can also be secondary to birth asphyxia.

In addition to these considerations, the affected neonate should be carefully examined for any radial abnormalities (suggestive of thrombocytopenia-absent radius [TAR] syndrome, amegakaryocytic thrombocytopenia with radioulnar synostosis [ATRUS], or Fanconi anemia). Although the thrombocytopenia associated with Fanconi almost always presents later in life (during childhood), neonatal cases have been reported. In these patients, thumb abnormalities are frequently found, and chromosomal fragility testing is nearly always diagnostic. If the infant has radial abnormalities with normal-appearing thumbs, TAR syndrome should be considered. The platelet count is usually $<50 \times 10^3/\mu L$, and the white cell count is elevated in >90% of TAR syndrome patients, sometimes exceeding $100 \times 10^3/\mu L$ and mimicking congenital leukemia. Infants who survive the first year of life generally do well because the platelet count then spontaneously improves to low-normal levels that are maintained through life. The inability to rotate the forearm on physical examination, in the presence of severe early-onset thrombocytopenia, suggests the rare diagnosis of congenital amegakaryocytic thrombocytopenia with proximal radioulnar synostosis. Radiologic examination of the upper extremities in these infants confirms the proximal synostosis of the radial and ulnar bones. Other genetic disorders associated with early-onset thrombocytopenia include trisomy 21, trisomy 18, trisomy 13, Turner syndrome, Noonan syndrome, and Jacobsen syndrome. Cases of Noonan syndrome presenting with mild dysmorphic features and very severe neonatal thrombocytopenia (mimicking congenital amegakaryocytic thrombocytopenia) have been described. The presence of hepatomegaly or splenomegaly is suggestive of a viral infection, although it can also be seen in hemophagocytic syndrome and liver failure from different etiologies. Other diagnoses, such as renal vein thrombosis, Kasabach-Merritt syndrome, and inborn errors of metabolism (mainly propionic acidemia and methylmalonic acidemia), should be considered and evaluated for based on specific clinical indications (i.e., hematuria in renal vein thrombosis, presence of a vascular tumor in Kasabach-Merritt syndrome).

B. Late-onset thrombocytopenia (Fig. 47.2). The most common causes of thrombocytopenia of any severity presenting after 72 hours of life are sepsis (bacterial or fungal) and necrotizing enterocolitis (NEC). Affected infants are usually ill appearing and have other signs suggestive of sepsis and/or NEC. However, *thrombocytopenia can be the first presenting sign of these*

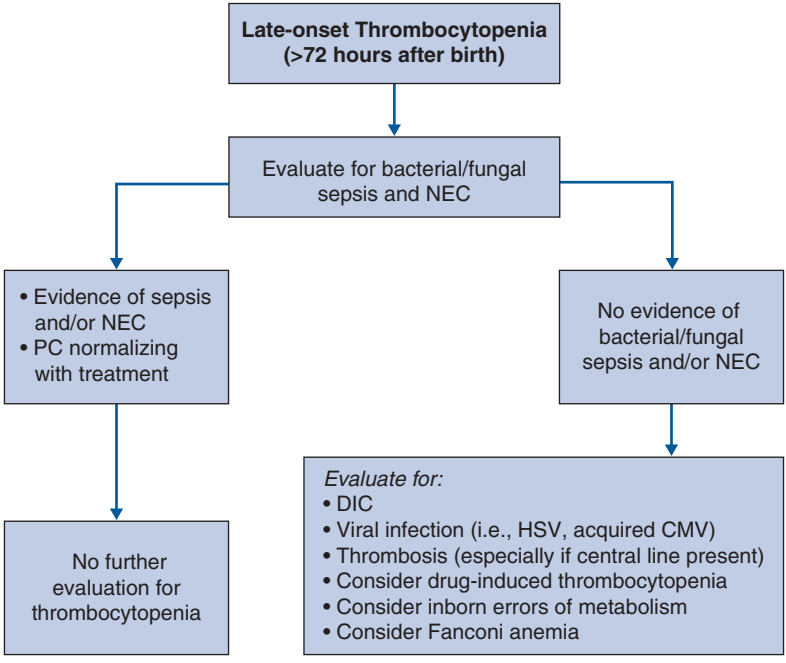

Figure 47.2. Guidelines for the evaluation of neonates with late-onset thrombocytopenia (>72 hours of life). NEC, necrotizing enterocolitis; PC, platelet count; DIC, disseminated intravascular coagulation; HSV, herpes simplex virus; CMV, cytomegalovirus.

processes and can precede clinical deterioration. Appropriate treatment (i.e., antibiotics, supportive respiratory and cardiovascular care, bowel rest in case of NEC, and surgery in case of surgical NEC) usually improves the platelet count in 1 to 2 weeks, although in some infants, the thrombocytopenia persists for several weeks. The reasons underlying this prolonged thrombocytopenia are unclear.

If bacterial/fungal sepsis and NEC are ruled out, viral infections such as herpes simplex virus, cytomegalovirus (CMV), or enterovirus should be considered. These are frequently accompanied by abnormal liver enzymes. If the infant has or has recently had a central venous or arterial catheter, thromboses should be part of the differential diagnosis. Finally, drug-induced thrombocytopenia should be considered if the infant is clinically well and is receiving heparin, antibiotics (penicillins, ciprofloxacin, cephalosporins, metronidazole, vancomycin, or rifampin), indomethacin, famotidine, cimetidine, phenobarbital, or phenytoin, among others. Other less common causes of late-onset thrombocytopenia include inborn errors of metabolism and Fanconi anemia (rare).

Novel tools to evaluate platelet production and aid in the evaluation of thrombocytopenia have been recently developed and are likely to become

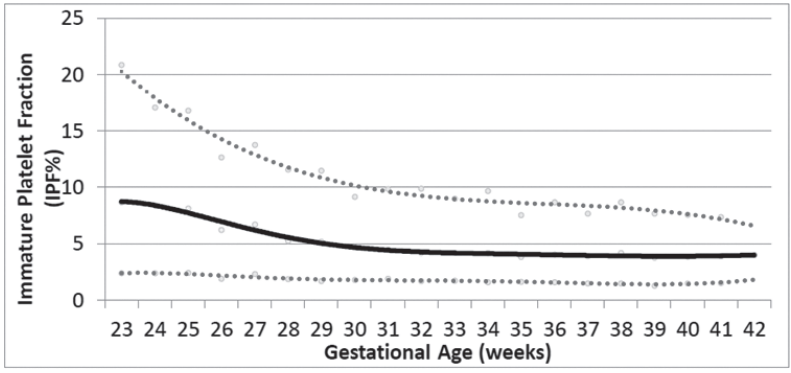

Figure 47. 3. Immature platelet fraction (IPF %) on the day of birth according to gestational age. *Lower* and *upper dashed lines* represent the 5th and 95th percentile reference intervals, and the *solid black line* represents the median. The *y* axis on the right shows total platelet count, and the *light gray solid line* represents the mean platelet count on the day of birth according to gestational age.

widely available to clinicians in the near future. Among those, the immature platelet fraction (IPF) measures the percentage of newly released platelets (<24 hours). The IPF can be measured in a standard hematologic cell counter (Sysmex 2100 XE or XN Hematology Analyzer) as part of the complete cell count and can help differentiate thrombocytopenias associated with decreased platelet production from those with increased platelet destruction, in a manner similar to the use of reticulocyte counts to evaluate anemia. Recent studies have established normal ranges for the IPF in neonates of different gestational ages at birth (Fig. 47.3) and have shown the usefulness of the IPF to evaluate mechanisms of thrombocytopenia and to predict platelet recovery in neonates. The IPF should be particularly helpful to guide the diagnostic evaluation of infants with thrombocytopenia of unclear etiology.

III. IMMUNE THROMBOCYTOPENIA. Immune thrombocytopenia occurs due to the passive transfer of antibodies from the maternal to the fetal circulation. There are two distinct types of immune-mediated thrombocytopenia: (i) neonatal alloimmune thrombocytopenia (NAIT) and (ii) autoimmune thrombocytopenia. In NAIT, the antibody is produced in the mother against a specific human platelet antigen (HPA) present in the fetus but absent in the mother. The antigen is inherited from the father of the fetus. The anti-HPA antibody produced in the maternal serum crosses the placenta and reaches the fetal circulation, leading to platelet destruction, inhibition of megakaryocyte development, and thrombocytopenia. In autoimmune thrombocytopenia, the antibody is directed against the mother's own platelets (autoantibodies). The maternal autoantibodies also cross the placenta, resulting in destruction of fetal platelets and thrombocytopenia.

A. NAIT. NAIT should be considered in any neonate who presents with severe thrombocytopenia at birth or shortly thereafter, particularly in the absence of other risk factors, clinical signs, or abnormalities in the physical exam.

In a study of >200 neonates with thrombocytopenia, using a platelet count $<50 \times 10^3/\mu L$ in the first day of life as a screening indicator identified 90% of the patients with NAIT. In addition, the combination of severe neonatal thrombocytopenia with a parenchymal (rather than intraventricular) intracranial hemorrhage (ICH) is highly suggestive of NAIT.

Laboratory investigation. When NAIT is suspected, blood should be collected from the mother and father and submitted for confirmatory testing (if accessible). The initial antigen screening should include HPA 1, 3, and 5. This evaluation should identify approximately 90% of cases of NAIT. However, if the diagnosis is strongly suspected and the initial evaluation is negative, further testing should be undertaken for HPA 9 and 15 (and HPA 4 if the parents are of Asian descent). If positive, these tests will reveal an antibody in the mother's plasma directed against the specific platelet antigen in the father. If blood cannot be collected from the parents in a timely fashion, neonatal serum may be screened for the presence of antiplatelet antibodies. However, a low antibody concentration in the neonate coupled with binding of the antibodies to the infant's platelets can lead to false-negative results. Due to the complexity of testing, evaluations should be performed in an experienced reference laboratory that has a large number of typed controls available for antibody detection and the appropriate DNA-based technology to type multiple antigens.

Brain imaging studies (cranial ultrasound) should be performed as soon as NAIT is suspected, regardless of the presence or absence of neurologic manifestations, because findings from these studies will dictate the aggressiveness of the treatment regimen for the affected infant and for the mother's future pregnancies. The clinical course of NAIT is short in most cases, often resolving almost entirely within 2 weeks. However, to confirm the diagnosis, it is important to follow the platelet count frequently until a normal count is achieved.

Management. The management of NAIT differs depending on the specific clinical scenario:

1. Suspected NAIT in an unknown pregnancy
2. Known case of NAIT
3. Antenatal management of pregnant woman with previous history of NAIT

a. Management of the neonate with suspected NAIT in an unknown pregnancy. Based on recent data demonstrating that a large proportion of infants with NAIT respond to **random donor platelet transfusions, this is now considered the first line of therapy for infants in whom NAIT is suspected**.

i. If the patient is clinically stable and does not have evidence of an ICH, platelets are usually given when the platelet count is $<25 \times 10^3/\mu L$, although this is arbitrary. In addition to platelets, if the diagnosis of NAIT is confirmed or strongly suspected, intravenous immunoglobulin (IVIG) (1 g/kg/day for up to 2 consecutive days) may be infused to increase the patient's own platelets and potentially to protect the transfused platelets. Because in NAIT the platelet count usually falls after birth, IVIG may be infused when the platelet count is between 25 and $50 \times 10^3/\mu L$ to try to prevent a further drop.

ii. If the patient has evidence of an ICH, the goal is to maintain a platelet count $>100 \times 10^3/\mu L$, but this may be challenging in neonates with NAIT. In all of these scenarios, it is important to keep in mind that some infants with NAIT fail to respond to random donor platelets and IVIG. For that reason, the blood bank should be immediately alerted about any infant with suspected NAIT, and arrangements should be made to secure a source of antigen-negative platelets (either from HPA-1b1b and 5a5a donors, which should be compatible in >90% of cases, or from the mother) as soon as possible if there is no response to the initial therapies. If maternal platelets are used, they need to be concentrated to decrease the amount of antiplatelet antibodies (present in the mother's plasma) infused into the infant. Platelets can also be washed to eliminate the plasma, but this induces more damage to the platelets than concentrating them. Of note, in some European countries, HPA-1b1b and 5a5a platelets are maintained in the blood bank inventory and are immediately available for use. In those cases, these are preferable to random donor platelets and/or IVIG and should be the first line of therapy.

iii. Methylprednisolone (1 mg/kg twice daily for 3 to 5 days) has also been used in individual case reports and small series but should only be considered in exceptional circumstances when the infant does not respond to random platelets and IVIG, and antigen-matched platelets are not readily available. We don't routinely use or recommend the use of steroids.

b. Management of the neonate with known NAIT. When a neonate is born to a mother who had a previous pregnancy affected by confirmed NAIT, genotypically matched platelets (e.g., HPA-1b1b platelets) should be available in the blood bank at the time of delivery and should be the first line of therapy if the infant is thrombocytopenic.

c. Antenatal management of pregnant women with previous history of NAIT. Mothers who delivered an infant with NAIT should be followed in high-risk obstetric clinics during all future pregnancies. The intensity of prenatal treatment will be based on the severity of the thrombocytopenia and the presence or absence of ICH in the previously affected fetus. This is particularly important to assess the risk of developing an ICH in the current pregnancy and to minimize this risk. Current recommendations involve maternal treatment with IVIG (1 to 2 g/kg/week) ± steroids (0.5 to 1.0 mg/kg/day prednisone), starting at 12 or at 20 to 26 weeks of gestation, depending on whether the previously affected fetus suffered an ICH and, if so, at what time during pregnancy. Most recent studies showed that the combination of IVIG and steroids is the most efficient treatment. Regarding the mode of delivery, elective cesarean section is recommended in most countries, regardless of ICH status, to avoid ICH.

B. Autoimmune thrombocytopenia. The diagnosis of neonatal autoimmune thrombocytopenia should be considered in any neonate who has early-onset thrombocytopenia and a maternal history of either immune thrombocytopenic purpura (ITP) or an autoimmune disease (with or without

thrombocytopenia). A retrospective study of obstetric patients who had ITP (including a high number of mothers who had thrombocytopenia during their pregnancies) demonstrated a relatively high incidence of affected babies: Twenty-five percent of neonates exhibited thrombocytopenia at birth; the thrombocytopenia was severe in 9%, and 15% received treatment for it. Other large studies confirmed an incidence of severe neonatal thrombocytopenia in this population ranging from 8.9% to 14.7%, with ICH occurring in 0.0% to 1.5% of affected neonates. Based on these data, it is recommended that all neonates born to mothers who have autoimmune diseases undergo a screening platelet count at or shortly after birth. If the platelet count is normal, no further evaluation is necessary. If the infant has mild thrombocytopenia, however, the platelet count should be repeated in 2 to 3 days because it usually reaches the nadir between days 2 and 5 after birth. If the platelet count is $<25 \times 10^3/\mu L$, IVIG (1 g/kg, repeated if necessary) is the first line of therapy. Random donor platelets, in addition to IVIG, should be provided if the infant has evidence of active bleeding, although some authors give them in addition to IVIG when the platelet count is $<25 \times 10^3/\mu L$ and provide IVIG alone for platelet counts between 25 and $50 \times 10^3/\mu L$. Cranial imaging (cranial ultrasound) should be obtained in all infants with platelet counts $<50 \times 10^3/\mu L$ to evaluate for ICH. Importantly, neonatal thrombocytopenia secondary to maternal ITP may last for weeks to months and requires long-term monitoring and sometimes a second dose of IVIG at 4 to 6 weeks of life.

Maternal management. Even if the mother has true ITP, it appears that fetal hemorrhage *in utero* is very rare, compared with the small but definite risk of such hemorrhage in alloimmune thrombocytopenia. Because of that, treatment of ITP during pregnancy is mostly based on the risk of maternal hemorrhage. A small prospective randomized trial of low-dose betamethasone (1.5 mg/day orally) failed to prevent thrombocytopenia in newborns. IVIG given prenatally to the mother with ITP has also not been clearly shown to affect the fetal platelet count.

There is in general little correlation between fetal platelet counts and either maternal platelet counts, platelet antibody levels, or history of maternal splenectomy. However, attempts to measure the fetal platelet count before delivery are not recommended due to the risk associated with such attempts. In regard to the mode of delivery, there is no evidence that cesarean section is safer for the fetus with thrombocytopenia than uncomplicated vaginal delivery. Given this fact, combined with the difficulty predicting severe thrombocytopenia in neonates and the very low risk of serious hemorrhage, the 2010 International Consensus Report on the Investigation and Management of Primary Immune Thrombocytopenia concluded that the mode of delivery in ITP patients should be determined by purely obstetric indications. However, interventions that increase the risk of bleeding in the fetus should be avoided, such as vacuum or forceps delivery.

IV. PLATELET TRANSFUSIONS IN THE NICU. Multiple studies have shown that there is great variability in neonatal transfusion practices in the United States and worldwide. To a large extent, this was due to the paucity of scientific evidence in the field and concerns regarding the bleeding risk (specifically

intracranial bleeding) in thrombocytopenic neonates. However, several studies found a very poor relationship between the degree of thrombocytopenia and the incidence of bleeding. Importantly, the strongest predictors of hemorrhage in neonates are gestational age <28 weeks, postnatal age <10 days, and a diagnosis of NEC, implying that factors other than the platelet count are the most important determinants of bleeding risk.

Until recently, only one randomized trial had compared different platelet transfusion thresholds in neonates, and it was limited to very low birth weight (VLBW) infants with platelet counts between 50 and 150 $\times$ $10^3/\mu L$ in the first week of life. This trial found no differences in the incidence or severity of intraventricular hemorrhages (IVHs) between neonates transfused for any platelet count <150 $\times$ $10^3/\mu L$ and those transfused only for counts <50 $\times$ $10^3/\mu L$, thus demonstrating that transfusing VLBW infants with platelet counts between 50 and 150 $\times$ $10^3/\mu L$ does not reduce the risk of IVH. However, this trial provided no guidance for preterm neonates with severe thrombocytopenia or with onset of thrombocytopenia after the first week of life.

In 2019, the PlaNeT-2 Platelets for Neonatal Transfusion - Study 2 trial was published. This large, multicenter, prospective trial randomized thrombocytopenic infants <34 weeks' gestation to receive platelet transfusions when the platelet count fell <50 $\times$ $10^3/\mu L$ (high threshold) or <25 $\times$ $10^3/\mu L$ (low threshold). The study found a significantly greater rate of death or major bleeding in the 28 days following randomization in neonates randomized to the high compared to the low threshold group (26% vs. 19%, respectively). In a subgroup analysis, findings were similar among neonates with a gestational age <28 weeks. However, neonates with a major bleed in the prior 72 hours or infants with severe IVH at the time of randomization were excluded from the study for 72 hours (after which they could be enrolled). Thus, by design, PlaNeT-2 did not address the effects of platelet transfusions on a preexisting IVH. In addition, for unknown reasons, 39% of neonates in the study received at least one platelet transfusion prior to enrollment.

Initial concerns about the generalizability of the findings to the highest risk neonates were largely alleviated by a subsequent subanalysis of PlaNeT-2 data that evaluated for possible heterogeneity of treatment effect. After categorizing the enrolled infants according to their baseline risk of death or major bleeding (based on clinical characteristics such as gestational age, postnatal age, and diagnosis), the investigators found that *the highest risk infants benefited from the lower platelet transfusion threshold as much (or more) as the infants at lowest risk*. Taken together, the currently available data supports the use of restrictive transfusion thresholds for most preterm neonates admitted to the NICU.

Although high-quality evidence like that provided by PlaNeT-2 is now available to guide platelet transfusion decisions in preterm neonates, data for near-term or term infants remain limited and largely derived from observational studies. However, three retrospective studies that investigated platelet transfusions among NICU patients of all gestational and postnatal ages also found an association between number of platelet transfusions and mortality, and concluded that some of this association could be related to the effects of platelet transfusions per se. Based on this combined evidence, we currently propose administering platelet transfusions to neonates according to the criteria shown in Table 47.1.

Table 47.1. Guidelines for Prophylactic Neonatal Platelet Transfusions

Platelet Count ($\times 10^3/\mu L$)	Guidelines
	If actively bleeding transfuse per clinician discretion
<25	*Transfuse all*
25–49	*Transfuse if:* ■ Major bleed in the past 48 hours (including severe IVH) ■ Immediately prior to surgical procedure, including lumbar puncture
50–100	*Transfuse if:* ■ NAIT with intracranial bleed ■ Within 24 hours of major neurosurgical intervention

Product administration guidelines: Transfuse 10 mL/kg of irradiated, CMV-safe platelets over 2 hours

IVH, intraventricular hemorrhage; CMV, cytomegalovirus; NAIT, neonatal alloimmune thrombocytopenia.

There is more consensus in regard to the platelet product that should be transfused. Most experts agree that neonates should receive 10 to 15 mL/kg of a standard platelet suspension, either a platelet concentrate ("random donor platelets") or apheresis platelets. Each random donor platelet unit has approximately 50 mL of volume and contains approximately 10×10^9 platelets per 10 μL. There is no need to pool more than one random donor unit for a neonatal transfusion, a practice that only increases donor exposures and induces platelet activation, without any benefit. The PlaNeT-2 finding of a higher incidence of bleeding among infants transfused at a higher platelet count threshold also raised concerns about the possibility that the rapid volume expansion caused by transfusing platelets over 30 to 60 minutes could contribute to the increased bleeding. Because of this concern, we currently recommend transfusing neonates with 10 mL/kg of platelets given over 2 hours. A prior study demonstrated similar platelet recovery in neonates transfused over 2 hours versus 30 minutes.

Two additional important considerations in neonatology are the prevention of transfusion-transmitted infections and graft-versus-host disease (GVHD). Most blood banks provide either CMV-negative or leukoreduced products to neonates, both of which significantly reduce (but do not eliminate) the risk of transfusion-transmitted CMV. Transfusion of CMV-negative *and* leukoreduced blood products effectively prevents transmission of CMV to VLBW infants. In addition, pathogen reduction technologies have been developed to eliminate/inactivate viral, bacterial, and parasitic pathogens in platelet products. These systems (INTERCEPT and MIRASOL) use a photoactive

compound (amotosalen in INTERCEPT and riboflavin in MIRASOL) that prevents DNA replication when exposed to ultraviolet light. Neonatal patients have been poorly represented in studies of both systems, and there is a potential concern for skin rashes among neonates who receive pathogen-reduced products containing psoralen (such as amotosalen) while also undergoing phototherapy (with peak wave length of 425 nm) for treatment of hyperbilirubinemia. Studies to determine any potential adverse effects of using pathogen-inactivated platelet products in the neonatal population are still needed. GVHD is effectively prevented by irradiating cellular blood products prior to transfusion. Of note, most neonatal cases of GVHD have been reported in neonates with underlying immunodeficiencies, receiving intrauterine or large volume transfusions (i.e., double exchange transfusions), or receiving blood products from a first-degree relative. These are all absolute indications for irradiating blood products.

Suggested Readings

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48 Viral Infections

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KEY POINTS

- Vertically transmitted (mother to child) viral infections of the fetus and newborn can generally be divided into three distinct categories by transmission modes—congenital, peripartum, and postnatal infections.
- Although classically the congenital infections have gone by the acronym TORCH (T = toxoplasmosis, O = other, R = rubella, C = cytomegalovirus, H = herpes simplex virus), the concept of obtaining "TORCH titers" for diagnostics in an infant is out of date with current viral diagnostic testing platforms.
- When congenital or perinatal infections are suspected, the diagnosis of each of the possible infectious agents should be considered separately and the appropriate most rapid diagnostic test is requested in order to implement therapy as quickly as possible.
- Congenital cytomegalovirus (CMV) infection is the most common congenital infection and a leading cause of birth defects and pediatric disabilities.
- Neonatal herpes simplex virus (HSV) infection is associated with a high risk of infant death and lifelong disabilities, yet the disease can be considerably ameliorated with early use of acyclovir in suspected cases.
- Global Zika virus (ZIKV) outbreaks in 2015 revealed it as the first flavivirus to result in a significant burden of congenital infections leading to microcephaly, ocular defects, and neurodevelopmental delays.
- Pediatric HIV-1 infections have been markedly reduced through the use of maternal and/or infant antiretroviral treatment (ART), yet break through infections and incomplete access/adherence to ART impede global elimination of vertical HIV-1 transmission.
- Infant infection after exposure to a hepatitis B surface antigen (HBsAg)-positive mother can be avoided through a combination of active (hepatitis B vaccine) and passive hepatitis B immune globulin (HBIG) immunization of the infant.

I. INTRODUCTION. Vertically transmitted (mother to child) viral infections of the fetus and newborn can generally be divided into three distinct categories by transmission modes. The first is **congenital infections**, which are transmitted to the fetus via the placenta *in utero*. The second category is **peripartum infections**, which are acquired intrapartum or during the delivery. The final

category is **postnatal infections**: viruses transmitted in the postpartum period, commonly via breast milk feeding. Classifying these infections into congenital and perinatal categories highlights aspects of their pathogenesis in the fetus and newborn infant. When these infections occur in older children or adults, they are typically benign. However, if the host is immunocompromised or if the immune system is not yet developed, such as in the neonate, clinical symptoms may be quite severe or even fatal. Congenital infections can have manifestations that can lead to spontaneous fetal loss, or become clinically apparent antenatally by ultrasonography or when the infant is born, whereas perinatal infections may not become clinically obvious until after the first few weeks of life.

Although classically the congenital infections have gone by the acronym TORCH (T = toxoplasmosis, O = other, R = rubella, C = cytomegalovirus, H = herpes simplex virus), the concept of obtaining "TORCH titers" for diagnostics in an infant is out of date with current viral diagnostic testing platforms. When congenital or perinatal infections are suspected, the diagnosis of each of the possible infectious agents should be considered separately and the appropriate most rapid diagnostic test requested in order to implement therapy as quickly as possible. Useless information is often obtained when the diagnosis is attempted by drawing a single serum sample to be sent for measurement of "TORCH" titers. These immunoglobulin G (IgG) antibodies are acquired by passive transmission to the fetus and merely reflect the maternal serostatus. Pathogen-specific immunoglobulin M (IgM) antibodies do reflect fetal/infant infection status but with variable sensitivity and specificity. The following discussion is divided by pathogen as to the usual timing of acquisition of infection (congenital or peripartum or postnatal) and in approximate order of prevalence. A summary of the diagnostic evaluations for separate viral infections is shown in Table 48.1.

II. CYTOMEGALOVIRUS (CMV) (CONGENITAL, PERIPARTUM, AND POSTNATAL).

CMV is a double-stranded enveloped DNA virus that results lifelong infection. It is a member of the herpesvirus family, is highly species-specific, and derives its name from the histopathologic appearance of infected cells, which have abundant cytoplasm and both intranuclear and cytoplasmic inclusions. CMV is the most common congenital viral infection. The high rate of congenital infection following maternal infection and its resulting brain damage and birth defects has led the Institute of Medicine to name the development of a CMV vaccine as a top priority.

A. Epidemiology.

CMV is present in saliva, urine, genital secretions, breast milk, and blood/blood products of infected persons and can be transmitted by exposure to any of these sources. Primary infection (acute infection) is usually asymptomatic in older infants, children, and adults but may manifest with mononucleosis-like symptoms, including a prolonged fever and a mild hepatitis. Latent infection is asymptomatic unless the host becomes immunocompromised. CMV infection is very common, with seroprevalence in the United States between 50% and 85% by age 40 years. Approximately 40% of pregnant women in the United States are infected, which is in contrast to >90% seropositivity in underdeveloped nations. Yet, the U.S. seroprevalence rates are highly dependent on race distribution and geography, with

Table 48.1. Diagnostic Techniques for Diagnosis of Perinatal Infections

Pathogen	Test of Choice	Sensitivity	Expense	Turnaround
HSV	Culture of SEM; PCR of blood or CSF	High	Moderate	Culture many days; PCR hours*
Parvovirus	PCR blood	High	Moderate	Hours*
Parvovirus	IgM	Moderate	Low	Days
CMV	PCR urine/saliva	High	Moderate	Hours*
CMV	Spin-enhanced urine culture (shell vial)	High	Moderate	Days
HIV	DNA PCR of blood if mother known HIV infected	High	High	Hours*
HIV	RNA PCR of plasma if mother not treated	High	Moderate	Hours*
HBV	HBsAg of blood	High	Low	Hours
HBV	DNA PCR of blood	High	Moderate	Hours*
HCV	RNA PCR of plasma <12 months	High	Moderate	Hours*
HCV	RIBA or ELISA >15 months	High	Low	Hours*
VZV	PCR of skin lesion	Moderate	Moderate	Hours
HEV	RNA PCR blood or CSF	High	Moderate	Hours*
HEV	Culture urine, oropharynx, stool	Moderate	High	Days
Rubella	Culture urine	Moderate	High	Many days
RSV	PCR of nasopharyngeal secretions	Moderate	Moderate	Hours

(continued)

Table 48.1. Diagnostic Techniques for Diagnosis of Perinatal Infections *(Continued)*

Pathogen	Test of Choice	Sensitivity	Expense	Turnaround
SARS-CoV-2	PCR of nasopharyngeal secretions	Moderate	Moderate	Hours
ZIKV	IgM	Moderate	Low	Days

*Polymerase chain reactions (PCRs) in general are done within a half day but often are a send-out test to a central lab requiring days to ship and retrieve data.

HSV, herpes simplex virus; SEM, skin, eye, or mouth; CSF, cerebrospinal fluid; IgM, immunoglobulin M; CMV, cytomegalovirus; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; RIBA, recombinant immunoblot assay; ELISA, enzyme-linked immunosorbent assay; VZV, varicella-zoster virus; HEV, hepatitis E virus; RSV, respiratory syncytial virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ZIKV, Zika virus.

Southeastern states having higher seroprevalence rates compared to the rest of the country and Latin and African American women demonstrating the highest preconception seroimmunity. Primary CMV infection occurs in approximately 1% to 4% of pregnant women, likely via sexual transmission or exposure to mucosal fluid of CMV-infected toddlers who shed high amounts of the virus. Primary maternal infection is a high-risk setting for the fetus, with a fetal transmission rate of 30% to 40%. This high fetal transmission rate in primary infection is in contrast to the 1% to 2% transmission rate in women infected with CMV prior to pregnancy. In this setting, virus is transmitted following maternal virus reactivation or reinfection. It is estimated that half to three quarters of congenital infections are due to nonprimary maternal CMV infection during pregnancy, depending on the population. Some reports indicate that infants who acquire congenital CMV infection in the setting of no preexisting immunity are more likely to be symptomatic and have long-term sequelae, but the risk of hearing loss is similar for infants born to mothers with and without preexisting immunity. Transmission to the fetus can occur at any point in pregnancy, but infection during early gestation likely carries a higher risk of severe fetal disease.

Congenital CMV occurs in approximately 0.5% to 1% of all live births in the United States and is the leading infectious cause of sensorineural hearing loss (SNHL), developmental delay, and occasional childhood death. In fact, CMV contributes to more cases of childhood deafness than that of *Haemophilus influenzae* bacterial meningitis in the prevaccine era. Annually, 30,000 to 40,000 CMV-infected infants are born in the United States (at least 1 in 150 live births), with 10% to 15% presenting with symptomatic disease at birth. Additionally, 10% to 15% of the asymptomatic neonates will develop significant sequelae in the first year of life, most commonly hearing loss. Therefore, >5,000 infants are severely affected or die from CMV infection in the United States each year (1 in 750 live births). Congenital CMV infection is more common among HIV-exposed infants,

and coinfected infants may have more rapid progression of HIV-1 disease. Therefore, screening for congenital CMV infection in HIV-exposed infants is advised.

Finally, only in unique settings can perinatal or postnatal transmission of CMV lead to neonatal disease, including postnatal infection of very low birth weight (VLBW, <1,500 g birth weight) preterm infants and children with congenital immunodeficiencies, such as severe combined immunodeficiency (SCID). In the neonatal intensive care unit, many postnatal CMV infections were previously caused by transfusion of CMV seropositive blood products, which has been essentially eliminated through the use of seronegative and leukoreduced blood products. Currently, postnatal transmission via breast milk feeding is the most common mode of infection in preterm infants, which can lead to a sepsis-like illness, pneumonitis, and enteritis. Some studies suggest an increased risk for bronchopulmonary dysplasia and neurodevelopmental impairment in VLBW preterm infants that acquire CMV, but large-scale prospective studies are needed to fully address this.

B. Clinical disease in congenital infection may present at birth or may manifest with symptoms later in infancy. Only VLBW preterm infants or immunosuppressed infants will have symptomatic disease from peripartum or postnatal CMV acquisition.

1. **Congenital symptomatic CMV disease** can present as an acute **fulminant** infection involving multiple organ systems with as high as 30% mortality. **Signs** include petechiae or purpura (50% to 79%), hepatosplenomegaly (40% to 74%), jaundice (40% to 70%), pneumonitis (5% to 10%), and/or "blueberry muffin spots" reflecting extramedullary hematopoiesis. **Laboratory abnormalities** include elevated hepatic transaminases and bilirubin levels (as much as half conjugated), anemia, and thrombocytopenia. Hyperbilirubinemia may be present at birth or develop over time and can persists beyond the period of physiologic jaundice. Approximately one-third of these infants are preterm, and one-third have intrauterine growth restriction (IUGR) and microcephaly.

   A second early presentation includes infants who are symptomatic, most commonly with SNHL, but without life-threatening complications. These babies may also be small for gestational age (SGA) (40% to 50%) or disproportionate microcephalic (35% to 50%) with or without intracranial calcifications. These calcifications may occur anywhere in the brain but are classically found in the periventricular area. Other findings of central nervous system (CNS) disease can include seizures, hypotonia, ventricular dilatation, cortical atrophy, and migrational disorders such as lissencephaly, pachygyria, and demyelination as well as chorioretinitis in approximately 10% to 15% of infants. The majority of infants with symptomatic congenital CMV will have at least one handicap. Microcephaly and head imaging abnormalities are the strongest early predictors for developmental abnormalities and neurologic dysfunction. These range from mild learning and language disability or mild hearing loss to IQ scores <50, motor abnormalities, deafness, and visual problems. Because SNHL is the most common sequela of CMV infection, any infant failing the newborn hearing screen also should be screened for CMV

infection in the absence of universal screening. Conversely, infants with documented congenital CMV infection should be frequently assessed for hearing loss as neonates and through the first few years of life and annually through school age given the risk of late-onset SNHL.

2. **Asymptomatic congenital infection** at birth in 5% to 15% of neonates can manifest as **late disease** in infancy, throughout the first 2 years of life. Abnormalities include developmental abnormalities, hearing loss, seizures, mental retardation, motor spasticity, and acquired microcephaly.

3. **Peripartum and postnatally acquired CMV infection** may occur (i) from intrapartum exposure to the virus within the maternal genital tract, (ii) from postnatal exposure to infected breast milk, (iii) from exposure to infected blood or blood products, or (iv) nosocomially through urine or saliva. The time from infection to disease presentation varies from 4 to 12 weeks. Almost all term infants who are infected perinatally or postnatally remain asymptomatic, with the exception of severely immunocompromised infants. Preterm VLBW infants can develop an acute infection syndrome including neutropenia, anemia, thrombocytopenia, and hepatitis. Data suggest that all infants regardless of gestational age should have hearing testing over the first 2 years of life if documented to have acquired CMV.

4. **CMV pneumonitis.** CMV has been associated with pneumonitis occurring primarily in preterm infants <4 months old. Symptoms and radiographic findings in CMV pneumonitis are similar to those seen in afebrile pneumonia of other causes in neonates and young infants, including *Chlamydia trachomatis*, *Ureaplasma urealyticum*, and respiratory syncytial virus (RSV). Symptoms include tachypnea, cough, coryza, and nasal congestion. Intercostal retractions and hypoxemia may be present, and apnea may occur. Radiographically, there is hyperinflation, diffusely increased pulmonary markings, thickened bronchial walls, and focal atelectasis. A small number of infants may have symptoms that are severe enough to require mechanical ventilation or an increased level of respiratory support. Long-term sequela include recurrent pulmonary problems, including wheezing, bronchopulmonary dysplasia (defined as prolonged oxygen dependence), and, in some cases, repeated hospitalizations for respiratory distress. Whether this presentation reflects congenital or perinatal CMV infection is unclear. Conversely, merely finding CMV in respiratory secretions of a preterm infant does not prove causality because CMV is present in saliva of infected infants.

5. **Transfusion-acquired CMV infection.** In the past, significant morbidity and mortality could occur in newborn infants receiving CMV-infected blood or blood products. Because both the cellular and humoral maternal immune systems are helpful in preventing infection or in ameliorating clinical disease, those most severely affected were preterm, low birth weight infants born to CMV-seronegative women. Mortality was estimated to be 20% in VLBW infants. Symptoms typically developed 4 to 12 weeks after transfusion; lasted for 2 to 3 weeks; and consisted of respiratory distress, pallor, and hepatosplenomegaly. Hematologic abnormalities were also

seen, including hemolysis, thrombocytopenia, and atypical lymphocytosis. Transfusion-acquired CMV is now rare in the United States, prevented by using blood/blood products from CMV-seronegative donors or filtered, leukoreduced products (see Chapter 42).

C. Diagnosis. CMV infection should be suspected in any infant having typical symptoms of infection or if there is a maternal history of seroconversion or a mononucleosis-like, febrile illness in pregnancy or ultrasound findings consistent with CMV infection (i.e., echogenic bowel, intracranial calcifications). The diagnosis is made if CMV is identified in amniotic fluid or urine, saliva, blood, or respiratory secretions of the infant and defined as *congenital* infection if found in the infant within the first 3 weeks of life and as *peripartum* or *postnatal* infection if negative in the first 3 weeks and positive after 4 weeks of life. Depending on when the fetus or infant infection occurred, blood is the earliest specimen to become positive and is highly specific for congenital disease when CMV is detected in blood of a newborn near birth; however, not all congenitally infected infants are viremic at birth. Thus, detection of CMV shedding in urine or saliva provides the highest sensitivity for diagnosis. A negative viral test from blood cannot rule out CMV infection, but a negative urine or saliva test in an untreated infant symptomatic for 4 weeks is very sensitive. For saliva samples, false negatives can occur in preterm infants, likely secondary to inadequate sample volume collection. There are three rapid diagnostic techniques:

1. **CMV polymerase chain reaction (PCR).** CMV may be detected by PCR in urine, saliva, or blood. The sensitivity and specificity of using this test for diagnosis is quite high for urine and saliva, but a negative PCR in blood does not rule out infection. Saliva is a preferred specimen in term infants due to ease of collection. In fact, a CMV PCR testing platform based on dried saliva "spots" on filter paper has been validated as highly sensitive and specific and may be amenable to being added to the current newborn screening tests that use dried blood spots.
2. **Spin-enhanced or "shell vial" culture.** Virus can be isolated from saliva and in high titer from urine. Depending on local laboratory specifications, the specimen is collected as fluid or with a Dacron swab, inoculated into viral transport medium, then inoculated into viral tissue culture medium containing a coverslip on which tissue culture cells (MRC5) have been grown and incubated. Viable CMV infects the cells, which are then lysed and stained with antibody to CMV antigens. Virus can be detected with high sensitivity and specificity within 24 to 72 hours of inoculation. It is much more rapid than standard tissue culture, which may take from 2 to 6 weeks for replication and identification. A negative result generally rules out CMV infection except in infants who may have acquired infection within the prior 2 to 3 weeks.
3. **CMV antigen.** Peripheral blood can be centrifuged and the buffy coat spread on a slide. The neutrophils are then lysed and stained with an antibody to CMV pp65 antigen. Positive results confirm CMV infection and viremia; however, negative results do not rule out CMV infection. This test is only used to follow efficacy of therapy and may be replaced by quantitative blood PCR tests.

a. CMV IgG and IgM. The determination of serum antibody titers to CMV has limited usefulness for the neonate, although negative IgG titers in both maternal and infant sera are sufficient to exclude congenital CMV infection. A positive IgM during pregnancy without the detection of CMV-specific IgG should be repeated to look for a new seroconversion, whereas a positive IgM in the presence of IgG should be further assessed with a CMV IgG avidity assay. Low maternal CMV IgG avidity would indicate recent infection, and therefore, the infant should be tested for CMV and followed closely after birth. The interpretation of a positive IgG titer in the newborn is complicated by the presence of transplacentally derived maternal IgG. Uninfected infants usually show a decline in IgG within 1 month and have no detectable titer by 4 to 12 months, whereas infected infants will continue to produce IgG. Tests for CMV-specific IgM have limited specificity but may help in the diagnosis of an infant infection.

If the diagnosis of congenital CMV infection is made, the newborn should have a thorough physical and neurologic examination, a head ultrasound, potentially followed by magnetic resonance imaging (MRI) scan of the brain, an ophthalmologic examination, and repeated hearing tests. Laboratory evaluation should include a complete blood count, liver function tests, and, preferably, cerebrospinal fluid (CSF) examination. In CMV-infected infants with symptomatic disease, approximately 90% with abnormal brain imaging will have CNS sequelae. However, about 30% of infants with normal brain imaging will also have sequelae. Infants with evidence of neurologic involvement should be considered as candidates for antiviral treatment.

D. Treatment. Ganciclovir and the oral prodrug, valganciclovir, have been effective in the treatment of and prophylaxis against dissemination of CMV in immunocompromised patients and infants. The earliest studies of infants with symptomatic CMV disease showed a strong trend toward efficacy in the intravenous (IV) ganciclovir-treated infants as assessed by stabilization or improvement of SNHL. Further studies indicated that extended treatment of symptomatic infants with valganciclovir for 6 months showed improvements in hearing loss and developmental delay over 6 weeks of treatment. The primary reported toxicity of valganciclovir treatment is mild neutropenia. Yet, the occurrence of neutropenia was equally common between 6 weeks and 6 months of age in infants who received the prolonged or short course of valganciclovir—indicating that the viral infection, as opposed to the drug treatment, is the primary contributor to the observed neutropenia. Families should be advised that although evidence is increasing as to ganciclovir's ability to improve long-term neurologic outcomes, there is a potential for future reproductive system effects because testicular atrophy and gonadal tumors were found in some animals treated with pharmacologic doses of ganciclovir. Studies are ongoing to determine if treatment improves outcomes of infected infants with isolated hearing loss or asymptomatic infants. Moreover, the efficacy of initiating treatment at >1 month of age in symptomatic infection is not known, demonstrating the importance of early diagnosis. Finally, although the treatment of postnatally acquired CMV infection is recommended in highly immunosuppressed infants, the effectiveness of treatment of symptomatic postnatal CMV infection in

preterm infants to ameliorate the disease course or improve long-term outcome is unknown. Thus, treatment should be recommended and supervised by a pediatric infectious disease specialist.

E. Prevention

1. **Screening.** Because only about 1% of women acquire primary CMV infection during pregnancy and there are no currently available prevention strategies in pregnant women that have been shown to be effective in randomized trials, screening for women at risk for seroconversion is generally not recommended. Isolation of virus from the cervix or urine of pregnant women cannot be used to predict fetal infection. In cases of documented primary maternal infection or seroconversion, quantitative PCR testing of amniotic fluid can determine whether the fetus acquired infection. However, counseling about a positive finding of fetal infection is difficult because approximately 80% of infected fetuses will only have mild or asymptomatic disease. Some investigators have found that higher CMV viral loads from the amniotic fluid tended to correlate with abnormal neurodevelopmental outcome. One case-control study suggested a protective benefit against severe neonatal disease by administering hyperimmune CMV immunoglobulin antenatally to women with low affinity antibody to CMV, but a subsequent randomized controlled trial did not demonstrate benefit in preventing congenital infection. Yet, pregnant women, and particularly those who are exposed to toddlers, can be counseled to reduce their CMV acquisition risk. The Centers for Disease Control and Prevention (CDC) recommends that (i) pregnant women practice hand washing with soap and water after contact with diapers or oral secretions; do not share food, utensils, toothbrushes, and pacifiers with children; and avoid saliva when kissing a child; (ii) pregnant women who develop a mononucleosis-like illness during pregnancy should be evaluated for CMV infection and counseled about risks to the unborn child; (iii) antibody testing can confirm prior CMV infection; (iv) the benefits of breastfeeding outweigh the minimal risk of acquiring CMV; and (v) there is no need to screen for CMV or exclude CMV-excreting children from schools or institutions.

2. **Immunization.** Passive immunization with hyperimmune anti-CMV immunoglobulin and active immunization with a live-attenuated CMV vaccine represent attractive therapies for prophylaxis against congenital CMV infections. However, data from clinical trials have not shown adequate efficacy of either of these approaches with current passive and active vaccine products. Two live-attenuated CMV vaccines have been developed, but their efficacy has not been clearly established. A subunit vaccine consisting of the major immunodominant glycoprotein present on the surface of the virus, glycoprotein B (gB), was studied for the prevention of maternal CMV acquisition following delivery, yet was only 50% efficacious in preventing CMV acquisition. Ongoing vaccine development has focused on distinct glycoprotein complexes and the elicitation of both humoral and cellular immunity, holding promising eventual development of a maternal CMV vaccine that will eliminate congenital CMV transmission, much like that of the rubella virus vaccine.

3. **Breast milk feeding.** Although breast milk is a common source for postnatal CMV infection in the newborn, symptomatic infection is rare in term infants. In this setting, protection against disseminated disease may be provided by transplacentally derived maternal IgG or antibody in breast milk. However, there may be insufficient transplacental IgG to provide adequate protection in preterm infants. For mothers of extremely premature and low birth weight infants known to be CMV seropositive, freezing breast milk will reduce the titer of CMV but will not eliminate active virus. Holder pasteurization (62.5°C for 30 minutes) of breast milk will eliminate CMV infectivity but also decreases other immune and nutritional components of breast milk. At present, there is no recommended method of minimizing the risk of exposure to CMV in breast milk for preterm infants; maternal breast milk is the preferred enteral nutrition in preterm infants. Methods to reduce acquisition of CMV via breast milk feeding for preterm infants are needed to eliminate this risk for preterm infants.
4. **Environmental restrictions.** Day care centers and hospitals are potential high-risk environments for acquiring CMV infection. Not surprisingly, a number of studies confirmed an increased risk of infection in day care workers. However, there does not appear to be an increased risk of infection in hospital personnel, indicating that hand hygiene and infection control measures practiced in hospital settings are sufficient to control the spread of CMV to workers. Unfortunately, such control may be difficult to achieve in day care centers. Good hand-washing technique should be suggested to pregnant women with children in day care settings and with children attending day care, especially if the women are known to be seronegative. The determination of CMV susceptibility of these women by serology may be useful for counseling.
5. **Transfusion product restrictions.** The risk of transfusion-acquired CMV infection in the neonate has been almost eliminated by the use of CMV antibody-negative donors, by freezing packed red blood cells (PRBCs) in glycerol, or by removing the white blood cells. It is particularly important to use blood from one of these sources in preterm, low birth weight infants, and other immunocompromised patients (see Chapter 42).

III. HERPES SIMPLEX VIRUS (HSV: PERINATAL).

HSV, a lifelong infection, is a double-stranded, enveloped DNA virus with two virologically distinct types: types 1 (HSV-1) and 2 (HSV-2). HSV-2 was previously the primary cause of genital lesions, yet HSV-1 has become the predominant virus type in genital lesions of young women. Both types produce clinically indistinguishable neonatal syndromes. The virus can cause localized disease of the infant's skin, eye, or mouth (SEM) or may disseminate by cell-to-cell contiguous spread or viremia. After adsorption and penetration into host cells, viral replication proceeds, resulting in cellular swelling, hemorrhagic necrosis, formation of intranuclear inclusions, cytolysis, and cell death.

A. Epidemiology. Acquisition of HSV results in lifelong disease, with periodic virus reactivation and mucosal shedding. At least 80% of the U.S. population

is infected with HSV-1 by the fifth decade of life, the cause of recurrent orolabial disease, and an increasing cause of genital disease. According to the 2015 to 2016 National Health and Nutrition Examination Survey, the overall seroprevalence of HSV-1 and HSV-2 in the United States in 14- to 49-year-olds is 48.1% and 12.1%, respectively, and is now decreasing over time. Women without prior exposure to HSV have a 4% chance of primary infection during pregnancy and a 2% chance of a nonprimary acute infection with either HSV-1 or HSV-2 (previously infected with the alternate HSV type). The majority of these new HSV acquisitions will be asymptomatic.

Infection in the newborn occurs as a result of direct exposure to the virus, most commonly in the perinatal period from maternal genital disease or asymptomatic virus shedding. In one study, the characteristic ulcerations of the genitalia were present only in two-thirds of the genital tracts from which HSV could be isolated. It is estimated that up to 0.4% of all women presenting for delivery are shedding virus, and >1% of all women with a history of recurrent HSV infection asymptomatically shed HSV at delivery. Yet, **it is critical to recognize that over three-quarters of mothers of infants with neonatal HSV do not have a history of HSV outbreaks**. Approximately 30% to 60% of infants will acquire HSV infection if maternal primary infection occurs near delivery, whereas <2% of infants are infected if born to a woman with preexisting immunity (recurrent disease). Additionally, one-third of infants born to mothers with newly acquired HSV-2 or HSV-1, although already infected with the other HSV type (nonprimary, first episode defined by detection of virus in the maternal genital tract at the time of delivery but no IgG response for the type-specific HSV identified), may acquire HSV infection. This may be due to protective maternal type–specific antibodies in the infant's serum or the birth canal. The overall incidence of newborn infection with HSV is estimated to be 1 in 2,000 to 1 in 3,000 in the United States.

B. Transmission

1. **Intrapartum transmission** is the most common cause of neonatal HSV infection. It is primarily associated with active shedding of virus from the cervix or vulva at the time of delivery. Up to 90% of newborn infections occur as a result of intrapartum transmission. Maternal immunity and the related amount and duration of maternal virus shedding are major determinants of peripartum transmission. Transmission risks are greatest with primary maternal infection during pregnancy, with nonprimary acute infection with HSV-1 or HSV-2 being the next highest risk setting. In fact, when maternal antibody is present, the risk of acquisition of HSV, even for the newborn exposed to HSV in the birth canal, is much lower than that of primary maternal infection. The exact mechanism of action of maternal antibody in preventing perinatal infection is not known, but transplacentally acquired antibody is associated with reduced risk of severe newborn disease following perinatal HSV exposure. The risk of intrapartum infection increases with ruptured membranes, especially when ruptured longer than 4 hours. Finally, direct methods for fetal monitoring, such as with scalp electrodes, increase the risk of fetal transmission in the setting of active shedding. It is best to avoid these techniques if possible in women with a history of recurrent infection or suspected primary HSV disease.

2. **Antenatal transmission.** *In utero* infection with HSV has been documented but is uncommon. Spontaneous abortion has occurred with primary maternal infection before 20 weeks' gestation, but the true risk to the fetus of early-trimester primary infection is not known. Fetal infections may occur by either transplacental or ascending routes and have been documented in the setting of both primary and, rarely, recurrent maternal disease. There may be a wide range of clinical manifestations, from localized skin or eye involvement to severe multiorgan disease, congenital malformations, and fetal demise. Survivors of *in utero* disease may exhibit the characteristic triad of cutaneous (lesions, ulcerations, scarring), ophthalmologic (chorioretinitis, optic atrophy, retinal dysplasia), and CNS disease (microcephaly, encephalomalacia, hydranencephaly, and/or intracranial calcifications), but the full triad occurs in less than one-third of those with congenital disease.

3. **Postnatal transmission.** A small percentage of neonatal HSV infections result from postnatal HSV exposure (~10%). Potential sources include symptomatic and asymptomatic oropharyngeal shedding by either parent, hospital personnel, or other contacts, and maternal breast lesions. Measures to minimize exposure from these sources are discussed in the following text.

C. **Clinical manifestations.** The morbidity and mortality of neonatal HSV best correlates with three categories of disease. These are (i) infections localized to the SEM, (ii) CNS disease with or without localized mucocutaneous disease, and (iii) disseminated infection with multiple organ involvement.

1. **SEM infection.** Approximately 50% of infants with HSV have disease localized to the skin, eye, or mucocutaneous membranes. Vesicles typically appear on the sixth to ninth day of neonatal life but may occur as late as 6 weeks of age. A cluster of vesicles may develop on the presenting part of the body, where extended direct contact with virus may have occurred, or at areas of local trauma (i.e., from scalp monitor). Vesicles occur in 90% of infants with localized mucocutaneous infection, and recurrent disease is common. There is a high risk of progression to disseminated disease if untreated, and significant morbidity can occur in these infants despite the absence of signs of disseminated disease at the time of diagnosis. All infants with apparent SEM disease should undergo a workup for disseminated and CNS disease. Infants with keratoconjunctivitis can develop chorioretinitis, cataracts, and retinopathy. Thus, ophthalmologic and neurologic follow-up is important in all infants with mucocutaneous HSV. With appropriate antiviral therapy, the majority of these infants will have no long-term morbidity. Infants with three or more recurrences of vesicles, likely reflecting poor immunologic control of virus replication, have an increased risk of neurologic complications.

2. **CNS infection.** Approximately one-third of neonates with HSV present with meningoencephalitis in the absence of disseminated disease and only 60% of these infants have mucocutaneous vesicles. These infants usually become symptomatic at 17 to 19 days of life with lethargy, seizures, temperature instability, and hypotonia but can present as late as

6 weeks of life. In the setting of disseminated disease, HSV is thought to invade the CNS from hematogenous spread. However, CNS infection in the absence of disseminated disease can occur, most often in infants having transplacentally derived viral-neutralizing antibodies, which may protect against widespread dissemination but not influence intraneuronal viral replication. Mortality is high without treatment but is approximately 5% with treatment. Prematurity and seizures are associated with higher mortality. Late treatment is associated with increased mortality, highlighting the need for early treatment when neonatal HSV infection is suspected. Approximately two-thirds of surviving infants have impaired neurodevelopment. Long-term sequelae from acute HSV encephalitis include microcephaly, hydranencephaly, porencephalic cysts, spasticity, blindness, deafness, chorioretinitis, and learning disabilities.

3. **Disseminated infection.** This is the most severe form of neonatal HSV infection. It accounts for approximately 25% of all infants with neonatal HSV infection and can result in death in >80% if untreated and approximately 30% with treatment. Pneumonitis and fulminant hepatitis are associated with greater mortality. Infants usually present on days 10 to 12 to medical attention but can present later. The liver, adrenals, and other visceral organs are usually involved. Approximately two-thirds of infants also have meningoencephalitis. Clinical findings include seizures, shock, respiratory distress, disseminated intravascular coagulation (DIC), and respiratory failure. A typical vesicular rash may be absent in as many as 20% of infants. Forty percent of the infants who survive have long-term morbidity, and up to 20% have neurodevelopmental impairment.

D. Diagnosis. HSV infection should be considered in the differential diagnosis of ill neonates with a variety of clinical presentations. These include CNS abnormalities (lethargy, seizures, hypotonia, irritability), fever, shock, DIC, hepatitis, and/or other sepsis-like illness. HSV also should be considered in infants with respiratory distress without an obvious bacterial cause or a clinical course and findings consistent with prematurity. The possibility of concomitant HSV infection with other commonly encountered problems of the preterm infant should be considered. **Viral isolation** or **PCR detection of viral DNA** in the appropriate clinical setting remains critical to the diagnosis. For all infants with suspected HSV disease, the following should be obtained: (i) swabs specimens from the mouth, nasopharynx, conjunctivae, and anus (surface specimens) for HSV culture or PCR; (ii) scraping specimen of skin vesicles for HSV culture or PCR; (iii) CSF sample for HSV PCR, and (iv) whole blood for HSV PCR. Cytopathogenic effects of HSV can usually be seen in 1 to 3 days, with cultures negative at 5 days likely to remain negative. Shell vial cultures can decrease the time of detection to 24 to 48 hours. Cultures are the gold standard for diagnosis to establish neonatal HSV disease but are dependent on proper specimen collection, stage of the lesion (crusting lesions less likely to be culture positive), and expertise of testing personnel. Rapid diagnostic tests are also available and include direct fluorescent staining and enzyme immunoassays, but these are slightly less sensitive than culture. Performance characteristics of PCR assays on skin and mucosal specimens from neonates have not been studied

but can be used if culture is unavailable. For CNS disease, HSV PCR of CSF is now the method of choice for diagnosis. An elevated CSF protein level and pleocytosis are often seen, but initial values may be within normal limits. Therefore, serial CSF examinations may be very important. Electroencephalography and computed tomography (CT)/MRI are also useful in the diagnosis of HSV meningoencephalitis. Serologic testing of the neonate is not useful for diagnosing neonatal disease because maternal HSV antibodies readily cross the placenta. For women, combined HSV-1 and HSV-2 serology is of little value because many women are infected with HSV-1 and because these tests usually have a relatively slow turnaround time; however, obtaining type-specific antibody (HSV-1 or HSV-2) has an 80% to 98% sensitivity and >96% specificity for identifying previous maternal infection and, thus, will assist in assessing infant risk of acquiring HSV. Laboratory abnormalities seen with disseminated disease include elevated hepatic transaminase levels, direct hyperbilirubinemia, neutropenia, thrombocytopenia, and coagulopathy. A diffuse interstitial pattern is usually observed on radiographs of infants with HSV pneumonitis. All infants with HSV should also have an ophthalmologic exam.

E. Treatment. Antiviral therapy with acyclovir, a nucleoside analog that selectively inhibits HSV replication, is highly efficacious against neonatal HSV disease, but the timing of therapy is critical. Treatment is indicated for all forms of neonatal HSV disease and should be started empirically as soon as infection is suspected. Initial antiviral studies were carried out with vidarabine, which reduced morbidity and mortality of HSV-infected neonates. Mortality with meningoencephalitis was reduced from 50% to 15% and in disseminated disease from 90% to 70%. Later studies found that acyclovir is as efficacious as vidarabine for the treatment of neonatal HSV. Furthermore, acyclovir is a selective inhibitor of viral replication with minimal side effects on the host and can be administered in relatively small volumes over short infusion times. The recommended treatment dose for all types of neonatal HSV is 60 mg/kg/day, divided every 8 hours. The recommended duration of therapy is 14 days for SEM disease and at least 21 days for infants with CNS or disseminated disease. All infants with CNS disease should have a repeat lumbar puncture (LP) near the end of therapy to document clearance. Those with positive CSF HSV PCR after 21 days of therapy should be continued on acyclovir and have weekly testing until negative. Infants with ocular involvement should have an ophthalmologic evaluation and treatment with topical ophthalmic antiviral agents in addition to parenteral therapy. Oral therapy such as with valacyclovir is not recommended for initial treatment. Oral acyclovir suppressive therapy following initial acute treatment is now recommended at a dose of 300 mg/m^2 per dose three times a day for 6 months for all infants with neonatal HSV of any type. This has been shown to reduce cutaneous recurrences and improve developmental outcomes. Other reports have demonstrated good outcomes in perinatally infected infants treated with suppressive therapy with higher doses of oral acyclovir for up to 2 years of life.

F. Prevention

1. **Pregnancy strategies.** Pregnant women known to be HSV seronegative (or seronegative for HSV-1 or HSV-2) should avoid genital sexual intercourse with a known HSV-seropositive partner in the third trimester.

For women who do acquire primary HSV during pregnancy or have recurrent outbreaks, several trials have shown efficacy and safety of treating pregnant women with clinically symptomatic primary HSV infection with a 10-day course of acyclovir (oral therapy or IV if more severe disease) and a subsequent reduction in cesarean section. The American College of Obstetrics and Gynecology recommends offering oral suppressive therapy to women with recurrent genital herpes lesions at ≥36 weeks' gestation, which decreases active lesions and therefore cesarean section deliveries. However, neonatal HSV disease has occurred in infants of women on suppressive therapy. It is also recommended that women with HSV-2 be tested for HIV because HSV-2–seropositive persons have a twofold greater risk for acquisition of HIV than those who are seronegative for HSV-2.

2. **Delivery strategies.** The principal problem in developing antenatal strategies for the prevention of HSV transmission is the inability to identify maternal shedding of virus at the time of delivery. Viral identification requires isolation in tissue culture or PCR, so any attempt to identify women who may be shedding HSV at delivery would require antenatal cervical sampling and rapid turnaround with virus detection. Unfortunately, such screening cultures taken before labor fail to predict active excretion at delivery. Until more rapid HSV detection techniques are available, the only clear recommendation that can be made is to deliver infants by cesarean section if genital lesions or prodromal symptoms are present at the start of labor. The efficacy of this approach may diminish when membranes are ruptured beyond 4 hours. Nevertheless, it is generally recommended that cesarean section be considered even with membrane rupture of longer durations. For women with a history of prior genital herpes, careful examination should be performed to determine whether lesions are present when labor commences. If lesions are observed, cesarean section should be offered. If no lesions are identified, vaginal delivery is appropriate, but a cervical swab should be obtained for culture and/or PCR and obtain maternal serology to determine if a new acquisition of a nonprimary infection with HSV-1 or HSV-2 has occurred. Women with known clinical disease or serologic evidence of primary or nonprimary first-episode infection can be offered acyclovir near term until delivery, enabling a vaginal delivery if there are no visible lesions, but the impact of this strategy on prevention of neonatal disease is not established.

3. **Management of the newborn at risk for HSV** (Table 48.2). At this time, there are no data to support the prophylactic use of antiviral agents or immunoglobulin to prevent transmission to the newborn infant when no active lesions are present at delivery. Infants inadvertently delivered vaginally in the setting of cervical lesions should be isolated from other infants in the nursery, and swabs should be obtained from the oropharynx/nasopharynx, conjunctivae, and anus for viral detection at 12 to 24 hours of age. Positive HSV culture or PCR before 12 to 24 hours of age may represent delivery contamination rather than infection. If the mother has no prior history of HSV, initiate acyclovir treatment while awaiting the laboratory results. If the mother can be identified as having recurrent

Table 48.2. Management of the Child Born to a Woman with Active Genital Herpes Simplex Virus (HSV) Infection

Maternal Primary or Nonprimary First-Episode Infection (HSV PCR or Culture of Genital Lesion Positive, Type-Specific HSV-1 or HSV-2 IgG Negative)
■ Consider offering an elective cesarean section, regardless of lesion status at delivery, or if membranes ruptured <4 hours.
■ At ~24 hours of life □ Swab infant's conjunctivae, nasopharynx/oropharynx, and anus for PCR and culture. □ Collect blood for HSV PCR and serum ALT. □ Collect CSF for HSV PCR, cell count, and chemistries. □ Start of IV acyclovir pending laboratory results.
■ Treat with acyclovir if PCR or culture positive or signs of neonatal HSV (60 mg/kg/day in 3 divided doses × 14 [SEM] or 21 [disseminated/CNS]).
■ If primary or nonprimary first-episode infection of the mother is confirmed, yet no signs of virus positive, some experts recommend 10 days of acyclovir treatment.
Recurrent Infection, Active at Delivery (HSV PCR or Culture of Genital Lesion Positive, Type-Specific HSV IgG Positive)
■ At ~24 hours of life □ Swab infant's conjunctivae, nasopharynx/oropharynx, and anus for PCR and culture. □ Collect blood for HSV PCR. □ Do not start therapy if infant is asymptomatic.
■ Treat with acyclovir if PCR or culture positive or signs of HSV infection.

PCR, polymerase chain reaction; IgG, immunoglobulin G; ALT, alanine aminotransferase; CSF, cerebrospinal fluid; IV, intravenous; SEM, skin, eye, or mouth; CNS, central nervous system.

infection, the risk of neonatal infection rate is low, and parents should be instructed to consult their pediatrician if a rash or other clinical changes (lethargy, tachypnea, poor feeding) develop. Weekly pediatric follow-up during the first month is recommended. If the mother is found to have either recent primary or nonprimary, first-episode infection and a genital lesion at delivery, it is recommended by some experts to treat the infant for 10 days of acyclovir even without symptomatology or detection of virus in the infant. Infants with a positive culture or PCR from any site or the evolution of clinical symptomatology should immediately have

cultures repeated and antiviral therapy started. Before starting acyclovir therapy, the infant should have conjunctival, nasopharyngeal, anal swabs for culture/PCR, plasma viral load, and a CSF evaluation for pleocytosis and HSV DNA PCR. Evidence of dissemination should be evaluated with hepatic transaminases, blood counts and coagulation tests for hematologic and clotting disorders, and a chest radiograph if respiratory symptoms develop.

4. **Postnatal strategies.** Infants and mothers with HSV lesions should be on contact isolation. Careful hand washing and preventing the infant from having direct contact with any lesions on the caregivers should be emphasized. Breastfeeding should be avoided if there are breast lesions, and women with oral HSV should wear a mask while breastfeeding. Hospital personnel with orolabial HSV infection represent a low risk to the newborn, although the use of face masks should be recommended if active lesions are present. Of course, hand washing or use of gloves should again be emphasized. The exception to these guidelines is nursery personnel with herpetic whitlows. Because they have a high risk of viral shedding, and as transmission can occur despite the use of gloves, these individuals should not care for newborns.

IV. PARVOVIRUS B19 (CONGENITAL).

Parvoviruses are small, unenveloped single-stranded DNA viruses. Humans are the only known host. The cellular receptor for parvovirus B19 is the P blood group antigen, which is found on erythrocytes, erythroblasts, megakaryocytes, endothelial cells, placenta, and fetal liver and heart cells. This tissue specificity correlates with sites of clinical abnormalities (which are usually anemia with or without thrombocytopenia and sometimes fetal myocarditis). Lack of the P antigen is extremely rare, but these persons are resistant to infection with parvovirus.

A. **Epidemiology.** Parvovirus transmission results after contact with respiratory secretions, blood/blood products, or by vertical transmission. Cases can occur sporadically or in outbreak settings (especially in schools in late winter and early spring). Secondary spread occurs in at least half of susceptible household contacts. Infection is very common, with 90% seropositivity of elderly persons. The prevalence of infection increases throughout childhood, such that approximately half of women of childbearing age are immune and the other half are susceptible to primary infection. The annual seroconversion rate in these women is 1.5%; however, because assessment of parvovirus infection status is not part of routine prenatal testing and because clinical infection is often asymptomatic, the rate of fetal infection in women who seroconvert during pregnancy is unknown. Women who are parents of young children, elementary school teachers, or childcare workers may be at greater risk for exposure. Unfortunately, the time of greatest transmissibility of parvovirus is before the onset of symptoms or rash. Additionally, 50% of contagious contacts may not have a rash, and 20% may be asymptomatic. The incubation period is usually 4 to 14 days but can be as long as 21 days. Rash and joint symptoms occur 2 to 3 weeks after infection. The virus is usually spread by means of respiratory secretions, which clear in patients with typical erythema infectiosum at or shortly after the onset of rash. The epidemiology of community outbreaks of erythema infectiosum suggests that the risk

of infection to susceptible schoolteachers is approximately 19% (compared with 50% for household contacts). This lowers the risk of parvovirus B19 fetal disease in pregnant schoolteachers to <1%. Therefore, special precautions are not necessary in this setting. In fact, there is likely to be widespread unapparent infection in both adults and children, providing a constant background exposure rate that cannot be altered.

The overall rate of vertical transmission of parvovirus from the mother with primary infection to her fetus is approximately 30%. The risk of fetal loss (3% to 6%) is greatest when maternal infection occurs in the first half of pregnancy and if hydrops fetalis develops. Fetal death usually occurs within 6 weeks of maternal infection. The risk of fetal hydrops is approximately 1%. Therefore, parvovirus B19 could be the cause of as many as 1,400 cases of fetal death or hydrops fetalis each year in the United States.

B. Transmission is from mothers to fetuses antenatally and therefore falls in the category of congenital infections.

C. Clinical manifestations

1. **Congenital infection.** Most cases of fetal infection resolve spontaneously with no adverse outcomes; however, infection can be associated with spontaneous abortion, hydrops fetalis, and still birth. Nonimmune hydrops fetalis usually results from aplastic anemia but also can occur secondary to myocarditis or chronic fetal hepatitis. Long-term neurodevelopmental outcomes for fetuses who were transfused *in utero* for hydrops are unclear, with recent studies suggesting a risk of long-term neurodevelopmental impairment and other studies finding no difference.
2. **Disease in children.** Parvovirus B19 has been associated with a variety of rashes, including the typical "slapped cheek" rash of erythema infectiosum (fifth disease). In approximately 60% of school-age children with erythema infectiosum, fever occurs 2 to 5 days before the facial rash appears. Associated symptoms include headache, sore throat, cough, nausea/vomiting/diarrhea, coryza/conjunctivitis, and arthralgia/arthritis, but these symptoms generally resolve with the appearance of the rash. The rash is usually symmetric and macular; starts on the trunk and moves peripherally to the arms, buttocks, and thighs; and may involve the palms and soles. The rash may be pruritic, may recur, and is thought to be immunologically mediated. Children are usually most infectious before the onset of rash. In group settings such as classrooms, the appearance of one clinically symptomatic child could reinforce the need for good hand-washing practices among potentially seronegative pregnant women.
3. **Disease in adults.** The typical school-age presentation of erythema infectiosum can occur in adults, but arthralgias and arthritis are more common. As many as 60% of adults with parvovirus B19 infection may have acute joint swelling, most commonly involving peripheral joints (symmetrically). Rash and joint symptoms occur 2 to 3 weeks after infection. Arthritis may persist for years and may be associated with the development of rheumatoid arthritis.

4. **Less common manifestations of parvovirus B19 infection**

a. Infection in patients with severe anemia or immunosuppression. Parvovirus B19 has been identified as a cause of persistent and profound anemia in patients with rapid red blood cell turnover, including those with sickle cell (SC) disease, hemoglobin (Hb) SC disease, thalassemia, hereditary spherocytosis, and cellular enzyme deficits, such as pyruvate kinase deficiency. Parvovirus B19 also has been associated with acute and chronic red blood cell aplasia in immunosuppressed patients.

b. Fetal infection. Although parvovirus B19 has genotypic variation, no antigenic variation between isolates has been demonstrated. Parvoviruses tend to infect rapidly dividing cells and can be transmitted across the placenta, posing a potential threat to the fetus. Based primarily on the demonstration of viral DNA in fetal tissue samples, parvovirus B19 is the most common infectious cause of nonimmune hydrops fetalis and has been implicated in approximately 15% of cases. The presumed pathogenic sequence is as follows: maternal primary infection → transplacental transfer of B19 virus → infection of red blood cell precursors → arrested red blood cell production → severe anemia (Hb <8 g/dL) → congestive heart failure → edema and hydrops. Furthermore, B19 DNA has been detected in cardiac tissues from aborted fetuses. B19 may cause fetal myocarditis which can contribute to the development of hydrops. Finally, fetal hepatitis with severe liver disease has been documented. Although there have been rare case reports of infants with fetal anomalies and parvovirus infection, it is unlikely that parvovirus causes fetal anomalies. Hence, therapeutic abortion should not be recommended in women infected with parvovirus during pregnancy. Rather, the pregnancy should be followed carefully by frequent examination and ultrasonography for signs of fetal involvement.

D. Diagnosis. Parvovirus B19 will not grow in standard tissue cultures because humans are the only host. Determination of serum IgG and IgM levels is the most practical test. Serum B19 IgG is absent in susceptible hosts, and IgM appears by day 3 of an acute infection. Serum IgM may be detected in as many as 90% of patients with acute B19 infection at the time of rash appearance, and serum levels begin to fall by the second to third month after infection. Serum IgG appears a few days after IgM and persists for years. IgM and IgG levels are not reliable for diagnosing an aplastic crisis or chronic infection in immunocompromised patients. Viral DNA can be detected by PCR, with high viral titers present during active infection. Viral DNA can be detected in serum and amniotic fluid. Low-level viremia may persist for years and does not necessarily indicate recent infection. Viral antigens may be directly detected in tissues by radioimmunoassay, enzyme-linked immunosorbent assay (ELISA), immunofluorescence, *in situ* nucleic acid hybridization, or PCR. These techniques may be valuable for certain clinical settings, such as the examination of tissues from fetuses with nonimmune hydrops or determination of infection (PCR).

E. Treatment. Treatment is generally supportive. Intravenous immunoglobulin (IVIG) has been used with reported success in a limited number of patients with severe hematologic disorders related to persistent parvovirus infection. The rationale for this therapy stems from the observations that (i) the primary

immune response to B19 infection is the production of specific IgM and IgG, (ii) the appearance of systemic antibody coincides with the resolution of clinical symptoms, and (iii) specific antibody prevents infection. However, no controlled studies have been performed to establish the efficacy of IVIG prophylaxis or therapy for B19 infections. There are no recommendations for use of IVIG in pregnancy. In the carefully followed pregnancy in which hydrops fetalis is worsening, intrauterine blood transfusions may be considered, especially if the fetal Hb is <8 g/dL. The risk/benefit of this procedure to the mother and fetus should be assessed because some hydropic fetuses will improve without intervention. In some cases, if there is also fetal myocardiopathy secondary to parvovirus infection, the cardiac function may be inadequate to handle transfusion. Attempts to identify other causes of fetal hydrops are important (see Chapter 26).

F. Prevention. The three groups of pregnant women of interest when considering the potential risk of fetal parvovirus disease are (i) those exposed to an infected household contact, (ii) school teachers, and (iii) health care providers. In each, the measurement of serum IgG and IgM levels may be useful to determine who is at risk or acutely infected after B19 exposure. The risk of fetal B19 disease is small for asymptomatic pregnant women in communities where outbreaks of erythema infectiosum occur. In this setting, no special diagnostic tests or precautions may be indicated. However, household contacts with erythema infectiosum patient place pregnant women at increased risk for acute B19 infection. The estimated risk of B19 infection in a susceptible adult with a household contact is approximately 50%. Considering an estimated risk of 5% for severe fetal disease with acute maternal B19 infection, the risk of hydrops fetalis is approximately 2.5% for susceptible pregnant women exposed to an infected household contact during the first 18 weeks of gestation. Management of these women may include the following:

1. **Determination of susceptibility of acute infection** by serum IgG and IgM and PCR
2. In susceptible or acutely infected women, **serial fetal ultrasonography** to monitor fetal growth and the possible evolution of hydrops. Doppler assessment of peak systolic velocity of the fetal middle cerebral artery should be performed because it is an accurate predictor of fetal anemia.
3. Fetal infection can be diagnosed by parvovirus B19 PCR on amniotic fluid. **Fetal IgM, hematocrit, and parvovirus DNA PCR** can be detected by percutaneous umbilical blood sampling (PUBS). This may be useful to confirm B19 etiology when hydrops fetalis is present. A fetal hematocrit should be checked in preparation for fetal blood transfusion if severe fetal anemia is suspected on ultrasound.
4. Considering the high prevalence of B19, the low risk of severe fetal disease, and the fact that attempts to avoid potential high-risk settings only reduce but do not eliminate exposure; exclusion of pregnant school teachers from the workplace is not recommended. A similar approach may be taken for pregnant health care providers where the principal exposure will be from infected children presenting to the emergency room or physician's office. However, in the majority of cases, the typical rash of erythema infectiosum may already be present, at which time infectivity

is low. Furthermore, precautions directed at minimizing exposure to respiratory secretions may be taken to decrease the risk of transmission. Particular care should be exercised on pediatric wards where there are immunocompromised patients or patients with hemolytic anemias in whom B19 disease is suspected. These patients may shed virus well beyond the period of initial clinical symptoms, particularly when presenting with aplastic crisis. In this setting, there may be a significant risk for the spread of B19 to susceptible health care workers or other patients at risk for B19-induced aplastic crisis. To minimize this risk, patients with aplastic crises from B19 infections should be maintained on contact precautions, masks should be worn for close contact, and pregnant health care providers should not care for these patients.

V. HIV (CONGENITAL AND PERINATAL). HIV is a retrovirus in the Retroviridae family and the causative agent of lifelong infection and AIDS, for which there is no cure. The virus binds to the host $CD4^+$ cell and a chemokine coreceptor, and the viral core enters the host cell cytoplasm. The virus uses reverse transcriptase to synthesize DNA from its viral RNA, and this viral DNA integrates into the host genome. On cell activation, the viral DNA is transcribed to RNA, and viral proteins are synthesized. The virion acquires its outer envelope coat on budding from the host cell surface and is then infectious for other $CD4^+$ cells. The genome consists of the three genes found in all retroviruses (*gag, pol, env*), along with at least six additional genes, including gp120, which is necessary for the binding of virus to target cells. When HIV-infected lymphocytes are activated, such as in intercurrent illnesses, many virions may be transcribed, and the cell can be lysed or apoptosis enhanced, each resulting in host cell death. Because $CD4^+$ T lymphocytes are central to developing an appropriate immune response to almost all pathogens, the host with $CD4^+$ T-cell counts $<200/\mu L$ is highly susceptible to opportunistic infections and malignancies which define AIDS.

A. Epidemiology. HIV-1 is the principal cause of HIV infection and perinatal HIV infections in the United States and throughout the world. A related virus, HIV-2, has a more benign clinical course and is primarily geographically limited to Western Africa. Humans are the only known reservoir for HIV-1 and HIV-2, and latent virus persists even when plasma viral load is undetectable.

1. **Domestically**, the CDC reports that there are currently 1.2 million people living with HIV-1 in the United States. Although the transmission rate has decreased by nearly two-thirds from its peak, the annual new infection rate of approximately 40,000 has been relatively unchanged since the late 1990s. Of these new infections, certain groups have disproportionately high infection rates, including men who have sex with men (MSM) and African Americans. Remarkably, 1 in 7 HIV-infected individuals is unaware of their transmission status, thwarting efforts to further reduce transmission. The decreased death rate in recent years is in large part attributed to access to more potent antiretroviral therapies available since 1996. In the year 2017, there were about 16,350 deaths in individuals with HIV.

Approximately 23% of those living with HIV infection in the United States are **women**, most of childbearing age, with higher rates in African American women. For 85% of these women, the leading risk behavior is heterosexual contact with a known HIV-infected person or unknown risk behavior (presumably heterosexual contact with a person of unknown positive status). Yet, in 2011, only 45% of HIV-infected women were engaged in care and only 32% had achieved viral remission. Whereas enormous successes in reduction of mother-to-child transmission have been realized with introduction of antiretroviral prophylaxis and treatment—zidovudine in 1994 and potent antiretrovirals in 1996—it is estimated that 100 to 200 infants still acquire perinatal HIV infection yearly. The vast majority of these infected infants are born to women who were unaware of their diagnosis or presented late for prenatal care. The CDC currently recommends routine antenatal "opt-out" HIV testing, which has been shown to be far more effective in identifying HIV-infected persons than systems in which written informed consent is required. At present, >90% of HIV-infected pregnant women receive antiretroviral therapy at or before delivery.

2. **Globally**, the World Health Organization (WHO) estimated that by the end of 2018, there were 37.9 million persons living with HIV (18.8 million women and 1.7 million children younger than 15 years). New HIV infections were estimated in 2018 to be 1.7 million, including 160,000 children. HIV-related deaths in 2018 were 770,000 (100,000 in children). All of these numbers are much improved from the peak of the epidemic, reflecting the global response to HIV prevention and treatment access. Currently, approximately 68% of HIV-infected women receive antiretroviral regimens (antiretroviral treatment [ART]) during pregnancy in countries of high HIV prevalence, and it is recommended that these women stay on treatment throughout the breastfeeding period and beyond. Yet, adherence and maintenance in care postpartum has been problematic. Although breastfeeding has been found to increase the rate of perinatal transmission by up to 14%, formula feeding is associated with high rates of morbidity and mortality from malnutrition and other infections in some areas, including respiratory and gastrointestinal infections. It has been demonstrated that exclusive breastfeeding in the first 6 months of life has a lower risk of HIV-1 acquisition compared to mixed feeding. Moreover, maternal treatment with antiretroviral has been shown to considerably reduce postpartum HIV transmission. Therefore, in areas where formula feeding is unsafe or unfeasible, the WHO recommends exclusive breastfeeding for the first 6 months of life and continued breastfeeding until 1 year of life while the mother continues on ART. In areas of high HIV prevalence, acute maternal infection during pregnancy or breastfeeding is a very high-risk setting for infant HIV acquisition and a scenario that is not addressed by antiretroviral-based prevention strategies. Moreover, the rising incidence of HIV infection in young women in some countries of high HIV prevalence is especially challenging for further reductions in infant HIV acquisition, suggesting that only the development of a

universal HIV vaccine administered in infancy will completely eliminate pediatric HIV infections. Unquestionably, HIV has posed one of the most serious and challenging health problems of the late 20th and early 21st centuries. Although there are still many remaining challenges of implementation, access, adherence, and monitoring, significant progress is being made.

B. Transmission. There are three principal routes for HIV transmission: sexual contact, parenteral inoculation, and maternal–fetal or maternal–newborn transfer.

1. **Sexual contact.** This remains the principal mode of transmission of HIV in the United States and worldwide. Both semen and vaginal secretions have been found to contain HIV. The principal risk behavior for 85% of mothers of children reported with HIV is heterosexual contact.

2. **Parenteral inoculation.** Parenteral transmission of HIV results from the direct inoculation of infected blood or blood products. The primary groups affected have been IV drug users and patients receiving transfusions or factor concentrates. Screening of blood donors for risk factors for infection, universal HIV antibody and viral testing of donated blood, and the special preparation of clotting factor to eliminate the risk of viral contamination have greatly reduced the incidence of transfusion-acquired HIV. The most likely reason for false-negative HIV serology is the seronegative window that occurs between the time of initial infection and the production of antiviral antibody. The odds of transfusion-acquired HIV infection from the transfusion of a single unit of tested blood have been estimated to be from 1:250,000 to 1:150,000.

3. **Congenital and perinatal transmission.** More than 90% of pediatric AIDS cases have resulted from maternal blood exposure antenatally, at birth, or postnatally through breast milk. The rate of transmission of HIV from untreated infected mothers to their fetuses and newborn infants has been estimated to be between 15% and 40%. HIV has been isolated from cord blood specimens, and products of conception have demonstrated HIV infection as early as 14 to 20 weeks' gestation; however, it is believed that most of the infection is transmitted in late third trimester or at delivery. The mechanism of transplacental transfer of HIV is not known, but HIV can infect trophoblast and placental macrophage cell lines. Neither infection nor quantity of virus present in the placenta correlates with congenital infection. This may suggest that the placenta in general acts as a protective barrier to transmission or conversely as a focus of potential transmission. In a study of 100 sets of twins delivered to HIV-infected mothers, twin A was infected in 50% delivered vaginally and 38% delivered by cesarean. Twin B was infected in 19% of both vaginal and cesarean deliveries. This study as well as the Women and Infants Transmission Study and a meta-analysis of transmission studies suggests that intrapartum infection occurs as a correlate of duration of ruptured membranes and that elective (without onset of labor) cesarean section deliveries may be preventive, primarily if the maternal HIV viral load is not controlled at delivery.

C. Clinical disease. In untreated patients, $CD4^+$ cell loss progresses, with the median duration of the asymptomatic phase being approximately 10 years in adults. After this phase, the patient becomes symptomatic, generally with opportunistic infections, especially tuberculosis, and death occurs within 5 years.

1. **HIV infection in infants** manifests with an initially high viral load, which declines over the first 5 years of life as the immune system develops. Current U.S. and WHO guidelines suggest treating all infants diagnosed with HIV infection in the first year of life so that the immune system can develop normally, and many experts continue treatment to assure suppression of HIV. Although previous algorithms of when to initiate treatment in HIV-infected children were based on clinical course and $CD4^+$ T-cell percentages, it is now recommended that all infected children be treated with combination antiretroviral treatment (cART) from diagnosis. In fact, use of highly potent antiretroviral regimens has been associated with long-term viral remission off therapy in at least one infant, the "Mississippi baby," who remained without evidence of viral replication off therapy for nearly 2 years, providing hope that future HIV remission or cure can be achieved with additional treatment agents to reduce the size of the latent virus reservoir. Willingness of the care provider to assure the infant or child receives every dose every day is a critical component of success.
2. **HIV in pregnancy.** HIV-infected pregnant women should receive closely monitored prenatal care, including screening for other sexually transmitted diseases (gonorrhea, herpes, chlamydia, hepatitis B and C, and syphilis), as well as tested for infection with CMV and toxoplasmosis. The mother should also have a tuberculin skin test and, when appropriate, be offered hepatitis B, pneumococcal, and influenza vaccines. If not already on ART, a triple-drug regimen should be initiated as soon as possible in pregnancy with the goal of complete virologic control well prior to delivery. Generally, drug regimens used in nonpregnant individuals are similar to those recommended in pregnancy. Exceptions to these recommendations include efavirenz, which has shown teratogenic effects in animal studies; the combination of didanosine and stavudine, which has been associated with rare cases of maternal hepatic steatosis and death; nevirapine, which has resulted in fulminant hepatitis in women with higher $CD4^+$ lymphocyte counts; dolutegravir, which has been linked to neural tube defects when started prior to conception; and cobicistat-boosted regimens, which have decreased drug levels during pregnancy. Therefore, these agents should be used cautiously in pregnancy. Recently, the ongoing international Promoting Maternal and Infant Survival Everywhere (PROMISE) study reported that triple-drug therapy with lamivudine, zidovudine, and ritonavir-boosted lopinavir (the lamivudine combination) or tenofovir, emtricitabine, and ritonavir-boosted lopinavir (the tenofovir combination) reduced transmission detected at 2 weeks of age to 0.5%, significantly lower than that of a two-drug regimen. Yet, both regimens were associated with a higher risk of infant prematurity, and the tenofovir-containing arm demonstrated a higher risk of death, raising concerns on the safety of these regimens in areas of limited health care resources to adequately care for preterm infants.

Currently in the United States, the rate of vertical transmission is <2% in women who are diagnosed and take antiretroviral therapy before delivery. This makes perinatal transmission of HIV an essentially preventable disease when women have antenatal counseling and testing and receive antiretroviral therapy for themselves and their infants. HIV testing, although no longer requiring consent, is not a mandatory component of antenatal care; hence, every obstetric provider and pediatrician should offer testing and counseling to all pregnant women, so they may consider therapeutic options for themselves and prophylactic options for their fetuses. *Pneumocystis jirovecii* and possibly *Mycobacterium avium intracellulare* prophylaxis also should be considered in pregnancy.

3. **HIV infection in children.** Most pediatric AIDS cases occur in infants and young children, reflecting the preponderance of congenital and perinatally acquired infections. A bimodal distribution of symptoms has been described: a rapid progression of symptoms and disease within the first year of life ("rapid progressors") or a slower progression with deterioration at 5 to 6 years of age. In North America, it is estimated that 15% to 20% of infants are rapid progressors. Data suggest developing countries have a similar bimodal disease presentation but an increase in the number of rapid progressors, with 25% to 45% mortality by 1 year, up to 53% mortality by 2 years, and 62% mortality by 5 years. Timing of infection also impacts the severity, with children infect in the first 1 to 2 months of life having higher mortality. Children should be prescribed antiretroviral regimens based on the goal of maintaining a $CD4^+$ lymphocyte percentage of >15%, and many experts would suggest 25%, along with a moderately low or suppressed HIV viral load. In developed countries, pediatric HIV infection should be considered a treatable chronic infection, not a disease with a limited life span or poor quality of life.

   The clinical presentation differs in children compared with adults. The HIV-infected newborn is usually asymptomatic but may present with lymphadenopathy and/or hepatosplenomegaly. Generally, the infant infected peripartum does not develop signs or symptoms until after the first 2 weeks of life. These include lymphadenopathy and hepatosplenomegaly (as in adults), poor weight gain as might be found in chronic viral infection, and, occasionally, neuromotor abnormalities or encephalopathy. Before antiretroviral therapy was available to children, 50% to 90% of HIV-infected children had CNS involvement characterized by an encephalopathy that was often clinically devastating. Although the clinical presentation may vary, developmental delay or loss of developmental milestones and diminished cognitive function are common features. Not infrequently, an infant is diagnosed with AIDS between the ages of 2 and 6 months when he or she presents with *P. jirovecii* pneumonia. This is an interstitial pneumonia often without auscultatory findings. Patients present with low-grade fever, tachypnea, and, often, tachycardia. Progressive hypoxia ensues and may result in mortality as high as 90%. This is the AIDS-defining illness at presentation in 37% of pediatric patients, with a peak incidence at the age of 4 months. Treatment is IV trimethoprim-sulfamethoxazole and steroids. Prophylaxis to

prevent such life-threatening infections is of course preferable to acquisition of disease. It is now recommended by the Public Health Service that all HIV-infected infants be started on *P. jirovecii* pneumonia prophylaxis at the age of 1 month. A second condition, possibly unique to pediatric AIDS, is the development of chronic interstitial lung disease, referred to as *lymphoid interstitial pneumonitis* (LIP). LIP is characterized by a diffuse lymphocytic and plasma cell infiltrate. The clinical course of LIP is quite variable but may be progressive, resulting in marked respiratory distress (tachypnea, retractions, wheezing, and hypoxemia). There is an association with Epstein-Barr virus infection, but the significance of this is uncertain. After the initial presentation, the prognosis appears to be more favorable for children with symptomatic HIV infection when the AIDS-defining illness is LIP. In addition to LIP, recurrent bacterial infections are a frequent feature of pediatric AIDS, owing in part to the early occurrence of B cell dysfunction with dysfunctional hypergammaglobulinemia. Both focal and disseminated infections are encountered, with sepsis being most common. The organism usually isolated from the bloodstream is *Streptococcus pneumoniae*, but a variety of other bacteria have been recovered, especially from hospitalized patients. Pneumococcal disease is less common now that conjugated pneumococcal vaccines are standard of care for infants in the first 6 months of life. Other manifestations of HIV infection that may be more common in children are parotitis and cardiac dysfunction. Older children present with the more typical AIDS-defining opportunistic infections when the $CD4^+$ T-cell count wanes.

D. Diagnosis. The diagnosis of HIV infection in adults is made by the detection of HIV-specific antibody and antigen by an immunoassay with confirmation by Western blot analysis.

Serology is of limited value in diagnosing vertically transmitted HIV infection in infants <24 months old because maternal IgG crosses the placenta and can persist in infants throughout the first year or more of life. In the presence of an AIDS-defining illness and a positive antibody test, the diagnosis is made even if the infant is younger than 24 months of age. However, the picture is less clear in infants with minimal or no symptomatology. Therefore, viral detection tests must be used to identify infected infants born to HIV-seropositive mothers. These include the following:

1. PCR for viral RNA in plasma, or viral load. The mainstay of early viral diagnostic testing of the infant born to an HIV-infected mother remains HIV PCR to detect both viral RNA and DNA, with a DNA test often recommended to avoid possible issues of delayed/cleared RNA viremia in the setting of maternal or infant prophylactic ART. The blood samples for these tests should be collected in anticoagulant, but not heparin, to avoid interference with PCR. Older tests of viral culture and p24 antigen detection are generally no longer used. Culture is sensitive and specific but is expensive, technically difficult, and may require weeks before results are obtained. The p24 antigen assay suffers from a lack of sensitivity, particularly in infants, and can be replaced by acid-dissociated p24 antigen detection, which has a much greater sensitivity. The importance of obtaining an early diagnosis is clear: to provide even very young infants

the benefit of ART, which is hoped to reduce viral load and possibly prevent or reduce the latent viral burden at tissue sites, including the CNS, as well as to maintain normal numbers of $CD4^+$ T cells throughout immunologic development.

2. PCR to detect viral DNA in peripheral blood cells. Infants exposed to maternal HIV infection should have the following tests: HIV DNA or RNA at birth (umbilical cord should not be used because of the risk of maternal contamination), 14 to 21 days, 1 to 2 months of age, and 4 to 6 months of age. An infant is considered infected if two samples from two different time points are positive. Infants who are DNA PCR or high-level RNA PCR positive in the first 3 days of life are considered to have been infected *in utero*; infants who test negative in the first 3 days and positive for HIV thereafter are considered to have peripartum-acquired HIV. This differentiation is relevant because offering potent antiretroviral therapy at the time of delivery, even in undiagnosed and/or untreated mothers, may be highly effective in reducing vertical transmission. Rapid diagnostic testing for HIV in previously untested women at presentation for delivery with institution of prophylactic therapy has been shown to reduce transmission. On the basis of this kind of information, investigators are targeting the intrapartum interval to offer potent, rapidly active preventive treatments such as antiretroviral therapy (especially using nevirapine). Intrapartum transmission is likely to account for at least 50% of HIV infections in infants. Testing should be offered to anyone engaging in risk behaviors for HIV transmission and for all pregnant women.

E. Treatment. The major part of the management of HIV infection is ART. Recent studies have confirmed that this should be offered to all infected patients regardless of $CD4^+$ T-cell count to improve the long-term outcome and reduce transmission to uninfected individuals. At present, there is no cure for HIV infection, but the goal of ART is to suppress the HIV viral load and to maintain or reconstitute $CD4^+$ T-cell numbers. Generally, these agents are of four classes:

1. Nucleoside or nucleotide analog reverse transcriptase inhibitors (NRTIs) (e.g., zidovudine/AZT). These agents prevent viral RNA from being reverse transcribed to DNA; therefore, infection of cells can be aborted.
2. Nonnucleoside analog reverse transcriptase inhibitors (NNRTIs) (e.g., nevirapine). These agents also act to prevent reverse transcription (RT) but at a slightly different site on the enzyme. They are generally more potent than the NRTIs, but resistance can develop rapidly if the viral load is not controlled.
3. Protease inhibitors (PIs) act to prevent processing of viral proteins. These agents are quite potent but are highly protein bound, and therefore, little crosses the placenta, making these excellent agents to treat maternal viral load but limit exposure of the fetus.
4. Integrase inhibitors act to prevent virion production and are increasingly a component of antiretroviral therapy. Generally, although initial prophylaxis regimens of infants born to HIV-infected mothers often include zidovudine with or without nevirapine (NRTI and NNRTI, respectively),

initial therapy of an infected infant should include two NRTIs and either a PI or an NNRTI—often zidovudine/lamivudine or emtricitabine/lopinavir-boosted ritonavir.

Other possible therapies being investigated include other sites of action in the retroviral life cycle such as fusion inhibitors, viral entry inhibitors, and immune-based therapies. The combination ART regimen that was used in the "Mississippi baby" who was born to a viremic mother and infected peripartum but achieved a unique long-term remission when the child was lost to follow-up and stopped treatment, included zidovudine (2 mg/kg every 6 hours), lamivudine (4 mg/kg twice daily), nevirapine (2 mg/kg twice daily), and the nevirapine later switched to ritonavir-boosted lopinavir at 1 week of age (prior to the U.S. Food and Drug Administration [FDA] warning against beginning ritonavir-boosted lopinavir before 14 days of age due to cases of heart block). Thus, this early, aggressive treatment regimen and similar regimens are being evaluated for its ability to result in this type of remission for other perinatally infected infants.

Optimization of nutrition, routine immunizations, prophylaxis against opportunistic infections (most notably *P. jirovecii*), and the prompt recognition and treatment of HIV-related complications (e.g., opportunistic infections, cardiac dysfunction) are paramount to the improvement in the longevity and the quality of life for HIV-infected patients. In the newborn, special attention should be given to the possibility of congenitally and perinatally transmitted pathogens, such as tuberculosis, CMV, toxoplasmosis, and sexually transmitted diseases, which may have a relatively high prevalence in HIV-infected adults.

F. Prevention. In this chapter, we only focus on prevention strategies to reduce **maternal-to-child transmission** both in the United States and globally.

1. **Domestically**, efforts to prevent mother-to-child transmission of HIV have been highly successful. Combined information from the randomized Pediatric AIDS Clinical Trials Group studies PACTG 076 and PACTG 185 found that HIV-infected pregnant women who received zidovudine antenatally, intrapartum IV at 2 mg/kg for the first hour of labor followed by 1 mg/kg/hour until delivery, and to their infants orally at 2 mg/kg every 6 hours for the first 6 weeks of life, had a markedly lower transmission compared to placebo recipients (8.3% of the infants in the zidovudine-receiving group were infected vs. 25.5% in the placebo group for 076). Therefore, since 1994, it has been the standard of care to offer the 076 algorithm as a backbone of antiretroviral regimens for pregnant women. With the development of highly active cART and its recommended use throughout pregnancy, the recommendation for intrapartum zidovudine has been modified to include only women with HIV viral load >1,000 copies/mL, unknown viral load, or problems with adherence; yet, the infant prophylaxis regimen has continued to be recommended for all HIV-exposed infants. Two- or three-drug regimens should be used for infant prophylaxis if maternal viral load is >50 copies/mL around the time of delivery. Elective cesarean section (before onset of labor) can further reduce transmission if the HIV viral load remains >1,000 copies/mL around delivery. There is no added

benefit to elective cesarean if the HIV viral load is suppressed below this value. Several studies have shown that higher maternal viral load, along with lower $CD4^+$ T-cell counts, is a strong correlate of vertical transmission; therefore, it is imperative to treat pregnant women with an optimized antiretroviral regimen to suppress viral load. Resistance testing should also be performed even for women who have never been treated because it is estimated that as many as 15% of previously untreated persons will have an HIV isolate that has resistance to one or more antiretrovirals. It is advised that care of HIV-infected pregnant women be offered in concert with obstetricians, internists, and pediatricians with experience taking care of HIV-infected patients for optimal outcome. Current standard of care in the United States is to suppress maternal viral load to nondetectable levels during pregnancy (and after pregnancy to optimize maternal health) using combinations of the agents that are approved to treat HIV infection and are safe for use during pregnancy. The rate of vertical transmission is <1% for women with a nondetectable viral load.

Occasionally, mothers learn for the first time that they are HIV infected during their pregnancy. The appropriate social support network must be effectively in place to achieve the best pregnancy outcome possible; optimization of the mother–baby pair is key in effecting the best possible outcome.

Any instrumentation, including fetal scalp electrodes and pH sampling, during the intrapartum period that would expose the fetus to maternal blood and secretions should be avoided in HIV-positive women. Postpartum, the mother should be advised to avoid allowing her infant to contact her blood or secretions. Breastfeeding is contraindicated for HIV-infected women in the United States due to the relative safety of alternative feeding and reliable availability of formula and clean water.

2. **Globally**, there has also been significant progress in limiting perinatal HIV infection. A trial in Uganda (HIVNET 012) offered a single dose of nevirapine to HIV-infected women in labor and followed this with a single dose of nevirapine at 3 days of life to the infants. The rate of perinatal transmission was markedly reduced in the nevirapine arm. Nevirapine was found to readily cross the placenta, and with the two-dose regimen for the mother–infant pair, the nevirapine level in the infant's blood was higher than the level needed to reduce HIV viral load for at least a week. However, by 18 months of age, the infant mortality in the nevirapine-treated group equaled that in the other group, most likely because of HIV transmission from breastfeeding. Several studies later established that continuing maternal ART and/or infant antiretroviral prophylaxis during the breastfeeding period significantly reduced postnatal HIV transmission. Although exclusive breastfeeding and early weaning at 6 months of age when feasible and safe was a suggested strategy to reduce breast milk transmission, the suggested weaning period was extended to after 12 months of age after several studies showed an increase in malnutrition and diarrheal illness after rapid weaning at 6 months of age. WHO 2013 guidelines for treatment of pregnant women, dubbed "option B+," recommends

that HIV-seropositive women be offered antenatal treatment with a triple-antiretroviral regimen as soon as the infection is diagnosed and continue the treatment intrapartum, throughout the period of breastfeeding and beyond while providing the infant prophylaxis with daily nevirapine until 6 weeks of age. Additional recommendations include that each country should decide whether HIV-seropositive women should exclusively formula feed their infants or breastfeed with concomitant antiretroviral therapy based on the risks of formula feeding (malnutrition, unclean water, increased risk of other infections). If breastfeeding is recommended, women should be counseled to exclusively breastfeed for the first 6 months with complementary foods added at 6 months and weaning at 12 months, if adequate nutrition is available and safe for the baby at that time. In studies of women in endemic areas who were not HIV infected at the time of delivery but who seroconverted postpartum, some infants seroconverted almost simultaneously with their mothers. It may be that infants whose mothers acquire primary HIV infection during lactation are at a higher risk for acquisition of HIV exposure through breast milk than are those exposed to virus in a chronically infected mother, and this mode of transmission likely accounts for a large proportion of the ongoing infant HIV transmission. Therefore, pursuit of a universally protective HIV vaccine for infants to provide immunity during the breastfeeding period, and potentially allowing for late boosting of immunity prior to sexual debut, remains an important endeavor to ending pediatric HIV.

VI. HEPATITIS. Acute viral hepatitis is defined by the following clinical criteria: (i) symptoms consistent with viral hepatitis, (ii) elevation of serum aminotransaminase levels to >2.5 times the upper limit of normal, and (iii) the absence of other causes of liver disease. At least five agents have been identified as causes of viral hepatitis: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis D virus (HDV), hepatitis C virus (HCV) (formerly posttransfusion non-A, non-B [NANB] hepatitis virus), and hepatitis E virus (HEV) (enteric, epidemic NANB hepatitis virus). Very few suspected cases of perinatal transmission of HAV have been reported and is generally not considered to be vertically transmitted and thus will not be discussed further. HDV, also referred to as the delta agent, is a defective virus that requires coinfection or superinfection with HBV. HDV is coated with hepatitis B surface antigen (HBsAg). Specific antibodies to HDV can be detected in infected individuals, but there is no known therapy to prevent infection in exposed HBsAg-positive patients. For the newborn, therapy directed at the prevention of HBV infection should also prevent HDV infection because coinfection is required.

A. HBV (congenital and peripartum). This double-stranded DNA virus is a member of the Hepadnaviridae family and is one of the most common causes of acute and chronic hepatitis worldwide. The virus has a major surface antigen (HBsAg), a core antigen, a regulatory X protein, and the viral polymerase soluble e antigen (hepatitis B e antigen [HBeAg]). The hepatocellular cytotoxicity of HBV is related to the host immune response as

opposed to the virus itself. The virus is highly transmissible via contact with blood and/or body fluids of infected individuals.

1. **Epidemiology.** In endemic populations, the carrier state is high, and perinatal transmission is a common event. The risk of chronic HBV infection is inversely proportional to age, with a 90% carriage rate following infection in neonates. The overall incidence of HBV infections in the United States is relatively low. Approximately 19,000 acute infections occur yearly, with <1% resulting in death from fulminate disease. The incubation period for HBV infection is approximately 90 days (range 45 to 160 days). **High-risk groups for HBV infection** in the United States include the following:
   a. Persons born in endemic areas. Alaskan natives and Pacific Islanders and natives of China, Southeast Asia, most of Africa, parts of the Middle East, and the Amazon basin; descendants of individuals from endemic areas
   b. Persons with high-risk behavior. MSM, IV drug use, and multiple sex partners
   c. Close contacts with HBV-infected persons (sex partners, family members)
   d. Selected patient populations, particularly those receiving multiple blood or blood product transfusions
   e. Selected occupational groups, including health care providers
2. **Transmission** occurs by percutaneous or permucosal routes from infected blood or body fluids. The transmission of HBV from infected mothers to their newborns can occur *in utero* (<2%), at the time of delivery from exposure to maternal blood during labor or after delivery. The majority of cases result from exposure at delivery. When acute maternal HBV infection occurs during the first and second trimesters of pregnancy, there is lower risk to the newborns (~10% perinatal transmission) because antigenemia is usually cleared by term and anti-HBV antibodies are present. Acute maternal HBV infection during late pregnancy or near the time of delivery, however, may result in up to 90% transmission rate in the absence of any prophylaxis and is most common in women who have both HBsAg and HBeAg detected in blood, indicating high plasma HBV DNA level. Breastfeeding does not increase the risk of infant infection if appropriate hepatitis B vaccines and HBV hyperimmune globulin (hepatitis B immune globulin [HBIG]) are given.
3. **Clinical disease**
   a. Acute hepatitis. The likelihood of developing symptoms of acute hepatitis is dependent on age, which <1% of infants showing symptoms and 30% to 50% of people older than 5 years of age showing symptoms. Symptoms are nonspecific and include anorexia, malaise, nausea, hepatitis, and jaundice.
   b. Chronic hepatitis. Age at diagnosis is the most important factor determining risk of progression to chronic disease. Ninety percent of infants infected in the first year, 25% to 50% of those in infected age 1 to 5 years, and 5% to 10% infected older children and adults will progress to chronic disease. Patients with chronic active hepatitis are at

increased risk for developing cirrhosis and hepatocellular carcinoma, and approximately 5,000 of these patients die each year in the United States from HBV-related hepatic complications (primarily cirrhosis). Without treatment, 25% of infants and children that acquire chronic HBV will die from HBV-related hepatic complications.

4. **Diagnosis.** The diagnosis is made by specific serology and by the detection of viral antigens. The specific tests are as follows:
   a. HBsAg determination. Usually found 1 to 2 months after exposure and lasts a variable period of time
   b. Anti-HBsAg. Appears after resolution of infection or immunization and provides long-term immunity
   c. Anti-hepatitis B core antigen (anti-HBcAg). Present with all HBV infections and lasts for an indefinite period of time
   d. Anti-HBc IgM. Appears early in infection, is detectable for 4 to 6 months after infection, and is a good marker for acute or recent infection
   e. HBeAg. Present in both acute and chronic infections and correlates with viral replication and high infectivity
   f. anti-HBeAg. Develops with resolution of viral replication and correlates with reduction in infectivity. Infectivity correlates best with HBeAg positivity, but any patient positive for HBsAg is potentially infectious. Acute infection can be diagnosed by the presence of clinical symptoms and a positive HBsAg or anti-HBc IgM. The chronic carrier state is defined as the presence of HBsAg on two occasions, 6 months apart, or the presence of HBsAg without anti-HBc IgM.
5. **Treatment.** There is no specific therapy for uncomplicated acute HBV infection in infants (or adults). Treatments such as lamivudine, tenofovir, or etanercept may be suggested by infectious disease specialists to further reduce the possibility of transmission, especially in women with higher HBV viral loads. In addition, treatment of chronic HBV disease is recommended to decrease the risk of progression to severe liver disease.
6. **Prevention.** The principal strategy for the prevention of neonatal HBV disease has been to use a combination of passive and active immunoprophylaxis for **newborns** at high risk for infection as well as routine active neonatal immunization to protect against postnatal exposure (Table 48.3). High-risk term and preterm infants born to HBsAg-positive mothers should receive HBIG and active HBV vaccination within 12 hours of life. For infants weighing <2,000 g, this HBV vaccine dose should not be counted as part of the three-dose vaccines series. Universal immunization is now routinely recommended for all U.S. infants, children, and high-risk adults. The recommended schedule begins during the newborn period and is a three-dose series—the first is given at 24 hours of life; the second dose is given 1 to 2 months later; and the third dose is given at the age of 6 months for infants of mothers with HBsAg-positive or unknown status and between 6 and 18 months for infants of mothers with negative HBsAg status. For infants weighing <2,000 g at birth born the HBsAg-negative mothers, the first dose should be delayed until 1 month of age or discharge, whichever is first. The *Red Book: 2015 Report of the Committee on Infectious Diseases* by the American Academy

Table 48.3. Hepatitis B Prevention in Neonates

	Active Immunization: Either		Passive Immunization HBIG
	Recombivax HB (Merck)	Engerix-B (GlaxoSmithKline)	Engerix-B (GlaxoSmithKline)
Infants of HBsAg-negative mothers	5 μg (0.5 mL)	10 μg (0.5 mL)	—
Infants of HBsAg-positive mothers	5 μg (0.5 mL)	10 μg (0.5 mL)	0.5 mL

Both active vaccine regimens use a three-dose schedule.

HBIG, hepatitis B immune globulin; HBsAg, hepatitis B surface antigen.

of Pediatrics (AAP) is the best source for dosing based on gestational age and birth weight. Other methods of disease control have been considered; these include delivery by cesarean section. In one study in Taiwan, cesarean delivery in conjunction with maternal immunization dramatically reduced the incidence of perinatally acquired HBV from highly infective mothers. These results are promising and may offer a potential adjunctive therapy for very high-risk situations (e.g., HBsAg/HBeAg-positive women).

It is recommended that all pregnant women be screened for HBsAg. Screening should be done early in gestation. If the test result is negative, no further evaluation is recommended unless there is a potential exposure history. When there is any concern about a possible infectious contact, development of acute hepatitis, or high-risk behavior in a nonimmunized woman, testing should be repeated at the time of delivery. If the mother has emigrated from an endemic area, HBIG also should be considered unless the mother is known to be HBsAg negative. Perinatal transmission can be prevented in 95% of infants with appropriate active and passive immunoprophylaxis. For infants born to women with a high HBV load ($>10^6$), the risk of transmission is 15% to 30% even with appropriate prophylaxis. Treatment of mothers to reduce viral load with tenofovir or telbivudine may decrease the risk of transmission. Household transmission of HBV can occur with contact over extended periods. This is more likely in regions where HBV is endemic. Nevertheless, this possibility adds further support to the need for the immunization of infants born to HBsAg-positive women. Another potential route of infection is by means of breast milk. This mode of transmission appears to be very uncommon in developed countries; there has been no documented increase in the risk of HBV transmission by breastfeeding mothers who are HBsAg positive. This is true despite HBsAg being detected in breast milk. The risk of postnatal infection

via breastfeeding is certain to be negligible in infants who have received HBIG and hepatitis vaccine.

Prevention of nosocomial spread. For infants of HBsAg-positive mothers, maternal blood should be removed while wearing gown and gloves. Otherwise, standard precautions can be used. Immunization of health care workers is also strongly recommended, but if exposure should occur in a nonimmunized person, blood samples should be sent for hepatitis serology and HBIG administered as soon as possible unless the individual is known to be anti-HBs positive. This should apply to personnel having close contact without appropriate precautions as well as those exposed parenterally (e.g., from a contaminated needle).

B. HCV (congenital and peripartum). Hepatitis C is a single-strand RNA virus related to the Flaviviridae family and is the agent responsible for most NANB hepatitis in transfusion or organ transplant recipients. Like HBV, most hepatotoxicity that results from HCV is due to the cellular immune response against virus-infected cells. Signs and symptoms of HCV infection are the same as that for HAV and HBV.

1. **Epidemiology.** At least 7 HCV genotypes have been characterized based on sequence heterogeneity of the viral genome, with >50 subtypes. HCV is found worldwide, and different subtypes have been identified from the same area. Subtype 1a is the most common in the United States and has a poorer prognosis than other subtypes.

   a. Horizontal transmission. HCV is primarily transmitted by percutaneous blood exposure, with injection drug use is now the most common risk factor for infection. In addition to injection drug users and transfusion recipients, dialysis patients and sexual partners of HCV-infected persons are at risk, but 50% of identified persons are unable to define a risk factor. Transmission among family contacts is uncommon but can occur with inadvertent mucosal blood exposure.

   b. Vertical transmission. The seroprevalence of HCV in pregnant women in the United States is <2%, and the perinatal transmission rate is 5% to 6% from known positive women at delivery. The transmission rate may well be much higher and may approach 70% when the pregnant mother has a high viral load. Other factors that increase transmission risk include obstetric procedures (scalp monitoring, etc.), vaginal lacerations, and prolonged rupture of membranes. Mode of delivery does not affect transmission. HCV is transmitted at a higher frequency if the mother is also HIV infected, but this has not been assessed in women with a controlled HIV viral load and low HCV viral load. The mode of transmission is also unknown, but decreases with antiretroviral therapy. Detection of HCV by RNA PCR in cord blood would suggest that at least in some cases, *in utero* transmission occurs, yet by 18 months, some of these infants may become blood PCR negative. There is also a case report of one infant having been infected with an HCV strain different from all maternal strains at the time of delivery, suggesting *in utero* transmission. Conversely, PCR-negative infants at birth may develop PCR positivity later in infancy, suggesting perinatal infection. One study found 50% of vaginal samples collected at 30 weeks' gestation from HCV-positive mothers contain HCV, suggesting the possibility of

infection by passage through the birth canal. The potential risk of breastfeeding is not well defined. HCV has been detected in breast milk by PCR, but vertical transmission rates in breastfed and bottle-fed infants are similar. The CDC currently states that maternal HCV infection is not a contraindication to breastfeeding unless the mother's nipples are cracked or bleeding. The decision to breastfeed should be discussed with the mother on an individual basis.

2. **Clinical manifestations.** HCV accounts for 20% to 40% of viral hepatitis in the United States. The incubation period is 6 to 7 weeks (2 weeks to 6 months range) after exposure, and manifestations often present insidiously. Serum transaminase levels may fluctuate or remain chronically elevated for as long as 1 year. Chronic disease may develop in as many as 60% of community-acquired HCV infections. Cirrhosis may develop in as many as 30% of chronic disease cases but may be less likely in pediatric patients.
3. **Diagnosis.** Diagnosis of HCV can be made by HCV IgG enzyme or chemiluminescent immunoassays or PCR testing for HCV RNA. For HCV IgG, many assays are available, including laboratory-based immunoassay, rapid point-of-care tests, and home base tests. Third-generation immunoassays are at least 97% sensitive and 99% specific. Most patients have detectable antibody 15 weeks after exposure and 5 to 6 weeks after hepatitis. Persons who have had an acute infection that resolves will become antibody negative. HCV RNA is detectable 1 to 2 weeks after exposure and weeks before the onset of hepatitis. HCV RNA can persist intermittently for 6 to 12 months after acute infection, so a single negative test does not rule out disease. HCV genotyping is also available to determine appropriate antiviral therapy and is recommended for all children confirmed HCV infection.
   a. Perinatal. Maternal antibodies can persist for up to 18 months; therefore, serologic tests cannot be used for diagnosis. Infants born to known seropositive women should be tested for HCV RNA by PCR at 1 to 2 months of age and again at 1 year of life because up to 30% of infections in infants can spontaneously resolve. If both are negative, the infant is likely uninfected; however, the infant should be tested for anti-HCV antibodies at 18 months to confirm the absence of infection.
4. **Treatment.** Although only treatment with α-interferon and ribavirin is approved for use in children, newer direct antiviral agents have proved highly efficacious in the treatment of chronic HCV infection in adults and would likely be recommended for confirmed infection in children. Although none of these agents have been approved in pregnancy, they may be beneficial in the future to eliminate perinatal transmission.
5. **Prevention.** Blood products are routinely screened for antibody to HCV. Presence of the antibody likely also indicates presence of virus, and the unit is discarded if antibody is positive. **Thus, there is *no* benefit to IVIG given to the exposed infant or to the needle-stick recipient because products containing antibody are excluded from the lot**. Postexposure prophylaxis with antiviral agents is not currently recommended.

C. HEV. Enterically transmitted NANB viral hepatitis (HEV) is a single-stranded RNA virus in the Hepeviridae family and is the most common cause of viral hepatitis worldwide. It is primarily spread by fecal-contaminated water supplies in endemic areas (Africa, India) but can be spread through blood/blood products and person to person. Epidemics have been documented in parts of Asia, Africa, and Mexico, and shellfish have been implicated as sources of infection. Incubation is 15 to 60 days. The clinical picture in infected individuals is similar to that of HAV infection, with fever, malaise, jaundice, abdominal pain, and arthralgia. HEV infection has an unusually high incidence of mortality in pregnant women and increases the risk of fetal loss and perinatal mortality. Diagnosis of HEV can be made using anti-HEV IgM and IgG, thought there are no current FDA-approved assays. HEV RNA can also be detected in serum or stool in research settings or through the CDC. Treatment is generally supportive. The efficacy of immunoglobulin prophylaxis against this form of hepatitis is unknown, but because the infection is not endemic in the United States, commercial preparations in the United States would not be expected to be helpful.

D. Hepatitis G virus (HGV). HGV is a single-stranded RNA virus in the Flaviviridae family that shares 27% homology with HCV. HGV can be found worldwide and is found in approximately 1.5% of blood donors in the United States. Coinfection with HBV or HCV may be as much as 20%, suggesting common routes of transmission, such as transfusion or organ transplantation. Transplacental transmission is probably rare and may be associated with higher maternal viral loads. The clinical significance of HGV infection is unclear and difficult to study given the high association with other hepatitis viruses. HGV is diagnosed by RNA PCR in research settings, and there is no current treatment or prophylactic therapy.

VII. VARICELLA-ZOSTER VIRUS (VZV: CONGENITAL OR PERIPARTUM).

The causative agent of varicella (chickenpox) is a DNA virus and a member of the herpesvirus family. The same agent is responsible for herpes zoster (shingles); hence, this virus is referred to as VZV. Chickenpox results from primary VZV infection, following which the virus may remain latent in sensory nerve ganglia. Zoster results from reactivation of latent virus later in life or if the host becomes immunosuppressed.

A. Epidemiology. Before the use of varicella vaccine, there were approximately 3 million cases of varicella yearly in the United States, most occurring in school-age children. Most adults have antibodies to VZV, indicating prior infection, even when there is thought to be no history of chickenpox. It follows that varicella is an uncommon occurrence in pregnancy. The precise incidence of gestational varicella is uncertain but is certainly less than it was before widespread use of varicella vaccine. There are recommendations to immunize nonimmune adults at risk for infection unless they are pregnant. Alternatively, zoster is primarily a disease of adults. The incidence of zoster in pregnancy is also unknown, but the disease is likely to be uncommon as well. After maternal VZV infection in the first and early second trimesters, fetal infection can occur. The overall estimated risk of the congenital varicella syndrome is low, with only 0.4%

in the first 12 weeks of pregnancy, and 2% from 13 to 20 weeks' gestation and occurs primarily after gestational varicella but may rarely occur with maternal zoster.

VZV is highly contagious, with the primary mode of transmission being respiratory droplets from patients with chickenpox. Spread through contact with vesicular lesions also can occur. Typically, individuals with chickenpox are contagious from 1 to 2 days before the onset of rash until all lesions have dried and crusted over. The incubation period for primary disease extends from 10 to 21 days, with most infections occurring between 14 and 16 days. Transplacental transfer of VZV may take place, presumably secondary to maternal viremia, but its frequency is unknown. Varicella occurs in approximately 25% of newborns whose mothers developed varicella within the peripartum period. The onset of disease usually occurs 13 to 15 days after the onset of maternal rash. The greatest risk of severe infant disease is seen when maternal varicella occurs in the 5 days before or 2 days after delivery. In these cases, there is insufficient time for the fetus to acquire transplacentally derived VZV-specific antibodies. Symptoms generally begin 5 to 10 days after delivery, and the expected mortality is high, up to 30%. When *in utero* transmission of VZV occurs before the peripartum period, there is no obvious clinical impact in most fetuses; however, congenital varicella syndrome can occur.

B. Clinical manifestations

1. **Congenital varicella syndrome.** There is a strong association between gestational varicella and a spectrum of congenital defects comprising a unique syndrome. Characteristic findings include skin lesions (cicatricial), ocular defects (cataracts, chorioretinitis, Horner syndrome, microphthalmos, nystagmus), limb abnormalities (hypoplasia of bone and muscle), CNS abnormalities (cortical atrophy, seizures, intellectual disability), IUGR, and fetal demise or early death. The syndrome most commonly occurs with maternal VZV infection between weeks 7 and 20 of gestation.
2. **Zoster.** Zoster is uncommon in young infants but may occur as a consequence of *in utero* fetal infection with VZV. Similarly, children who develop zoster but have no history of varicella most likely acquired VZV *in utero*. Zoster in childhood is usually self-limiting, with only symptomatic therapy indicated in otherwise healthy children.
3. **Neonatal varicella.** Symptoms can range from mild illness similar to chicken pox to severe disseminated infection. Mild disease is likely due to the presence of maternal antibodies against the virus. Maternal infection 5 days before to 2 days after delivery leads to the most severe infection with up to 30% mortality. Varicella that occurs 10 to 28 after delivery is usually mild. However, all newborns are at much higher risk for severe infection than older infants and children. Varicella DNA has been detected in breast milk by PCR, but transmission is uncertain. Breastfeeding is encouraged for newborns infected with or exposed to varicella because breast milk antibodies may be protective.

C. Diagnosis. Diagnosis of congenital and neonatal varicella is usually made clinically, based on the characteristic rash, symptoms, and exposure history.

1. **Congenital varicella.** After maternal infection, the risk of congenital varicella syndrome can be determined *in utero* by VZV PCR of amniotic fluid or fetal blood with ultrasonography for detection of fetal anomalies. Normal results for both indicate a low risk for congenital varicella. Testing should be done a minimum of 5 weeks after maternal infection. Postnatal diagnosis can be made based on history and signs/symptoms. Infants with congenital varicella usually do not shed virus, and the determination of VZV-specific antibodies is often confounded by the presence of maternal antibodies. However, persistence of VZV IgG antibodies >7 months suggests fetal infection.

2. **Neonatal varicella.** With neonatal disease, the presence of a typical vesicular rash and a maternal history of peripartum varicella or postpartum exposure are all that are required to make the diagnosis. Laboratory confirmation can be made by (i) culture of virus in vesicular fluid, CSF, or tissue, although the sensitivity of this method is not optimal because the virus is quite labile; (ii) demonstration of a fourfold rise in VZV antibody titer by the fluorescent antibody to membrane antigen assay or by ELISA; and (iii) antigen can also be detected from cells at the base of a vesicle, buccal, or saliva by immunofluorescent antibody or PCR detection. The latter is sensitive, specific, and rapid and should be the preferred method of diagnosis when vesicles are present. The confirmation of VZV in a lesion should then be followed by measurement of VZV plasma viral load to have a baseline for following the effect of therapy, if implemented.

D. Treatment. Infants with congenital infection, resulting from *in utero* transmission before the peripartum period, are unlikely to have active viral disease, so antiviral therapy is not indicated. However, infants with perinatal varicella acquired from maternal infection near the time of delivery are at risk for severe disease. In this setting, therapy with acyclovir is generally recommended (30 mg/kg/day divided every 8 hours for 7 to 10 days). For exposures, including maternal infection between 5 days prior to and 2 days following delivery, VariZIG, a hyperimmune gammaglobulin product, should be administered within 96 hours of exposure. Alternatively, if VariZIG is unavailable, IVIG at a dose of 400 mg/kg may be given as postexposure prophylaxis because it will contain anti-VZV antibodies.

E. Prevention

1. **Vaccination** of women who are not immune to varicella should decrease the incidence of congenital and perinatal varicella. Women should not receive the vaccine if they are pregnant or in the 3 months before pregnancy. If this inadvertently occurs, the women should be enrolled in the National Registry. Additionally, acyclovir should also be considered for seronegative women exposed to varicella during pregnancy for 7 days. Although acyclovir crosses the placenta, it is unknown if maternal treatment reduces the risk of congenital varicella syndrome.

2. **Management of varicella in the nursery.** The risk of horizontal spread of varicella following exposure in the nursery appears to be low, possibly

because of a combination of factors, including (i) passive protection resulting from transplacentally derived antibody in infants born to varicella-immune mothers and (ii) brief exposure with a lack of intimate contact. Nevertheless, nursery outbreaks do occur, so steps should be taken to minimize the risk of nosocomial spread. The infected infants should be isolated in a separate room or airborne and contact precautions until all lesions are dry and crusted. For patients with varicella pneumonia, precautions are used for the duration of illness. Visitors and caregivers should be limited to individuals with a history of varicella. VariZIG can be given to all other exposed neonates, but this can be withheld from full-term infants whose mothers have evidence of varicella immunity. Neonates at <28 weeks' gestation should be given VariZIG or IVIG postexposure regardless of maternal status. Exposed personnel without a history of varicella and unknown immunization status should be tested for VZV antibodies. In the regular nursery, all exposed infants will ordinarily be discharged home before they could become infectious. Occasionally, an exposed infant needs to remain in the nursery for more than the incubation period of 8 days, and in this circumstance, isolation may be required (from days 8 to 21 after exposure). In the neonatal intensive care unit, exposed neonates are generally cohorted and isolated from new admissions within 8 days of exposure. If there is antepartum exposure within 21 days of hospital admission for a mother without a history of varicella, the mother and infant should be discharged as soon as possible from the hospital. If the exposure occurred 6 days or less before admission, and the mother is discharged within 48 hours, no further action is required. Otherwise, mothers hospitalized between 8 and 21 days after exposure should be kept isolated from the nursery and other patients. Personnel without a history of varicella should be kept from contact with a potentially infectious mother. If such an individual is inadvertently exposed, serologic testing should be performed to determine susceptibility, and further contact should be avoided until immunity is proven. If the mother at risk for infection has not developed varicella 48 hours after the staff member was exposed, no further action is required. Alternatively, if a susceptible staff member is exposed to any individual with active varicella lesions or in whom a varicella rash erupts within 48 hours of the exposure, contact with any patients should be restricted for that staff member from days 8 to 21 after exposure. Personnel without a history of varicella should have serologic testing, and if not immune, they should be vaccinated. For mothers in whom varicella has occurred in the 21 days before delivery, if there were resolution of the infectious stage before hospitalization, maternal isolation is not required. The newborn should be isolated from other infants (room in with mother). If the mother has active varicella lesions on admission to the hospital, isolate the mother and administer VariZIG to the newborn if maternal disease began <5 days before delivery or within 2 days postpartum (not 100% effective and may consider acyclovir in addition). The infant should be isolated from the mother until she is no longer infectious. If other neonates were exposed, VariZIG may be administered; these infants may require isolation if they are still hospitalized by day 8 after exposure.

VIII. ENTEROVIRUSES (CONGENITAL). The enteroviruses are RNA viruses belonging to the Picornaviridae family. There are >100 serotypes that used to be subclassified into four major groups (coxsackieviruses group A, coxsackieviruses group B, echoviruses, and polioviruses) but are now grouped into four species (enterovirus A, B, C, and D) based on genetic similarities. Infection is common and occurs throughout the world. Humans are the only known reservoir and all four groups cause disease in the neonate. Infections occur throughout the year, with a peak incidence between June and October. The viruses are shed from the upper respiratory and gastrointestinal tracts. In most children and adults, infections are asymptomatic or produce a nonspecific febrile illness.

A. Epidemiology. Most infections in newborns are caused by coxsackieviruses B and echoviruses. Up to 20% to 30% of neonatal infections are acquired transplacentally, which the rest occurring intrapartum or postnatally via exposure to maternal blood, secretions, or feces. The mode of transmission appears to be primarily transplacental, although this is less well understood for echoviruses. Clinical manifestations are most commonly seen with transmission in the perinatal period.

B. Clinical manifestations. Intrauterine enterovirus infection can lead to spontaneous abortion, stillbirth, and neonatal illness. Symptoms in the neonate usually appear 3 to 7 days after birth. Up to 60% of mothers of infected infants report a febrile illness during the last week of pregnancy. Clinical presentations vary from a mild nonspecific febrile illness to severe life-threatening disease. Neonates with severe illness usually presents either myocarditis or fulminant hepatitis. Infants with myocardial disease usually have encephalitis and hepatitis and is typically associated with group B coxsackieviruses. Fulminant hepatitis usually presents with hypotension, profuse bleeding, and multiorgan failure and usually associated with echoviruses. With myocarditis, there is a mortality of approximately 50%. The mortality from the sepsis-like illness is essentially 100%. Most (70%) of severe enteroviral infections in neonates are caused by *echovirus* 11. In most cases, infant outcome is correlated with acquired maternal neutralizing antibody and therefore timing of maternal infection.

C. Diagnosis. The primary task in symptomatic enterovirus infections is differentiating between viral and bacterial sepsis and meningitis. In almost all cases, presumptive therapy for possible bacterial disease must be initiated. Obtaining a careful history of a recent maternal viral illness, as well as that of other family members, particularly young siblings, and especially during the summer and fall months, may be helpful. The principal diagnostic laboratory aid generally available at this time is viral culture or PCR. Material for cultures should be obtained from the nose, throat, stool, blood, urine, and CSF and from blood, urine, stool, or CSF for PCR. Usually, evidence of viral growth can be detected within 1 week, although a longer time is required in some cases. The serotype may be determined by partial genomic sequencing, serotype-specific antibody staining, or neutralization assay of viral isolates.

D. Treatment. In general, treatment of symptomatic enteroviral disease in the newborn is supportive only. There are no approved specific antiviral agents known to be effective against *enteroviruses*. However, protection against severe

neonatal disease appears to correlate with the presence of specific transplacentally derived antibody. Furthermore, the administration of immune serum globulin appears to be beneficial in patients with agammaglobulinemia who have chronic enteroviral infection. Given these observations, it has been recommended that high-dose immune serum globulin be given to infants with severe, life-threatening enterovirus infections. It may also be beneficial to delay the time of delivery if acute maternal enteroviral infection is suspected, provided there are no maternal or fetal contraindications. This is done to allow transplacental passage of maternal antibody. The clinical presentation in infants with a sepsis-like syndrome frequently evolves into shock, fulminant hepatitis with hepatocellular necrosis, and DIC. In the initial stages of treatment, broad-spectrum antibiotic therapy is indicated for possible bacterial sepsis. Later, with the recognition of progressive viral disease, some form of antibiotic prophylaxis to suppress intestinal flora may be helpful. Neomycin (25 mg/kg every 6 hours) has been recommended. Drugs designed to prevent attachment of *enterovirus* to the host cell (e.g., pleconaril) are under study for neonatal enteroviral sepsis but not clinically available.

IX. RUBELLA (CONGENITAL).

This human-specific RNA virus is a member of the togavirus family. It causes a mild self-limiting infection in susceptible children and adults, but its effects on the fetus can be devastating.

A. Epidemiology.

Before widespread immunization beginning in 1969, rubella was a common childhood illness: Eighty-five percent of the population was immune by late adolescence and approximately 100% by ages 35 to 40 years. Epidemics occurred every 6 to 9 years, with pandemics arising with a greater and more variable cycle. During pandemics, susceptible women were at significant risk for exposure to rubella, resulting in a high number of fetal infections. A worldwide epidemic from 1963 to 1965 accounted for an estimated 11,000 fetal deaths and 20,000 cases of congenital rubella syndrome (CRS). The relative risk of fetal transmission and the development of CRS as a function of gestational age have been studied. With maternal infection in the first 12 weeks of gestation, the rate of fetal infection was 81%. The rate dropped to 54% for weeks 13 to 16, 36% for weeks 17 to 22, and 30% for weeks 23 to 30. During the last 10 weeks of gestation, the rate of fetal infection again rose: 60% for weeks 31 to 36 and 100% for weeks 36 and beyond. Fetal infection can occur at any time during pregnancy, but early-gestation infection may result in multiple organ anomalies. When maternofetal transmission occurred during the first 10 weeks of gestation, 100% of the infected fetuses had cardiac defects and deafness. Deafness was found in one-third of fetuses infected at 13 to 16 weeks, but no anomalies were found when fetal infection occurred beyond the 20th week of gestation. There are also case reports of vertical transmission with maternal reinfection and postnatal infection can occur through direct or droplet contact.

Introduction of the highly effective rubella vaccine in 1969 dramatically reduced the number of cases of CRS to <1 case per year by the year 2000, and the remaining cases were primarily in immigrant population. In fact, rubella was declared eliminated in the United States in 2004 and in the Americas in 2015. However, rubella continues to be endemic in many parts

of the world where the rubella vaccine is not universal, resulting in ongoing cases of CRS. In addition, declining vaccination rates in the United States has led to sporadic cases and potential reservoirs for transmission.

B. Clinical manifestations. Congenital rubella infection can result in spontaneous abortion, fetal infection, stillbirth, or IUGR. Classically, CRS is characterized by the constellation of cataracts, SNHL, and congenital heart disease. However, rubella can infect every part of the body and persist for long periods. The most common cardiac defects are patent ductus arteriosus and pulmonary artery stenosis. Common early features of CRS are IUGR, retinopathy, microphthalmia, meningoencephalitis, electroencephalographic abnormalities, hypotonia, dermatoglyphic abnormalities, hepatosplenomegaly, thrombocytopenic purpura, radiographic bone lucencies, and diabetes mellitus. In addition, rubella is a known cause of autism. The onset of some of the abnormalities of CRS may be delayed months to years. Many additional rare complications have been described, including myocarditis, glaucoma, microcephaly, chronic progressive panencephalitis, hepatitis, anemia, hypogammaglobulinemia, thymic hypoplasia, thyroid abnormalities, cryptorchidism, and polycystic kidney disease. A 20-year follow-up study of 125 patients with congenital rubella from the 1960s epidemic found ocular disease to be the most common disorder (78%), followed by sensorineural hearing deficits (66%), psychomotor retardation (62%), cardiac abnormalities (58%), and mental retardation (42%).

C. Diagnosis

1. **Maternal infection.** The diagnosis of acute rubella in pregnancy requires serologic testing. This is necessary because the clinical symptoms of rubella are nonspecific and can be seen with infection by other viral agents (e.g., *enteroviruses*, measles, and human parvovirus). Furthermore, a large number of individuals may have subclinical infection. Several sensitive and specific assays exist for the detection of rubella-specific antibody. Viral isolation from the nose, throat, and/or urine is possible, but this is costly and not practical in most instances. **Symptoms** typically begin 2 to 3 weeks after exposure and include malaise, low-grade fever, headache, mild coryza, and conjunctivitis occurring 1 to 5 days before the onset of rash. The rash is a salmon-pink macular or maculopapular exanthem that begins on the face and behind the ears and spreads downward over 1 to 2 days. The rash disappears in 5 to 7 days from onset, and posterior cervical lymphadenopathy is common. Approximately one-third of women may have arthralgias without arthritis. In women suspected of having acute rubella infection, confirmation can be made by demonstrating a fourfold or higher rise in serum IgG titers when measured at the time of symptoms and approximately 2 weeks later. When there is uncertainty about the interpretation of assay results, advice should be obtained from the laboratory running the test and an infectious diseases consultation.
2. **Recognized or suspected maternal exposure.** Any individual known to have been immunized with rubella vaccine after his or her first birthday is generally considered immune. However, it is best to determine immunity by measuring rubella-specific IgG, which has become a standard of practice in obstetric care. If a woman exposed to rubella is

known to be seropositive, she is immune, and the fetus is considered not to be at risk for infection. If the exposed woman is known to be seronegative, a serum sample should be obtained 3 to 4 weeks after exposure for determination of titer. A negative titer indicates that no infection has occurred, whereas a positive titer indicates infection. Women with an uncertain immune status and a known exposure to rubella should have serum samples obtained as soon as possible after exposure. If this is done within 7 to 10 days of exposure, and the titer is positive, the patient is rubella immune and no further testing is required. If the first titer is negative or was determined on serum taken >7 to 10 days after exposure, repeat testing (~3 weeks later) and careful clinical follow-up are necessary. When both the immune status and the time of exposure are uncertain, serum samples for titer determination should be obtained 3 weeks apart. If both titers are negative, no infection has occurred. Alternatively, infection is confirmed if seroconversion or a fourfold increase in titer is observed. Further testing and close clinical follow-up are required if titer results are inconclusive. In this situation, specific IgM determination may be helpful. It should be emphasized that all serum samples should be tested simultaneously by the same laboratory when one is determining changes in titers with time.

3. **Congenital rubella infection**

a. Antenatal diagnosis. The risk of severe fetal anomalies is highest with acute maternal rubella infection during the first 16 weeks of gestation. However, not all early-gestation infections result in adverse pregnancy outcomes. Approximately 20% of fetuses may not be infected when maternal rubella occurs in the first 12 weeks of gestation, and as many as 45% of fetuses may not be infected when maternal rubella occurs closer to 16 weeks of gestation. Unfortunately, there is no foolproof method of determining infected from uninfected fetuses early in pregnancy, but *in utero* diagnosis is being investigated. One method that has been used with some success is the determination of specific IgM in fetal blood obtained by percutaneous umbilical cord blood sampling. Direct detection of rubella antigen and RNA in a chorionic villous biopsy specimen also has been used successfully. Although these techniques offer promise, their use may be limited by sensitivity and specificity or the lack of widespread availability.

b. Postnatal diagnosis. Guidelines for the establishment of congenital rubella infection or CRS in neonates have been summarized by the CDC. The diagnosis of congenital infection is made by one of the following:

i. **Isolation/detection of rubella virus** (oropharynx, urine). Notify the laboratory in advance because special culture medium needs to be prepared. There are several commercially available but PCR assays for rubella RNA, but none that have cleared by the FDA to date. Virus may also be detectable in blood and cataract specimens.

ii. **Detection of rubella-specific IgM** in cord or neonatal blood within the first 6 months of life

iii. **Persistent rubella-specific titers over time** (i.e., no decline in titer as expected for transplacentally derived maternal IgG). If, in addition, there are congenital defects, the diagnosis of CRS is made.

D. Treatment. There is no specific therapy for either maternal or congenital rubella infection. Maternal disease is almost always mild and self-limiting. If primary maternal infection occurs during the first 5 months of pregnancy, termination options should be discussed with the mother. More than half of newborns with congenital rubella may be asymptomatic at birth. If infection is known to have occurred beyond the 20th week of gestation, it is unlikely that any abnormalities will develop, and parents should be reassured. Nevertheless, hearing evaluations should be repeated during childhood. Closer follow-up is required if early-gestation infection is suspected or the timing of infection is unknown. This is true for asymptomatic infants as well as those with obvious CRS. The principal reason for close follow-up is to identify delayed-onset abnormalities or progressive disorders, such as glaucoma. Unfortunately, there is no specific therapy to halt the progression of most of the complications of CRS.

E. Prevention. The primary means of prevention of CRS is by immunization of all susceptible persons. Immunization is recommended for all nonimmune individuals 12 months or older. Documentation of maternal immunity is an important aspect of good obstetric management. When a susceptible woman is identified, she should be reassured of the low risk of contracting rubella, but she should also be counseled to avoid contact with anyone known to have acute or recent rubella infection. Individuals with postnatal infection typically shed virus for 1 week before and 1 week after the onset of rash. On the other hand, infants with congenital infection may shed virus for many months, and contact should be avoided during the first year. Unfortunately, once exposure has occurred, little can be done to alter the chances of maternal and subsequently fetal disease. Hyperimmune globulin has not been shown to diminish the risk of maternal rubella following exposure or the rate of fetal transmission and is not recommended for routine postexposure prophylaxis after rubella exposure in pregnancy. However, it can be offered for pregnant women exposed to rubella early in pregnancy who do not want to terminate the pregnancy. The lack of proven efficacy must be emphasized in these cases. Susceptible women who do not become infected should be immunized soon after pregnancy. There have been reports of acute arthritis occurring in women immunized in the immediate postpartum period, and a small percentage of these women developed chronic joint or neurologic abnormalities or viremia. Vaccine-strain virus also may be shed in breast milk and transmitted to breastfed infants, some of whom may develop chronic viremia. Immunization during pregnancy is not recommended because of the theoretical risk to the fetus, and conception should be avoided for 3 months after immunization. Inadvertent immunizations during pregnancy have occurred, and fetal infection has been documented in a small percentage of these pregnancies; however, no cases of CRS have been identified. In fact, the rubella registry at the CDC has been closed, with the following conclusions: The number of inadvertent immunizations during pregnancy is too small to be able to state with certainty that no adverse pregnancy outcomes will occur, but these would appear to be very uncommon. Therefore, it is still recommended that immunization not be carried out during pregnancy, but when this has occurred, reassurance of little risk to the fetus can be given.

X. RSV (NEONATAL). RSV is an enveloped RNA paramyxovirus that is the leading cause of bronchiolitis and severe or even fatal lower respiratory tract disease, especially in preterm infants. Conditions that increase the risk of severe disease include cyanotic or complicated congenital heart disease, pulmonary hypertension, chronic lung disease, and immunocompromised states.

A. Epidemiology. Humans are the only source of infection. RSV is spread by respiratory secretions as droplets or fomites, which can survive on environmental surfaces for hours. Spread by hospital workers to infants occurs, especially in the winter and early spring months in temperate climates. Viral shedding is 3 to 8 days, but in very young infants may take weeks. The incubation period is 2 to 8 days.

B. Diagnosis. Rapid diagnosis is made by PCR or immunofluorescent antigen testing of respiratory secretions. This test can have up to 95% sensitivity and is quite specific. Many centers offer multiplex PCR assays that test for several respiratory viruses in a single assay. However, with the increased sensitivity of PCR testing, up to 25% of asymptomatic children test positive. Viral culture usually requires 3 to 5 days. Antibody testing is not recommended for diagnosis in young infants because of the low sensitivity and poor immune response to RSV in infants.

C. Treatment. Treatment is largely supportive, with hydration, supplemental oxygen, and mechanical ventilation as needed. Controversy exists as to whether nebulized bronchodilator therapy is beneficial, but after recent studies, is no longer recommended. In addition, corticosteroids are not recommended. Ribavirin has been marketed for treatment of infants with RSV infection because it does have *in vitro* activity; however, efficacy has never been repeatedly proven in randomized trials. This makes the risk of ribavirin (aerosol route, potentially toxic side effects to health care personnel, and high cost) important to consider on a case-by-case basis. The use of anti-RSV monoclonal antibody, palivizumab, may be considered for treatment in consultation with an infectious disease specialist for the most severely affected, immunocompromised infants but has not shown much efficacy in this setting.

D. Prevention. Palivizumab (Synagis), a humanized mouse monoclonal antibody given intramuscularly, has been approved by the FDA for prevention of RSV disease in children younger than 2 years of age with chronic lung disease or who were <35 weeks' gestation. Palivizumab is easy to administer, has a low volume, and is given just before and monthly throughout the RSV season (typically mid-November to March/April). Because the drug is costly and its protection incomplete, the AAP has made the following recommendations regarding which high-risk infants should receive palivizumab, last updated in 2014 (reaffirmed 2019):

1. **Infants who have required therapy for chronic lung disease born <32 weeks' gestation** during their first year of life, and for a second season if they continue to need respiratory support up to 6 months prior to the next RSV season
2. **Infants who are born at <29 weeks' gestation** without chronic lung disease during their first year of life

3. **Children** who are 24 months of age or younger with hemodynamically significant acyanotic congenital heart disease, including those receiving medications to control congestive heart failure, have severe pulmonary hypertension, or receive a heart transplant
4. **Infants with anatomic pulmonary abnormalities of the airway or neuromuscular disorder** during their first year of life
5. **Severely immunocompromised infants (such as SCID)** up to 24 months of age
6. **Infants with symptomatic cystic fibrosis** with evidence of chronic lung disease or nutritional compromise in the first 2 years of life

If an RSV outbreak is documented in a high-risk unit (e.g., pediatric intensive care unit), primary emphasis should be placed on proper infection-control practices. The need for and efficacy of antibody prophylaxis in these situations has not been documented. Each unit should evaluate the risk to its exposed infants and decide on the need for treatment. If the patient stays hospitalized, this may only require one dose. Palivizumab does not interfere with the routine immunization schedule.

E. Antibody preparations are not recommended for the following:

1. Healthy preterm babies >29 weeks' gestation without other risk factors
2. Patients with hemodynamically insignificant heart disease
3. Infants with lesions adequately corrected by surgery, unless they continue to require medication for congestive heart failure

Future anti-RSV monoclonal antibodies with longer half-lives may be made available in the United States at a lower price point than the current product and be comparable to the current costs of vaccines. Therefore, the recommendations may change once new monoclonal antibody prevention products are available. There is also considerable ongoing effort to develop RSV vaccines that can elicit potent neutralizing antibody responses in pregnant women and young infants.

XI. SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 (SARS-COV-2) (PERINATAL, NEONATAL).

SARS-CoV-2 is an enveloped RNA virus in the Coronaviridae family that has rapidly spread across the world and resulted in a global pandemic of >100 million cases and 2 million deaths between 2019 and 2020. This is a zoonotic virus that was first identified in Wuhan, China, and likely emerged from bats in 2019. Other coronaviruses in this family are known to cause common colds, gastrointestinal infections in livestock, as well as outbreaks with similar severe acute respiratory syndrome. In newborns, this virus causes cough, fever, and shortness of breath. Although complications include pneumonia, respiratory distress, and sepsis or pneumothorax, neonatal deaths have not been reported as of early 2021.

A. Epidemiology. SARS-CoV-2 spreads in the community and within indoor settings primarily by aerosolized and airborne respiratory droplets and may also spread through fomites. Mean incubation period ranges from 4 to 6 days. The estimated reproductive number (R_0) of 2 to 3 defines the expected number of cases derived from one case. For comparison to other

respiratory pathogens, SARS-CoV-2 is more transmissible than influenza but less transmissible than smallpox, pertussis, rubella, mumps, and measles. Superspreading events have been defined in group gatherings where one highly infectious person may infect more than the average R_0. High levels of community transmission are driven by a large portion of individuals with mild or asymptomatic infection. Although some children may demonstrate prolonged viral RNA shedding up to 1 month, it is unclear if this impacts potential for viral transmission.

The main group at risk for severe coronavirus 2019 (COVID-19) disease are the elderly. Infants are at a lower risk of severe disease compared to adults but at a slightly higher risk of severe COVID-19 as compared to children. In adults, males tend to be more vulnerable to severe disease than females.

Viral sequencing has revealed that reinfections are possible as early as 3 months from original infection. Severity of illness upon reinfection and correlates of protection remain to be defined. With ongoing transmission, new variants of SARS-CoV-2 are currently emerging across the world, and it is unclear whether immunity from prior infection and immunization can protect against these emerging strains.

B. Transmission (perinatal, congenital, postnatal). Neonates rarely may become infected with SARS-CoV-2 either during delivery by ingesting or aspirating vaginal secretions, *in utero* due to infected placenta and amniotic fluid, or postnatally by exposure to a sick family contact. Several cases of perinatal transmission have been described as a result of maternal infections near term, where infants demonstrate PCR-positive nasopharyngeal swabs and symptoms within 10 days of birth (late onset). Infants born to mothers with COVID-19 are at an increased risk of admission to the neonatal intensive care unit and 5% require resuscitation at delivery.

Less frequently, case reports describe evidence for congenital transmission with PCR positivity in nasopharyngeal or rectal swabs, presence of virus-specific IgM and IgG, and symptoms on the day of birth. One case described high viral load in placenta, amniotic fluid prior to rupture of membranes, as well as PCR positivity in multiple neonatal samples including blood and bronchoalveolar lavage fluid within hours of delivery. This suggests that transplacental transmission is possible with maternal infection late in gestation, although overall risk appears very low. Indeed, the majority of neonatal infections are due to environmental exposure and only 30% due to vertical transmission.

However, infections are more severe in pregnancy and maternal infections earlier in gestation may also pose risks to fetal health, such as fetal distress, low birth weight, preeclampsia, and premature delivery. Greater age and preexisting conditions such as high body mass, hypertension, and diabetes are also linked to with severe COVID-19 in pregnancy.

C. Clinical disease/manifestations. The large majority of neonates delivered to mothers with COVID-19 at the time of delivery remain well and are uninfected. In symptomatic infants, respiratory signs, fever, and gastrointestinal symptoms are most common. Neurologic manifestations are identified in nearly a fifth of infected infants. Lung abnormalities such as ground-glass opacities and interstitial-alveolar opacities are found in 2 out of 3 infants. Respiratory signs include tachypnea, intercostal retractions, rhinitis,

and cyanosis. In a review of 97 infants with COVID-19 symptoms, acute respiratory distress syndrome was not observed. Relevant gastrointestinal signs include feeding difficulties, vomiting, and diarrhea. Neurologic signs may manifest as hypertonia or hypotonia, irritability, lethargy, and apnea. Cardiologic signs include tachycardia and hypotension. Laboratory findings were abnormal in only a 14% reviewed, with lymphopenia, elevated liver enzymes, and increase in inflammatory markers such as C-reactive protein and procalcitonin. Although much of COVID-19 pathophysiology in adults is driven by a heightened inflammatory response, infants are less likely to develop such inflammatory responses.

Further studies are required to define disease presentation and prognosis in neonates. Current evidence suggests that up to one-third of symptomatic COVID-19–positive neonates and infants require intensive care and one-fifth are mechanically ventilated. Estimates for asymptomatic infections in neonates range from 20% to 32%. In general, hospitalized neonates have good prognosis after an average of 10 days of hospitalization. The median duration of symptoms in children is 5 days since onset, with resolution of illness and PCR negative test by 15 days post onset.

Unlike adults, some children may develop multisystem inflammatory syndrome (MIS-C) 2 to 4 weeks after acute COVID-19 infection. According to the WHO and CDC, this syndrome is defined by fever, elevated inflammatory markers, multisystem involvement, and exclusion of other potential causes. Although clinical features of MIS-C resemble Kawasaki disease shock syndrome, the epidemiology differs in that MIS-C occurs in older children and neither typically present in neonates. The pathophysiology of this postviral inflammation and disproportionate impact on Black and Hispanic children are not well understood.

D. Diagnosis in infants

1. **Molecular diagnosis.** Real-time RT-PCR to detect viral nucleic acids from a nasopharyngeal swab sample is currently the most reliable confirmatory test to detect SARS-CoV-2. This test detects viral RNA corresponding to the spike or nucleocapsid proteins and can be used on other biologic fluids including saliva, sputum, bronchoalveolar-lavage fluid, and feces. A negative result from a blood sample does not exclude SARS-CoV-2 infection. According to the AAP, testing of neonates is recommended at 24 hours and 48 hours of age as PCR positivity has been reported at 48 hours following an earlier negative test. For infants with a positive test, two consecutive negative tests at 48- to 72-hour intervals apart are recommended to establish resolution of the viral infection.
2. **Serology.** To ascertain recent infections, SARS-CoV-2–specific IgG and IgM can be measured, although this does not confirm active infection. Elevated SARS-CoV-2 IgG concentrations can be observed in infants, even with negative RT-PCR results due to passive transfer of maternal IgG across the placenta. SARS-CoV-2 IgM have been reported in infants and is potentially indicative of recent infection. However, a negative IgM test result cannot be used to rule out recent infection. Serologic testing may be more valuable for serosurveillance of SARS-CoV-2 infections than for diagnostics as part of ongoing efforts to end the pandemic.

3. **Influenza testing and coinfections.** Infants suspected of having SARS-CoV-2 infection must also receive concurrent testing for influenza, due to the possibilities of misdiagnosis and coinfection, particularly during influenza season. Prompt detection and confirmation of the infectious etiology is necessary due to the differences in management. Detection of other respiratory pathogens, such as RSV and *Mycoplasma pneumoniae*, does not exclude concurrent infection with SARS-CoV-2.

E. Treatment. Presently, there are no treatment options for COVID-19 in infants. Antivirals have been largely tested in adults and not infants. The recommended treatment for neonates is largely supportive to address symptoms.

F. Prevention. In the absence of treatment options, there is substantial emphasis on the prevention of infection in neonates. Hygiene measures are focused on reducing contact time with infected individuals/mother, mask usage for the infected individual as infants cannot don masks, and environmental disinfection.

1. **Delivery strategies.** If the mother is actively infected, it is recommended that she wear a surgical mask during delivery. Although expert opinion in the early days of the pandemic recommended cesarean section for prevention of mother-to-child COVID-19 transmission, evidence does not support this. Given the outcomes of mother and infant by mode of delivery, observational studies suggest that cesarean sections should only be performed when there is an indication for it and not solely to prevent COVID-19 transmission. In fact, maternal and neonatal outcomes may be worse with cesarean section as compared to normal vaginal delivery.

   Upon delivery, mothers may choose to temporarily separate from the infant, or the infant can room-in with mothers using infection prevention measures. This includes the use of isolettes, keeping ≥6 feet apart accept when caring for the infant, maternal masking, and hand washing. These infants should be isolated from other infants. In the absence of any mother–infant separation or infection prevention measure, there is 4 times greater odds of late-onset SARS-CoV-2 infections in neonates, although with maternal masking, hand hygiene, and regular sanitizing of skin surfaces, neonates with skin-to-skin contact with the COVID-19–infected mothers upon delivery did not develop disease. Additionally, the AAP recommends all health care personnel to don personal protective equipment for the protection of the baby and the health care staff.

2. **Breastfeeding and postnatal care.** The AAP supports postdelivery maternal rooming-in and breastfeeding of infants despite maternal infection, given that the mother dons a mask, sanitizes hands, and cleans her breast prior to breastfeeding or routine care. Although viral RNA has been found in breast milk, infectious virus has not been isolated, and therefore, the benefits of infant feeding and mother–infant bonding outweigh potential risks with appropriate hygiene precautions. If a neonate is in neonatal intensive care unit and the mother cannot be present in that environment due to infection status, the mother should express breast milk after hand hygiene precautions and uninfected caregivers

can feed the infant. After discharge, caregivers are encouraged to apply hygiene measures at home such as frequent hand and face washing; disinfection of daily supplies, floors, and furniture with 75% medical alcohol or chlorine disinfectants; good window ventilation; and high heat disinfection of pacifiers and bottles.

3. **Immunization.** In terms of active vaccination, mRNA vaccines, adenovirus-vectored vaccines, and inactivated vaccines have recently received emergency authorization for use in adults in several countries. Thus far, these vaccines have only been rigorously tested in adults and as of 2021 are not yet recommended for use in children or infants. The mRNA and adenovirus-vectored platforms are novel platforms that do not have precedence for use in the pediatric immunizations schedule. Age de-escalation clinical trials will be required to determine safety and efficacy in infants. However, protein subunit vaccine platforms, which demonstrate strong safety and immunogenicity profile infants (i.e., acellular pertussis and hepatitis B), are still in development for SARS-CoV-2. Additionally, efficient transplacental transfer of maternal SARS-CoV-2 IgG to the neonate has recently been demonstrated, supporting maternal immunization strategies to protect neonates, yet indicates that maternal antibody interference will need to be assessed in the development of infant vaccination.

   As an alternative to active immunization strategies, passive immunoglobulin and convalescent plasma therapies have also received emergency authorization for use in adults. However, testing in infants is lacking. Therefore, infant passive immunization is not recommended at this point.

XII. ZIKA VIRUS (ZIKV) (CONGENITAL, PERINATAL, NEONATAL).

ZIKV is an enveloped RNA virus in the Flaviviridae family, along with other human pathogens like dengue virus (DENV), West Nile, yellow fever, and Japanese encephalitis viruses in the same family. In 2015 to 2016, ZIKV caused an epidemic in the Americas, starting in northeast Brazil and rapidly spreading across the continents. In most adults, ZIKV results in a short-lived febrile illness and Guillain-Barré syndrome in 1 in 10,000 adults. However, infants bear the primary disease burden of this virus upon congenital transmission. The resulting cluster of symptoms in newborns, known as congenital Zika syndrome (CZS), includes microcephaly, neural and cardiovascular developmental defects, seizures, dysphagia, motor and vision impairments, and slower language development in the first year of life. The 2015 to 2016 outbreak of ZIKV in a susceptible population resulted in 11,000 cases of microcephaly in Brazil alone. These conditions result in lifelong disability and disease morbidity beyond the neonatal period.

A. **Epidemiology.** ZIKV results in explosive outbreaks driven by mosquito-transmitted disease that can reach >60% of a population in a time span of 4 to 7 months. The R_0 varies widely based on environmental conditions for transmission and susceptibility of the population, ranging from 1.3 to 12. The median incubation period for ZIKV disease is 6 days, with 9 to 10 days as the mean times for seroconversion and viral clearance. However, there have been several reports of prolonged viremia in pregnancy, and it is now known

that ZIKV may persist up to 3 times longer in pregnant as compared to nonpregnant women. In most adults, symptoms last for 2 to 7 days and are mild (fever, rash, conjunctivitis, arthralgia, myalgia, and headache). However, a large proportion of ZIKV infections are asymptomatic, even in pregnancy. Estimates on the prevalence of asymptomatic infections vary across populations from 29% to 82% of all ZIKV infections.

The threat of ZIKV epidemics is highest in tropical areas, where year-round transmission may be feasible due to a favorable climate for mosquitoes. Whereas temperate areas, such as the United States and Europe, will be at risk of imported travel-related cases from tropical areas during warmer seasons. In general, arboviruses spread seasonally after rainfall, which promotes the growth of mosquitoes. However, as the temperatures increase with climate change, the mosquito habitat expands farther from the tropics. It is projected that this shift may render ~1 billion additional susceptible people at risk for future outbreaks by the end of the century. Future ZIKV epidemics are likely because urban monkeys in tropical areas may serve as an animal reservoir for reemergence once population herd immunity from the recent outbreak wanes. As a result, related flaviviruses, like DENV, are known to reemerge in 3 to 5 year cycles.

B. Transmission (congenital and perinatal). Pregnant women can be infected either through ZIKV-carrying mosquitoes or via sexual transmission. The virus can then cross the placenta or ascend the uterine tract to transmit to the fetus. However, the majority of congenital transmission are mediated by infections in pregnancy due to mosquito bites. Studies find that 1 in 10 ZIKV-infected pregnancies may result in microcephaly and brain damage. Congenital transmission can occur during any trimester in pregnancy, and risk of adverse birth defects is greatest in the first trimester. Yet, delayed-onset neurodevelopmental abnormalities are being found in several children who were apparently healthy at birth, suggesting that this rate of congenital transmission based on abnormal outcomes at birth may be an underestimate.

Symptomatic maternal infection is not associated with increased risk of birth defects as compared to asymptomatic maternal infection. However, prolonged viremia of >30 days postinfection is related to more adverse fetal and neonatal outcomes as compared to ZIKV-infected mothers without prolonged viremia. For maternal infections within 2 weeks of delivery, the virus may pass to the infant at the time of delivery. Perinatal infections with ZIKV are similar to those in children and adults and may result in maculopapular rash, conjunctivitis, arthralgia, and fever. This route of transmission may not result in the developmental defects observed with congenital transmission, although the rate of perinatal transmission and clinical spectrum of disease is unknown. Postnatal infections in infancy are possible by mosquito bites, although there is limited evidence on the long-term consequences of this given the recency of the ZIKV epidemic. Infant exposure to mosquitoes is typically lower than older age groups that are more mobile in the environment. Also, although some case reports indicate the breast milk may contain viral RNA and/or infectious viruses in fewer cases, the risk of ZIKV transmission by breast milk is low. As per the CDC and WHO, the benefits of breastfeeding outweigh the risks of ZIKV transmission via this route.

C. Clinical disease/manifestations

1. **Monitoring fetal disease.** Repeated ultrasounds are recommended to follow neurodevelopment of the fetus and assess for growth restriction in a ZIKV-positive pregnancy. Fetal microcephaly or delayed increase in head circumference are often detected starting mid to late second trimester and warrant further assessment. Fetal microcephaly is based on *in utero* measurements as per the INTERGROWTH-21st Fetal Growth Standard for Head Circumference at Birth. Note that microcephaly detected *in utero* may not necessarily predict postnatal microcephaly and postnatal head and growth measurements are required. ZIKV-related neurodevelopmental damage has been characterized as intracranial calcifications, overlapping fetal cranial bones and sutures, ventriculomegaly, herniation of brain tissue, thrombosis in cerebral sinuses, and abnormalities in cortex, corpus callosum, cerebellum, and brainstem. Associated anatomical features may include arthrogryposis and microphthalmia. Also, intrauterine fetal growth restriction has also been observed in ZIKV infections during pregnancy. Because microcephaly can skew measures of biparietal diameter and head circumference, fetal weight and growth should be calculated using femur length and abdominal circumference for gestational age instead. Evidence of abnormalities on ultrasound is an indication for further evaluation using MRI.
2. **CZS in neonates.** CZS defines a cluster of birth defects and congenital anomalies related to the pathophysiology arising from neurotropism of ZIKV during fetal development. Although a range of ZIKV-related symptoms have been described over the past few years, five key features have predominated these reports and distinguish ZIKV from other congenital anomalies. As per the CDC, congenital ZIKV infection can be defined by: "(1) severe microcephaly with partially collapsed skull; (2) thin cerebral cortices with subcortical calcifications; (3) macular scarring and focal pigmentary retinal mottling; (4) congenital contractures; and (5) marked early hypertonia and symptoms of extrapyramidal involvement." At birth, microcephaly is defined as a head circumference less than the 3rd percentile for gestational age and sex. Long-term sequelae of microcephaly consist of seizures, vision and hearing dysfunctions, and developmental disabilities. Recent evidence from 6- to 42-month-old normocephalic children who were exposed to *in utero* ZIKV suggests that head circumference *z* score at birth is directly associated with anatomical and neurocognitive anomalies. Importantly, as the *in utero* ZIKV-exposed infants from the 2015 to 2016 outbreak continue to grow, there will be more to learn about the clinical spectrum of disease due to congenital ZIKV infection.

   Other neural abnormalities related to ZIKV infection *in utero* include structural disorders of the brain, hydrocephalus, and neuronal migration disorders. These neural defects may give rise to hyperreflexia, irritability, tremors, brainstem dysfunction, and dysphagia.

   Ocular damage can occur on the retina and in particular a central area known as the macula. Eye-related defects include focal pigmentary mottling, chorioretinal atrophy, retinal lesions, iris colobomas, congenital glaucoma, microphthalmia, lens subluxation, cataracts, and intraocular calcifications. The optic nerve could be damaged as well due to hypoplasia, cupping, and atrophy. Finally, cardiac defects have also been

identified in 40% of infants exposed to ZIKV *in utero*, indicating a need for postnatal echocardiography during newborn follow-up.

3. **Delayed developmental defects.** In the 3 to 4 years of follow-up of children exposed to ZIKV *in utero*, additional developmental defects have been linked to ZIKV in children who were apparently healthy at birth. Delay in language skills, as detected by the Bayley III test, has been noted as the most affected developmental attribute across multiple studies, with up to 37% of *in utero* exposed children being impacted by 15 months of age. A case series found delays in motor performance and cognition in 24% and 5% of children, respectively, by 15 months of age. Also, a prospective cohort reported that 25% of infants who demonstrated normal hearing and vision scores at birth developed abnormalities by 7 to 32 months of age. However, infant developmental trajectories may also resolve over time. In 49% of infants with neurodevelopmental abnormalities in the first month of life, neurodevelopmental scores were found to be in the normal range upon retesting the second or third year of life. These findings underscore the importance of follow-up despite initial clinical assessment. Studies are still ongoing to identify the long-term consequences of *in utero* exposure to ZIKV.

D. Diagnosis

1. **Molecular diagnostics.** Pregnant women living in outbreak areas with symptoms or travel exposure history may be tested via a PCR test for the presence of viral RNA specific to the envelope protein. Viral RNA is reliably detected in blood as the virus disseminates in body through circulation. Although the PCR diagnostic is most effective in acute infection (7 to 10 days), the CDC supports longer testing in pregnancy due to the potential for prolonged viremia in pregnancy. The brief window of PCR positivity has been a challenge to diagnosing recent infections when pregnant patients present for care >10 days after symptoms.
2. **Serology.** Antibody-based diagnostics are considered less reliable than the PCR test because antibodies to ZIKV and related DENVs may cross-react with one another due to the extent of similarity among the viruses. Serologic tests tend to have low sensitivity and specificity in discriminating ZIKV and DENV antibodies because these viruses are often coendemic and populations tend to prior exposure to the related DENV. Although IgM antibodies are only present briefly after infection, an IgM-based diagnostic from the CDC has gained Emergency Use Authorization, to be applied in conjunction with the PCR test. Pregnant women living in outbreak areas with symptoms or travel exposure history may be tested for the presence of ZIKV-specific IgM for up to 12 weeks from exposure. Yet, recent studies suggest that ZIKV-specific IgM can be found long after infection in some individuals, diminishing the value of this test in identifying recent infections. Consequently, a negative IgM does not rule out recent ZIKV infection. Finally, virus neutralization test is considered the gold standard for distinguishing prior infection with ZIKV and DENV, when sera are tested for neutralization of ZIKV and all four DENV serotypes. However, the neutralization test requires extensive laboratory capacity, is labor intensive, and does not distinguish acute/recent infection, only beyond 3 months from exposure.

E. Treatment. Currently, there are no treatments available for CZS. Care recommendations for neonates with congenital ZIKV infection are primarily clinical evaluations and supportive management of CNS complications and dysfunction

1. **Initial evaluation at birth.** Comprehensive physical and vision exams, automated auditory brainstem response, and head ultrasound must be conducted at birth. Infants suspected of *in utero* ZIKV exposure may be tested for ZIKV RNA or IgM, even though the molecular test is most effective within 10 to 14 days of acute infection and there is no reliable infant diagnostic. Other congenital infections (toxoplasmosis, rubella, CMV, HSV, syphilis, VZV, parvovirus) and genetic causes of structural and functional deficits should be ruled out.

2. **Follow-up in first 6 months of life.** The CDC recommends the following monthly evaluations in the first 6 months of life: vision screening, developmental screening, and growth parameter measurements. Further counselling may be offered to the family in anticipation of requirements for psychosocial support and assistance with establishing a home environment optimized for care delivery.

3. **Further clinical guidance.** Infants with CZS may also require neurology, ophthalmology, and endocrinology consultations to identify possible central motor dysfunction, auditory dysfunction, cortical visual impairment, hypothalamic or pituitary dysfunction, and other neurodevelopmental abnormalities. Consultations with gastroenterology, pulmonology, and otolaryngology may be necessary to further evaluate for dysphagia and aspiration difficulties. Referral to developmental specialists, lactation specialist, nutritionist, speech and/or occupational therapist, physical therapist, and family/social services is recommended to provide support in the care of an infant with CZS.

F. Prevention. In the absence of viable treatment options, prevention of infection during pregnancy is a key strategy to protecting the health of neonates.

1. **Minimizing ZIKV exposure by mosquitoes.** Pregnant women are advised not to travel to areas with ongoing ZIKV circulation by the CDC, which maintains an updated map or areas with ZIKV circulation. If travel or livelihood in an area with ZIKV cannot be avoided, pregnant women are advised to minimize mosquito bites through covering skin, use of Environmental Protection Agency registered insect repellants, use air-conditioning, sleep in mosquito bed nets, and stay in locations with window and door screens. Evidence suggests even households with fans experience fewer mosquito-borne illnesses. Also, indoor and outdoor mosquito control measures can be applied by eliminating sources of standing water.

2. **Minimizing exposure by sexual transmission.** The CDC recommends that pregnant women living in, or having partners that travel to, ZIKV areas use condoms always, or abstain from sexual intercourse throughout gestation. This is particularly important as semen may have prolonged viral RNA shedding as compared to other bodily fluids. Median time to loss of ZIKV RNA detection in serum is 11 days in serum, 34 days in urine, and 42 days in semen. In particular, 95% of men clear viral RNA from semen in 4 months, suggesting that in some partners, duration of risk of sexual ZIKV transmission is extended.

3. **Immunization.** Despite 5 years since the major initial ZIKV outbreak in the Americas, there is no licensed vaccine for ZIKV. The leading vaccine candidate is a DNA vaccine that has been stuck in phase 2b clinical trials of safety and immunogenicity due to lack of ongoing viral circulation globally to test the candidate. Live-attenuated virus vaccine platforms have shown to be immunogenic for related yellow fever and DENVs. Yet, these platforms are typically contradicted for use in pregnancy, a time period of greatest risk for congenital ZIKV transmission. As maternal ZIKV-specific IgG can be efficiently transferred across the placenta, maternal immunization may be valuable way to protect the newborn. In addition to active immunization, passive immunoglobulin prophylaxis may be a possibility for pregnant women in the future.

Suggested Readings

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49 Bacterial and Fungal Infections

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KEY POINTS

- Risk factors for neonatal early-onset sepsis (EOS) include prematurity, maternal colonization with group B *Streptococcus* (GBS), intrapartum fever and other signs of intraamniotic infection (chorioamnionitis), and duration of membranes; risk is modified by the administration of intrapartum antibiotics.
- Empiric antibiotic therapy includes broad coverage for organisms known to cause EOS, usually a β-lactam antibiotic and an aminoglycoside. The most common microbial causes of EOS include GBS, *Escherichia coli*, viridans Streptococci, *Enterococcus*, and a variety of *Enterobacteriaceae* such as *Klebsiella* and *Haemophilus* spp.
- Risk for neonatal late-onset sepsis (LOS) increases with lower gestational age and birth weight (BW) and with longer duration of central venous access, mechanical ventilation, and use of total parenteral nutrition.
- Empiric antibiotic therapy for LOS should be tailored to the local microbiology of infection, which may include different relative contributions of coagulase-negative staphylococci (CONS), methicillin-sensitive and methicillin-resistant *Staphylococcus aureus*, β-lactam–resistant gram-negative organisms, and *Candida* spp.

I. BACTERIAL SEPSIS AND MENINGITIS

A. Introduction. Bacterial sepsis and meningitis continue to be major causes of morbidity and mortality in newborns, particularly in premature infants. Although improvements in neonatal intensive care have decreased the impact of early-onset sepsis (EOS) in term infants, preterm infants remain at high risk for both EOS and its sequelae. Very low birth weight (VLBW) infants are also at risk for late-onset sepsis (LOS) (hospital acquired). Neonatal survivors of sepsis can have severe neurologic sequelae due to central nervous system (CNS) infection, white matter damage from systemic inflammation, as well as from secondary hypoxemia resulting from septic shock, persistent pulmonary hypertension, and severe parenchymal lung disease.

B. Epidemiology of EOS. EOS is defined by isolation of pathogenic organisms from blood or cerebrospinal fluid (CSF) culture at 0 to 6 days after birth. The overall incidence of EOS in the United States has decreased significantly since the Centers for Disease Control and Prevention (CDC) first published recommendations for intrapartum antibiotic prophylaxis (IAP) against group B *Streptococcus* (GBS) in 1996. Studies conducted in 21st century show the overall incidence of EOS to be ≤1 case per 1,000 live births. The incidence is twice as high among moderately premature infants compared to term infants and highest among VLBW (<1,500 g) infants with recent reports ranging from 10 to 15 cases per 1,000 VLBW births.

C. Risk factors for EOS. The pathogenesis of EOS is that of ascending colonization of the maternal genital tract and uterine compartment with gastrointestinal and genitourinary flora, and subsequent transition to invasive infection of the fetus or newborn. Maternal and infant characteristics associated with the development of EOS have been most rigorously studied with respect to GBS EOS. Maternal factors predictive of GBS disease include documented maternal GBS colonization, intrapartum fever (>38°C) and other signs of intraamniotic infection (chorioamnionitis), and prolonged rupture of membranes (ROM) (>18 hours). Neonatal risk factors include prematurity (<37 weeks' gestation) and low birth weight (BW) (<2,500 g). These risk for infection is reduced by the administration of intrapartum antibiotics.

D. Clinical presentation of EOS. Early-onset disease can manifest as asymptomatic bacteremia, generalized sepsis, pneumonia, and/or meningitis. The clinical signs of EOS are usually apparent in the first hours of life; >90% of infants are symptomatic by 24 to 48 hours of age. Respiratory distress is the most common presenting symptom. Respiratory symptoms can range in severity from mild tachypnea and grunting, with or without a supplemental oxygen requirement, to respiratory failure. Persistent pulmonary hypertension of the newborn (PPHN) can also accompany sepsis. Other less specific signs of sepsis include irritability, lethargy, temperature instability, poor perfusion, and hypotension. Disseminated intravascular coagulation (DIC) with purpura and petechiae can occur in more severe septic shock. Gastrointestinal symptoms can include poor feeding, vomiting, and ileus. Meningitis may present with seizure activity, apnea, and depressed sensorium but may complicate sepsis without specific neurologic symptoms, underscoring the importance of the lumbar puncture (LP) in the evaluation of sepsis.

Other diagnoses to be considered in the immediate newborn period in the infant with signs of sepsis include transient tachypnea of the newborn, meconium aspiration syndrome, intracranial hemorrhage, congenital viral disease, and congenital cyanotic heart disease. In infants presenting at older than 24 hours of age, closure of the ductus arteriosus in the setting of a ductal-dependent cardiac anomaly (such as critical coarctation of the aorta or hypoplastic left heart syndrome) can mimic sepsis. Other diagnoses that should be considered in the infant presenting beyond the first few hours of life with a sepsis-like picture include bowel obstruction, necrotizing enterocolitis (NEC), and inborn errors of metabolism.

E. Evaluation of the symptomatic infant for EOS. **Laboratory evaluation** of the symptomatic infant suspected of EOS includes at minimum blood culture. Markers of inflammation such as the complete blood count (**CBC**) with differential, C-reactive protein (CRP), and procalcitonin (PCT) are commonly obtained, although there is controversy regarding optimal use of these tests. Other laboratory abnormalities can include hyperglycemia or hypoglycemia, abnormal liver and renal function tests and metabolic acidosis. Thrombocytopenia as well as evidence of DIC (elevated prothrombin time, partial thromboplastin time, and international normalized ratio; decreased fibrinogen) can be found in more severely ill infants, particularly those born preterm. For infants with a strong clinical suspicion of sepsis, **an LP for CSF cell count, protein and glucose concentration, Gram stain, and culture** should be performed before the administration of antibiotics if the infant's clinical condition allows. The LP may be deferred until after the institution of antibiotic therapy if the infant is clinically unstable, or if later culture results or clinical course demonstrates that sepsis was present. Infants with respiratory symptoms should have a **chest radiograph** as well as other indicated evaluation such as arterial blood gas measurement. Radiographic abnormalities caused by retained fetal lung fluid or atelectasis usually resolve within 48 hours. **Neonatal pneumonia** will present with persistent focal or diffuse radiographic abnormalities and variable degrees of respiratory distress. Neonatal pneumonia (particularly that caused by GBS) can be accompanied by primary or secondary surfactant deficiency.

F. Treatment of EOS. **Empiric antibiotic therapy** includes broad coverage for organisms known to cause EOS, usually a β-lactam antibiotic and an aminoglycoside. In our institutions, we use ampicillin and gentamicin as initial therapy. We add a third-generation cephalosporin (cefepime or ceftazidime) to the empiric treatment of critically ill infants for whom there is a strong clinical suspicion for sepsis to optimize therapy for ampicillin-resistant enteric gram-negative organisms, primarily ampicillin-resistant *Escherichia coli* (see Table 49.1 for treatment recommendations). **Supportive treatments for sepsis** include the use of mechanical ventilation, exogenous surfactant therapy for pneumonia and respiratory distress syndrome (RDS), volume and pressor support for hypotension and poor perfusion, and anticonvulsants for seizures. **Echocardiography** may be of benefit in the severely ill, cyanotic infant to determine if significant pulmonary hypertension or cardiac failure is present. Infants born at ≥34 weeks with symptomatic pulmonary hypertension may benefit from treatment with inhaled nitric oxide (**iNO**). Extracorporeal membrane oxygenation (**ECMO**) can be offered to infants ≥34 weeks if respiratory and circulatory failure occurs despite all conventional measures of intensive care. ECMO is not generally available to infants <34 weeks' gestation and <2 kg BW (see Chapter 39).

A variety of **adjunctive immunotherapies** for both EOS and LOS have been trialed since the 1980s to enhance immune responsiveness or as modulators of immune response. Double-volume exchange transfusions, granulocyte infusions, treatment with granulocyte-colony stimulating factor (G-CSF) and granulocyte macrophage-colony stimulating factor (GM-CSF), lactoferrin, and probiotics have all been investigated with variable results and are not generally recommended. An international, multicenter randomized, placebo-controlled trial of intravenous immunoglobulin (IVIG)

Table 49.1. Empiric and Definitive Antibiotic Regimens for Sepsis and Meningitis

Empiric Therapy			
EOS	Ampicillin and aminoglycoside *Concern for meningitis*: addition of extended-spectrum cephalosporin or carbapenem *High-risk for ampicillin-resistant Escherichia coli infection*: addition of extended-spectrum cephalosporin		
LOS	Optimally informed by local microbiology of LOS Typical regimens: ■ Oxacillin/aminoglycoside ■ Vancomycin/aminoglycoside ■ Vancomycin/cefepime		
Definitive Therapy (after organism identification and antibiotic susceptibility available)			
Organism	**Antibiotic***	**Bacteremia**	**Meningitis†**
GBS	Ampicillin or penicillin G	10 days	14–21 days
Escherichia coli	Ampicillin *or* cephalosporin *or* aminoglycoside *Meningeal infection*: combination therapy with ampicillin or cephalosporin and aminoglycoside. Aminoglycoside can be discontinued when CSF is sterile.	10–14 days	21 days
Klebsiella	Cephalosporin *or* aminoglycoside *Meningeal infection*: combination therapy with cephalosporin and aminoglycoside. Aminoglycoside can be discontinued when CSF is sterile.	10–14 days	21 days
Enterobacter,‡ *Serratia*, *Pseudomonas*, *Citrobacter*	*Nonmeningeal infection*: extended spectrum β-lactamase *or* cefepime; plus aminoglycoside *Meningeal infection*: carbapenem	10–14 days	21 days

(continued)

Table 49.1. ***(Continued)***

Definitive Therapy
(after organism identification and antibiotic susceptibility available)

Organism	Antibiotic*	Bacteremia	Meningitis†
ESBL-producing gram-negative organisms	Carbapenem (± aminoglycoside) *Consultation with infectious disease specialist strongly advised*	10–14 days	21 days
*Enterococcus***	Ampicillin *or* vancomycin; plus gentamicin	10 days	21 days
Listeria	Ampicillin and gentamicin	10–14 days	14–21 days
CONS	Vancomycin	7 days	14 days
Staphylococcus aureus††	Nafcillin or oxacillin	10–14 days	21 days
MRSA	Vancomycin	10–14 days	21 days

*All recommended definitive regimens assume that susceptibility data is available to inform antibiotic choices. The narrowest spectrum appropriate choice should be made. Treatment courses are counted from the first documented negative blood and CSF cultures. In late-onset infections, all treatment courses assume central catheters have been removed. With CONS infections, the clinician may choose to retain the catheter during antibiotic treatment, but if repeated cultures remain positive, the catheters must be removed.

†In cases of meningitis, repeat lumbar punctures should be performed to ensure CSF sterility before narrowing of antibiotic to monotherapy. Total meningitis treatment courses is counted from time blood and CSF cultures are sterile.

‡*Enterobacter* and *Citrobacter* spp. have inducible, chromosomally encoded cephalosporinases. Cephalosporins other than the fourth-generation cefepime should not be used to treat infections with these organisms **even if** initial *in vitro* antibiotic sensitivity data suggest sensitivity to third-generation cephalosporins. There are some reports in the literature of cefepime-resistant *Enterobacter*.

**Enterococci are resistant to all cephalosporins. Ampicillin-resistant strains of enterococci are common in hospitals and require treatment with vancomycin. Treatment of vancomycin-resistant strains (vancomycin-resistant enterococci) requires consultation with an infectious disease specialist.

††Uncomplicated methicillin-sensitive *S. aureus* and MRSA bacteremias may be treated for only 10 days if central catheters have been removed. Persistent bacteremias can require treatment for 3–4 weeks. Bacteremias complicated by deep infections such as osteomyelitis or infectious arthritis often require surgical drainage and treatment for up to 6 weeks. The use of additional agents such as linezolid, daptomycin, and rifampin to eradicate persistent *S. aureus* infection or to treat *vancomycin-intermediate S. aureus* (VISA) and *vancomycin-resistant S. aureus* (VRSA) strains requires consultation with an infectious disease specialist.

EOS, early-onset sepsis; LOS, late-onset sepsis; GBS, group B *Streptococcus*; CSF, cerebrospinal fluid; ESBL, extended-spectrum β-lactamase; CONS, coagulase-negative staphylococci; MRSA, methicillin-resistant *S. aureus*.

administration to infants with suspected or proven sepsis found no change in the primary outcome of death or major disability at 2 years of age, nor any change in a number of secondary outcomes, including second episodes of sepsis. IVIG is not recommended for treatment of neonatal sepsis.

G. Evaluation of the asymptomatic infant at risk for EOS. There are a number of clinical factors that place infants at risk for EOS. These factors also identify a group of asymptomatic infants (see subsequent text) who may have colonization or bacteremia that places them at risk for the development of symptomatic EOS. Blood cultures are the definitive determination of bacteremia. A number of laboratory tests have been evaluated for their ability to predict which of the at-risk infants will go on to develop symptomatic or culture-confirmed sepsis, but no single test has adequate sensitivity and specificity.

1. **Blood culture.** With advances in the development of computer-assisted, continuous-read culture systems, most blood cultures will be positive within 24 to 36 hours of incubation if organisms are present. Most institutions, including ours, empirically treat infants for sepsis for a minimum of 36 to 48 hours with the assumption that true positive cultures will turn positive within that period. At least 1 mL (and up to 3 mL) of blood should be placed in an aerobic pediatric blood culture bottle. The use of two culture bottles for each sepsis evaluation aids in the distinction of true bacteremia versus contaminants. Depending on the clinical scenario, one aerobic and one anaerobic culture bottle is optimal, despite the fact that most blood culture systems do not provide pediatric-specific anaerobic culture bottles. Certain organisms causing EOS (such as *Bacteroides fragilis*) will only grow under anaerobic conditions; 5% to 15% of culture-proven EOS in preterm infants is due to strictly anaerobic species when anaerobic blood culture is performed. NEC may also be complicated by anaerobic bacteremia. Additionally, GBS, staphylococci, and many gram-negative organisms grow in a facultative fashion, and the use of two culture bottles increases the likelihood of detecting low-level bacteremia with these organisms.
2. **White blood cell (WBC).** The WBC and differential is readily available and commonly used to evaluate both symptomatic and asymptomatic infants at risk for sepsis. Interpretation of neonatal WBC has been compromised by the impact of differences mediated by gestational age, postnatal age, mode of delivery, and maternal conditions. Maternal fever, neonatal asphyxia, meconium aspiration syndrome, pneumothorax, and hemolytic disease have all been associated with neutrophilia; maternal pregnancy-induced hypertension and preeclampsia are associated with neonatal neutropenia as well as thrombocytopenia.

   One finding common to all published neonatal WBC data is the "roller coaster" shape of the WBC and absolute neutrophil count (ANC) and immature to total neutrophil ratio (I/T) curves in the first 72 hours of life. This suggests that optimal interpretation of WBC data to predict EOS should account for the natural rise and fall in WBC during this period. Recent studies support the use of CBC only after the first few hours of life, when placed in the proper clinical context and used as part of an algorithm to evaluate infants for sepsis risk. The WBC and ANC are most predictive of infection when these values were low (WBC $<$5,000 and ANC $<$1,000). An elevated WBC ($>$20,000) is

neither worrisome nor reassuring in neonates. The I/T ratio is most informative if measured at >4 hours after birth, with low values (<0.15) reassuring, whereas elevated values (>0.3) are associated with EOS. The combination of low ANC and elevated I/T ratio is the most predictive combination of WBC indices for EOS.

Although studies demonstrate that no component of the WBC is very sensitive among term and late-preterm infants for the prediction of sepsis, there are little data to guide interpretation of the WBC among VLBW infants at risk for EOS. The WBC and its components may be of more value in the VLBW infant and/or in the evaluation of late-onset infection, especially if interpreted in relation to values obtained prior to the concern for infection.

3. **CRP.** CRP is a nonspecific marker of inflammation or tissue necrosis. Elevations in CRP are found in bacterial sepsis and meningitis. A single determination of CRP at birth lacks both sensitivity and specificity for infection. Serial CRP determinations at the time of blood culture, 12 to 24 hours and 48 hours later, have been used to manage infants at risk for EOS and LOS. Some centers use serial CRP measurements to determine length of antibiotic treatment for infants with culture-negative clinical sepsis, despite the absence of data to support the efficacy of this practice.
4. **Cytokine measurements.** Advances in the understanding of the immune responses to infection and in the measurement of small peptide molecules have allowed investigation into the utility of these inflammatory molecules in predicting infection in neonates at risk. Serum levels of interleukin 6, interleukin 8, interleukin 10, interleukin 1β, G-CSF, tumor necrosis factor alpha (TNF-α), and PCT as well as measurements of inflammatory cell-surface markers such as CD64 have been variably correlated with culture-proven, clinical, and viral sepsis. The need for serial measurements and the availability of the specific assays so far limit the use of cytokine markers in diagnosing neonatal infection. PCT is increasingly available in clinical settings and correlates with bacterial infection; however, there is a natural rise in PCT levels in the hours after birth for all infants, normal ranges vary with gestational age, and like CRP, PCT levels rise in response to noninfectious inflammatory signals. In addition, most studies of biomarkers have been performed on infants who are symptomatic and being evaluated for sepsis. None of these has yet proven useful in predicting infection in initially well-appearing infants.
5. **Other strategies.** **Urine latex particle agglutination testing for GBS** remains available at some institutions; we do not use this test due to very poor predictive value. Latex particle testing of CSF for both GBS and *E. coli* K1 can be of use in evaluating CSF after the institution of antibiotic treatment.
6. **LP.** The use of routine LP in the evaluation of **asymptomatic neonates** at risk for EOS remains controversial. A study from 1988 to 1992 identified 4 infants among 169,849 live births who had culture-confirmed, early-onset meningitis in the absence of symptoms and in the absence of bacteremia. Multiple studies from the 1990s failed to identify meningitis among asymptomatic term newborns deemed at risk for EOS. Contemporary studies demonstrate that early-onset meningitis in the absence of

bacteremia is uncommon. CDC surveillance data in the United States from 2006 to 2015 found that culture-confirmed, early-onset GBS meningitis occurred in the absence of GBS bacteremia at a rate of approximately 1 case in 400,000 live births. This study did not comment on newborn clinical condition in these rare cases. Current national guidelines from the United States and Great Britain for evaluation of infants at risk for EOS endorse the selective use of LP when there is strong clinical suspicion for sepsis and/or specifically for meningitis. We do not perform LPs for the evaluation of **asymptomatic term infants** at risk for EOS. **It is our current policy to perform LPs only** on (i) infants with positive blood cultures and (ii) symptomatic infants with a high risk for EOS whose condition is stable enough to tolerate LP and (iii) rarely, infants with negative blood cultures who are treated empirically for the clinical diagnosis of sepsis.

When LPs are performed after the administration of antibiotics, a clinical evaluation of the presence of meningitis is made, taking into account the blood culture results, the CSF cell count, protein, and glucose levels as well as the clinical scenario. We recommend sending two separate CSF samples for cell count from the same LP in these circumstances to account for the role of possible fluctuation in CSF cell count measurements. Interpretation of CSF WBC values can be challenging. **Normal CSF WBC counts** in term, noninfected infants are variable, with most studies reporting a mean of <20 cells/mm^3, with ranges of up to 90 cells, and widely varying levels of polymorphonuclear cells on the differential. One recent study assessed CSF parameters among neonate without bacterial or viral blood or CSF infection, in CSF samples with <500 red blood cell (RBC)/mm^3. This study reported a mean CSF WBC 3/mm^3 with an upper reference limit of 14 cells; no significant differences were found between term and preterm infants. Another study of culture-proven, early-onset meningitis demonstrated only 80% sensitivity and specificity for CSF WBC values >20. The presence of blood in the CSF, due to subarachnoid or intraventricular hemorrhage, or to blood contamination of CSF samples by "traumatic" LPs, can yield abnormal cell counts that may be due to the presence of blood in the CSF rather than true infection. Adjustment of the WBC in "traumatic" LP results (those with >500 RBC/mm^3) using different algorithms has not been shown to substantially improve the sensitivity and specificity of the WBC in predicting culture-confirmed meningitis.

H. Approach for the evaluation of the infant born at ≥35 weeks' gestation at risk for EOS. Assessing risk of EOS among term and late-preterm infants is a common clinical task in birth centers. Depending on the local structure of neonatal care, EOS evaluation may be performed by pediatric residents, community pediatricians, newborn hospitalists, midwives, and/or neonatal intensive care specialists. The use of a written protocol to guide assessment can ensure consistency among caregivers. Such a guideline should (i) establish criteria for EOS evaluation, (ii) specify laboratory testing standards, and (iii) provide guidance for empiric administration of antibiotics. The American Academy of Pediatrics (AAP) published two updated consensus EOS management statements in 2018, one for infants born ≥35 weeks' and the other <35 weeks' gestation. Three basic approaches are recommended for evaluating infants born ≥35 weeks' gestation (Table 49.2).

Table 49.2. EOS Risk Assessment among Infants Born ≥35 0/7 Weeks' Gestation

	Categorical Approach	Neonatal Early-Onset Sepsis Calculator*	Observation Only
Risk factors considered	■ Signs of newborn clinical illness (unspecified) ■ Maternal intrapartum temperature ≥38°C ■ Inadequate intrapartum antibiotic prophylaxis in a GBS-colonized mother	■ GA at birth ■ Highest maternal intrapartum temperature ■ Duration of ROM ■ Maternal GBS status ■ Type and duration of intrapartum antibiotics ■ Infant clinical status over the first 6–12 hours of age	■ Signs of newborn clinical illness (unspecified) ■ Maternal intrapartum temperature ≥38°C ■ Inadequate intrapartum antibiotic prophylaxis in a GBS-colonized mother
Infant clinical status	Determination of what constitutes "signs of newborn clinical illness" is left to local center determination	Guidance on content and duration of vital signs and specifics of clinical status provided by the decision tool to determine if infant is well appearing, equivocal, or clinically ill	Determination of what constitutes "signs of newborn clinical illness" is left to local center determination.

(continued)

Table 49.2. EOS Risk Assessment among Infants Born ≥35 0/7 Weeks' Gestation *(Continued)*

	Categorical Approach	Neonatal Early-Onset Sepsis Calculator*	Observation Only
Recommended clinical actions	■ Blood culture and empiric antibiotics recommended for infants □ With clinical illness □ Born to mothers with intrapartum temperature ≥38°C/100.4°F ■ Clinical observation for 24–36 hours in the birth hospital for infants born to mothers with inadequate GBS prophylaxis	Recommended actions are provided based on final risk estimate at birth as well as the risk estimate adjusted for clinical condition.	■ Blood culture and empiric antibiotics recommended for infants with clinical illness ■ At-risk infants who appear well at birth should have serial, structured clinical assessments from birth through 36–48 hours of age and undergo EOS evaluation if signs of illness develop

*Neonatal Early-Onset Sepsis Calculator found at https://neonatalsepsiscalculator.kaiserpermanente.org/.

EOS, early-onset sepsis; GBS, group B *Streptococcus*; GA, gestational age; ROM, rupture of membranes.

Source: Adapted from Puopolo KM, Benitz WE, Zaoutis TE; for Committee on Fetus and Newborn; Committee on Infectious Diseases. Management of neonates born at ≥35 0/7 weeks' gestation with suspected or proven early-onset bacterial sepsis. *Pediatrics*. 2018;142(6):e20182894.

Each approach has its advantages and limitations, and each will result in different proportions of newborns undergoing laboratory evaluation and empirically treated with antibiotics. At our institutions, we use the neonatal EOS calculator (https://neonatalsepsiscalculator.kaiserpermanente.org) approach. The sepsis risk calculator is a clinical decision tool based on two multivariate prediction models developed using a cohort of >600,000 infants born ≥34 weeks' gestation. This tool takes a Bayesian perspective, beginning with the baseline risk in the population, and updating individual infant EOS risk using objective data available at the time of birth, combined with the infant's evolving clinical condition in the first 6 to 12 hours after birth. Objective data considered include gestational age, maximum maternal intrapartum temperature during labor, duration of ROM, maternal GBS colonization status, and duration and type of maternal intrapartum antibiotic exposure. The newborn clinical condition is assessed by specific vital sign parameters as well as by need for supplemental oxygen and/or respiratory support, hemodynamic instability, and signs of encephalopathy/perinatal depression. The diagnostic performance of the calculator and safety for EOS clinical management was reported in a study including >200,000 live births, conducted in a large integrated health care system. The study found significant reduction in use of empiric antibiotics without change in detection of culture-confirmed cases or in hospital readmissions. Three issues should be considered with use of the sepsis risk calculator approach. First, the calculator website provides different options to account for differences in the baseline EOS risk within a specific newborn population. Second, the thresholds for specific clinical actions provided on the calculator website may not be universally appropriate; the tool may be best used with consideration of the local structure of newborn care. Finally, and most important, the multivariate models were derived using a cohort that reflects U.S. obstetric practice. These models are unlikely to be applicable to low-resource settings.

I. **Algorithm for the evaluation of the infant born at <35 weeks' gestation at risk for EOS.** Preterm infants are at a significantly greater risk for culture-confirmed EOS and for mortality from EOS compared to those born at term. In a multicenter study of >40,000 VLBW infants born from 2009 to 2014, 78% of VLBW infants and 88% of extremely low BW (ELBW, BW <1,000 g) infants were administered empiric antibiotics within 3 days of birth due to risk of EOS. Delivery criteria can be used to identify preterm infants born in a context with minimal exposure to factors that promote the pathogenesis of EOS (Fig. 49.1). To meet criteria for low-risk preterm delivery, all the low-risk criteria must apply. Infants born by induced labor for maternal or fetal indications are exposed to the factors that promote the pathogenesis of EOS; the infant's clinical condition and adequacy of indicated GBS prophylaxis should determine the need to rule out EOS. Preterm infants at highest risk of EOS are those born due to concern for intra-amniotic infection (clinical chorioamnionitis); one study of 15,433 infants born <29 weeks' gestation at National Institutes of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) centers demonstrated that infants born to women with clinical concern for infection confirmed after birth by identification of histologic

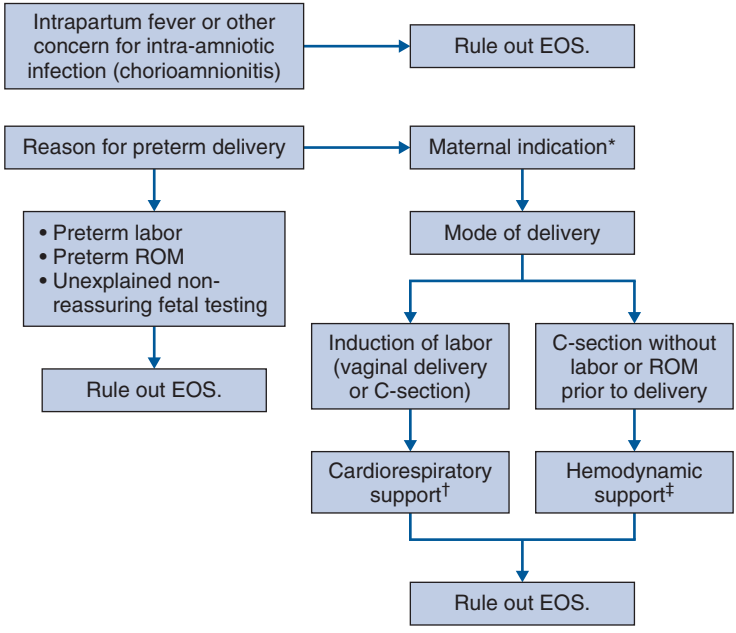

Figure 49.1. Early-onset sepsis (EOS) risk assessment for infants born ≤34 6/7 weeks' gestation. *Examples of maternal noninfectious indications for delivery may include preeclampsia; maternal chronic illness such as sickle cell disease, renal failure, or cancer. Planned delivery for fetal growth restriction may also be included in this category. †Cardiorespiratory support includes need for supplemental oxygen >1 hour after birth, continuous positive airway pressure (CPAP), mechanical ventilation, and/or need for hemodynamic support. ‡Hemodynamic support includes volume or pressor support for poor perfusion or low blood pressure (without clear indication such as acute anemia). ROM, rupture of membranes. (Reproduced from Mukhopadhyay S, Sengupta S, Puopolo KM. Challenges and opportunities for antibiotic stewardship among preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2019;104[3]:F327–F332. Copyright © 2019 Author(s), with permission from BMJ Publishing Group Ltd.)

chorioamnionitis on placental pathology are at the highest risk of EOS. AAP guidance supports care of low-risk preterm infants with close monitoring and without routine initiation of empiric antibiotics. We use a local algorithm based on Figure 49.1. We compared 727 VLBW infants managed at our center before and 381 VLBW infants managed after adoption of this approach. We observed significant decreases in initiation of empiric antibiotics among the 381 infants, without adverse events.

J. Specific organisms causing EOS. The bacterial species responsible for EOS vary by locality and time period. In the United States since the 1980s, GBS has been the leading cause of neonatal EOS. Despite the implementation of screening-based GBS IAP, it remains the leading cause of EOS in term infants. However, coincident with the increased use of GBS IAP, gram-negative enteric bacteria have become the leading cause of EOS in

preterm infants. Enteric bacilli causing EOS include *E. coli*, other *Enterobacteriaceae* (*Klebsiella*, *Pseudomonas*, *Haemophilus*, and *Enterobacter* spp.), and the anaerobe *B. fragilis*. Less common organisms that can cause serious early-onset disease include *Listeria monocytogenes* and *Citrobacter diversus*. Staphylococci and enterococci can be found in EOS but more commonly cause nosocomial sepsis and are discussed under that heading in the subsequent text. Fungal species can cause EOS primarily in very preterm infants; this is also discussed separately in the subsequent text.

1. **GBS.** GBS (*Streptococcus agalactiae*) frequently colonizes the human genital and gastrointestinal tracts and the upper respiratory tract in young infants. In addition to causing neonatal disease, GBS is a frequent cause of urinary tract infection (UTI), chorioamnionitis, postpartum endometritis, and bacteremia in pregnant women. There is some evidence suggesting that vaginal colonization with a high inoculum of GBS during pregnancy contributes to premature birth.

   a. Microbiology. GBS are facultative diplococci that are easily cultivated in selective laboratory media. GBS are primarily identified by the Lancefield group B carbohydrate antigen and are further subtyped into 10 distinct serotypes (types Ia, Ib, II to IX) by analysis of capsular polysaccharide composition. Serotype data from 1,743 neonatal patients with GBS disease was described as part of the CDC multistate surveillance report. More than 99% of neonatal diseases in the United States were caused by types Ia, Ib, II, III, IV, and V GBS. Type III GBS are associated with the development of meningitis and caused 27% of early-onset GBS disease and 56% of late-onset GBS disease.

   b. Pathogenesis. Neonatal GBS infection is acquired *in utero* or during passage through the birth canal. Because not all women are colonized with GBS, documented colonization with GBS is the strongest predictor of GBS EOS. Approximately 20% to 30% of American women are colonized with GBS at any given time. A longitudinal study of GBS colonization in a cohort of primarily young, sexually active women demonstrated that 45% of initially GBS-negative women acquired colonization at some time over a 12-month period. In the absence of IAP, approximately 50% of infants born to mothers colonized with GBS are found to be colonized with this organism at birth. Approximately 1% to 2% of all colonized infants develop invasive GBS disease, with clinical factors such as gestational age and duration of ROM contributing to risk for any individual infant (see subsequent text). Lack of maternally derived, protective capsular polysaccharide-specific antibody is associated with the development of invasive GBS disease. Other factors predisposing the newborn to GBS disease are less well understood, but relative deficiencies in complement, neutrophil function, and innate immunity may be important. GBS express multiple virulence determinants associated with epithelial colonization, host tissue invasion, and immune evasion; these include polysaccharide capsule, lipoteichoic acid, surface proteins and adhesins, pili proteins, and beta-hemolysin and other secreted toxins, many of which are expressed in conjunction with environment-responsive two-component regulatory systems.

Table 49.3. Risk Factors for Early-Onset Group B *Streptococcus* (GBS) Sepsis in the Absence of Intrapartum Antibiotic Prophylaxis

Risk Factor	Odds Ratio (95% CI)
Maternal GBS colonization	204 (100–419)
BW <1,000 g	24.8 (12.2–50.2)
BW <2,500 g	7.37 (4.48–12.1)
Prolonged ROM >18 hours	7.28 (4.42–12.0)
Chorioamnionitis	6.42 (2.32–17.8)
Intrapartum fever >37.5°C	4.05 (2.17–7.56)

CI, confidence interval; BW, birth weight; ROM, rupture of membranes.

Source: Data from Benitz WE, Gould JB, Druzin MML. Risk factors for early-onset group B streptococcal sepsis: estimation of odds ratios by critical literature review. *Pediatrics* 1999;103(6):e77.

c. Clinical risk factors for GBS EOS (Table 49.3). GBS bacteriuria during pregnancy is associated with heavy colonization of the rectovaginal tract and is considered a significant risk factor for EOS. Black race and maternal age <20 years are associated with higher rates of GBS EOS, although it is not entirely clear whether this reflects only higher rates of GBS colonization in these populations. Multiple gestation is **not** an independent risk factor for GBS EOS.

d. Prevention of GBS infection. Multiple trials have demonstrated that the use of intrapartum penicillin or ampicillin significantly reduces the rate of neonatal colonization with GBS and the incidence of early-onset GBS disease. IAP for the prevention of GBS EOS can be administered to pregnant women during labor based on (i) specific risk factors for early-onset GBS infection or (ii) the results of antepartum screening of pregnant women for GBS colonization. Beginning in 1996, the CDC issued guidelines recommending the use of IAP to prevent neonatal GBS EOS. Updated guidelines by the American College of Obstetricians and Gynecologist (ACOG) and AAP were published 2019 to 2020. These guidelines recommend universal screening of pregnant women for GBS by vaginal-rectal swab culture at 36 0/7 to 37 6/7 weeks' gestation and management of IAP based on screening results. Pregnant women with documented GBS bacteriuria during pregnancy or who previously delivered an infant who developed invasive GBS disease need not be screened because these women should be given IAP **regardless of current GBS colonization status**. IAP is also recommended for all women who present in preterm labor with unknown GBS status. For women in labor at ≥37 weeks' gestation with unknown GBS status, IAP is recommended

if intrapartum maternal fever ≥100.4°F/38°C occurs, or if duration of ROM is ≥18 hours prior to delivery, and can be considered in the absence of these factors if the woman was known to be GBS colonized in a prior pregnancy. Penicillin, ampicillin, and cefazolin administered >4 hours prior to delivery are considered adequate IAP. There is no data directly supporting the efficacy of any antibiotic other than penicillin, ampicillin, or cefazolin for GBS IAP, highlighting the challenge to providing adequate IAP to the roughly 10% of women who report penicillin allergy. ACOG recommends consideration of skin testing to confirm allergy history for pregnant women, and documentation of allergy history on laboratory requisitions to ensure antibiotic susceptibility testing of GBS isolates. Because a significant proportion of GBS isolates (15% to 40%) are resistant to macrolide antibiotics, it is recommended that any GBS isolates identified on screening of penicillin-allergic women be tested for antibiotic susceptibility including specific testing for inducible clindamycin resistance. For the woman with a non–life-threatening penicillin allergy, cefazolin is the recommended antibiotic for IAP. If a woman has a documented history of anaphylactic penicillin or cephalosporin allergy (including urticaria, angioedema, and/or respiratory distress), clindamycin is recommended if the colonizing isolate is fully susceptible to this antibiotic; otherwise, vancomycin is the recommended agent. For the purpose of infant management; however, the administration of clindamycin or vancomycin is not considered adequate IAP.

e. Current status of GBS EOS. Prior to the widespread us of IAP, GBS EOS incidence in the United States in 1993 was 1.7 cases per 1,000 live births. In 2018, the incidence of GBS EOS was 0.25 cases per 1,000 live births; no significant difference in incidence occurred over the prior 10 years. There is ongoing racial disparity with the incidence among Black infants roughly 3 times that of White infants. Approximately one-quarter of all GBS EOS now occurs among infants born at <37 weeks' gestation. With the use of antenatal screening, we have reported that most GBS EOS in term infants now occurs in infants born to women with **negative** antepartum screens for GBS colonization; 40% of cases identified in 2006 to 2015 CDC surveillance occurred among infants born to mother with negative antenatal testing. These "false-negative" screens may be due to improper culture technique or acquisition of GBS between the time of culture and start of labor. Antenatal bacterial culture to identify maternal GBS colonization remains the recommended screening approach. Multiple nucleic-acid amplification tests (NAATs) are available for rapid identification of GBS from vaginal-rectal swabs at point of care, or from bacterial cultures after a period of growth in enrichment broth. ACOG currently recommends use of NAAT for point-of-care testing (where available) only for women who present in labor with unknown GBS status. Due to concern for false-negative results when used in this manner, IAP is still recommended if risk factors develop during labor. Use of NAAT after an 18- to 24-hour period of enrichment broth culture is acceptable practice. However, if antibiotic susceptibility testing is needed due to maternal penicillin allergy, full specimen processing by subculture onto agar plates is required.

f. Evaluation of infants after maternal GBS IAP. All current approaches to EOS risk assessment for term and preterm infants account for maternal GBS status and for the content and timing of intrapartum antibiotics. **Only the administration of penicillin, ampicillin, or cefazolin ≥4 hours prior to delivery constitutes adequate IAP.**

g. Treatment of infants with invasive GBS disease. When GBS is identified as the causative organism in EOS, antibiotic treatment should be narrowed to ampicillin or penicillin G alone. Dosing is based on birth gestation and postnatal age (Table 49.4). The total duration of therapy should be at least 10 days for sepsis without a focus, 14 to 21 days for meningitis, and 28 days for osteomyelitis. Bone and joint infections that involve the hip or shoulder require surgical drainage in addition to antibiotic therapy.

h. Recurrent GBS infection. Recurrent GBS infections are not infrequent, with reported incidences ranging from 1% to 6%. Infants usually fail to have a specific antibody response after infection with GBS, and GBS can be isolated from mucosal surfaces of infants even after appropriate antibiotic treatment for invasive disease. Occasionally, reinfection with a new strain of GBS occurs. Treatment of recurrent GBS infections is the same as for primary infection except that susceptibility testing of the GBS strain to penicillin is recommended if not routinely performed. Rifampin, which eliminates colonization in other infections such as

Table 49.4. Antibiotic Therapy for Neonatal GBS Disease

	GA ≤34 weeks		GA >34 weeks	
	PNA ≤7 days	PNA >7 days	PNA ≤7 days	PNA >7 days
Bacteremia				
Ampicillin	50 mg/kg every 12 hours	75 mg/kg every 12 hours	50 mg/kg every 8 hours	50 mg/kg every 8 hours
Penicillin G	50,000 U/kg every 12 hours	50,000 U/kg every 8 hours	50,000 U/kg every 12 hours	50,000 U/kg every 8 hours
Meningitis				
Ampicillin	100 mg/kg every 8 hours	75 mg/kg every 6 hours	100 mg/kg every 8 hours	75 mg/kg every 6 hours
Penicillin G	150,000 U/kg every 8 hours	125,000 U/kg every 6 hours	150,000 U/kg every 8 hours	125,000 U/kg every 6 hours

GBS, group B *Streptococcus*; GA, gestational age; PNA, postnatal age.

Source: Adapted with permission of American Academy of Pediatrics: from Table 4.2. Antibacterial drugs for neonates (<28 postnatal days of age). In: Kimberlin DW, Brady MT, Jackson MA, et al, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:915–919; permission conveyed through Copyright Clearance Center, Inc.

meningococcal disease, does not reliably eradicate mucosal colonization with GBS. In addition, neither maternal GBS IAP nor neonatal antibiotic administration prevents the development of primary late-onset GBS disease (infection occurring ≥7 days of life).

2. ***E. coli* and other enteric gram-negative bacilli.** With the implementation of IAP against GBS, an **increasing proportion** of EOS cases are caused by gram-negative organisms. Whether GBS IAP policies are contributing to an absolute increase in the **incidence** of EOS caused by gram-negative organisms, and in particular, of ampicillin-resistant gram-negative organisms, is a matter of ongoing controversy. **However, increases in non-GBS EOS and ampicillin-resistant EOS are reported in among VLBW infants.** In a report of NICHD NRN data from 2015 to 2017, 83% of *E. coli* EOS among preterm infants were resistant to ampicillin. Approximately 8% isolates from all EOS cases were resistant to both ampicillin and gentamicin. Trends in the microbiology of EOS likely vary to some extent by geographic region and center and may be influenced by local obstetrical practices as well as by local variation in indigenous maternal bacterial flora.

   a. Microbiology and pathogenesis. *E. coli* are aerobic gram-negative rods found universally in the human intestinal tract and commonly in the human vagina and urinary tract. There are hundreds of different lipopolysaccharide (LPS), flagellar, and capsular antigenic types of *E. coli*, but EOS *E. coli* infections, particularly those complicated by meningitis, are primarily due to strains with the K1-type polysaccharide capsule. *E. coli* with the K1 antigen are resistant to the bactericidal effect of normal human serum; strains that possess both a complete LPS and K1 capsule have been shown to specifically evade both complement-mediated bacteriolysis and neutrophil-mediated killing. The K1 antigen has been shown to be a primary factor in the development of meningitis in a rat model of *E. coli* infection. The K1 capsule is a poor immunogen and despite widespread carriage of this strain in the population, there is usually little protective maternal antibody available to the infant. In addition to the K1 antigen, surface fimbriae, or pili, have been associated with adherence to vaginal and uroepithelial surfaces and may also function as a virulence mechanism in EOS.

   b. Treatment. When there is a strong clinical suspicion for sepsis in a critically ill infant, the possibility of ampicillin-resistant *E. coli* must be considered. The addition of a third- or fourth-generation cephalosporin such as or ceftazidime or cefepime is recommended in this setting. *E. coli* bacteremia should be treated with a total of 14 days of antibiotic according to the identified sensitivities. *E. coli* meningitis is treated with a 21-day course of an appropriate antibiotic as indicated by susceptibility data.

3. ***L. monocytogenes.*** Although uncommon, *L. monocytogenes* deserves special note due to its unique role in pregnancy. *L. monocytogenes* are gram-positive, β-hemolytic, motile bacteria that frequently cause disease in animals and most commonly infect humans through the ingestion of contaminated food. These bacteria do not cause significant disease in immunocompetent adults but can cause severe illness in the elderly, in immunocompromised patients, in pregnant women and their fetuses,

and in newborns. There is both preclinical animal model and human epidemiologic evidence indicating that *L. monocytogenes* is particularly virulent in pregnancy. The bacteria readily invade the placenta and can infect the developing fetus either by ascending infection, direct tissue invasion, or hematogenous spread, causing spontaneous abortion or preterm labor and delivery, and often fulminant early-onset disease. Like GBS, *L. monocytogenes* can also cause late-onset neonatal infection, the pathogenesis of which is not fully understood. More than 90% of late-onset infections are complicated by meningitis. Listeriosis is a reportable disease: the annual incidence of laboratory-confirmed infection in the United States is 0.24 cases/100,000 population, but the true incidence is estimated to be at least double this finding. Most cases occur among persons 65 years old or older. Pregnant women are thought to have 10 times the attack rate of nonpregnant persons, but the true incidence of listeriosis in pregnancy is difficult to determine because many cases are undiagnosed when they result in spontaneous abortion of the previable fetus. In 2014, 15% of cases in CDC active surveillance were associated with pregnancy. Hispanic ethnicity was found in 47% of cases. Fetal death was associated with 24% of reported cases, whereas 6% of reported cases resulted in death of a live-born infant. The frequency of neonatal EOS among live births caused by *Listeria* is estimated to be approximately 1 to 2 cases per 100,000 live births. Approximately two to three outbreaks of listeriosis of varying severity are reported each year in the United States with sources including cheese, cantaloupes, pasteurized milk, hard-boiled eggs, and sprouts. Infection in pregnant women may not be recognized or may cause a mild febrile illness with or without gastrointestinal symptoms before resulting in pregnancy loss or preterm labor.

a. Microbiology and pathogenesis. *L. monocytogenes* are distinguished from other gram-positive rods by tumbling motility that is most prominent at room temperature. The organisms can be gram variable and, depending on growth stage, can also appear cocci-like and can therefore be initially misdiagnosed on a Gram stain. *L. monocytogenes* is an intracellular pathogen that can invade cells as well as persist in phagocytic cells (monocytes, macrophages). *Listeria* possess a variety of virulence factors, including surface proteins that promote cellular invasion, and enzymes (listeriolysin O, phospholipase) that enhance the ability of the organism to persist intracellularly. On pathologic examination of tissues infected with *Listeria*, miliary granulomas and areas of necrosis and suppuration are seen. The liver is prominently involved. Both T cell–mediated killing as well as immunoglobulin M (IgM) complement–mediated killing is involved in host response to listeriosis. Deficiencies in both of these arms of the newborn immune system may contribute to the virulence of *L. monocytogenes* in the neonate; similarly, it is hypothesized that local downregulation of the immune response in the pregnant uterus may account for proliferation of the bacteria in the placenta.

b. Treatment. EOS due to *L. monocytogenes* is treated with ampicillin and gentamicin for 14 days; meningitis is treated for 21 days. *L. monocytogenes* is resistant to cephalosporins. In the case of meningitis, it is

recommended that LPs be repeated daily until sterilization of the CSF is achieved. Additional therapy with rifampin or trimethoprim-sulfamethoxazole as well as cerebral imaging is recommended if the organism persists in the CSF for longer than 2 days. *L. monocytogenes* can persist in the stool of preterm infants even after adequate systemic treatment of the infection; thus, proper infection control measures must be observed to prevent nosocomial spread of the organism.

4. **Other organisms responsible for EOS.** Bacteria causing EOS vary with time and locality. Beyond GBS and *E. coli*, there are a number of pathogens that cause EOS in the United States in the era of IAP for GBS. Viridans streptococci (species such as *Streptococcus bovis*, *Streptococcus mitis*, *Streptococcus oralis*, and *Streptococcus sanguis*, which are part of the oral flora), enterococci, and *S. aureus* are next in frequency. A variety of gram-negative organisms (*Klebsiella*, *Haemophilus*, *Enterobacter*, and *Pseudomonas* spp.) and the anaerobe *B. fragilis* cause most of the remaining infections. Gram-negative organisms, especially *E. coli* and *Klebsiella*, predominate in some Asian and South American countries.

K. LOS. Late-onset neonatal sepsis is defined as occurring from 7 to 90 days after birth. LOS can be divided into two distinct entities: disease occurring in otherwise healthy term infants in the community and disease affecting premature infants in the neonatal intensive care unit (NICU). The latter is often referred to as hospital-acquired infection because the risk factors for LOS in premature infants are related to the necessities of their care (i.e., the presence of central lines) and the bacteria that cause LOS are often acquired in the NICU. For epidemiologic purposes, LOS infections occurring in VLBW infants in the NICU are defined as those occurring at >72 hours after birth. This section is primarily devoted to LOS in the NICU population, but disease in otherwise **healthy term and near-term infants** deserves mention. In these infants, LOS is largely caused by gram-negative species such as *E. coli* and *Klebsiella* spp. and GBS. Causes of bacteremia in older infants (such as *Streptococcus pneumoniae* and *Neisseria meningitidis*) occur less frequently. The **risk factors for late-onset GBS disease** are not as well defined as for early-onset disease but like early-onset disease are related to prematurity, young maternal age, colonization of the infant from maternal and community (or less commonly, hospital) sources, and lack of maternally derived protective antibody. The use of IAP for GBS has had no significant impact on the rate of GBS LOS; the incidence of GBS LOS was reported to be 0.31 cases per 1,000 live births from 2006 to 2015. Preterm infants account for a disproportionate number of GBS late-onset infections, with approximately 40% to 50% of late-onset GBS cases occurring in infants born at <37 weeks' gestation and increasing risk associated with decreasing gestational age at delivery. GBS LOS is more often complicated by meningitis than early-onset disease and is predominantly caused by polysaccharide serotype III strains. Although mortality from GBS LOS is low (1% to 5% in term and preterm infants, respectively), sequelae in survivors of GBS meningitis can be severe. A study of GBS meningitis occurring in infants born at ≥36 weeks' gestation from 1998 to 2006 revealed that a quarter of all infants died or survived with significant neurologic impairment.

Gram-negative bacteremia is often associated with UTI. Different series report 20% to 30% of UTIs in infants younger than 1 month of age are complicated by bacteremia. Mortality is low if promptly treated, and sequelae are few unless meningitis occurs. *L. monocytogenes* can also cause late-onset disease, with onset commonly by 30 days of life and has a high case fatality rate of up to 30%. Late-onset listeriosis is frequently complicated by meningitis, but unlike late-onset GBS meningitis, the morbidity and long-term sequelae are infrequent if the disease is diagnosed and treated in timely fashion.

Term infants with LOS generally present with fever and/or poor feeding and lethargy to the private pediatrician or emergency department. Evaluation in the infant younger than 3 months old in most centers includes at minimum CBC with white cell differential; urinalysis; CSF cell count; glucose and protein; and cultures of blood, urine, and CSF. Chest radiograph and PCT are used in some centers. Different criteria have been published to identify febrile young infants at low-enough risk of invasive infection to justify outpatient management. Infants younger than 1 month are frequently hospitalized for empiric intravenous (IV) therapy that includes coverage for GBS, *Listeria*, and gram-negative organisms (commonly ampicillin and cefotaxime).

L. Epidemiology of LOS in premature infants. Most LOS occurs in the NICU among low BW infants. NICHD NRN data from 2008 to 2012 found 24% of VLBW infants had at least one episode of blood culture–confirmed infection beyond 3 days of age. The incidence of infection varied with gestational age at birth, ranging from 46% at 23 weeks' to 12% at 28 weeks' gestation. NRN data from 2000 to 2011 revealed a decrease in LOS incidence among ELBW infants from 41% to 34%, but LOS attributable remained unchanged at 18%. Mortality among ELBW infants was 39% among those with late-onset fungal infections.

M. Risk factors for LOS. A number of clinical factors are associated with an increased risk of LOS. The incidence of LOS is inversely related to BW. The risk of developing LOS associated with central catheters, parenteral nutrition, and mechanical ventilation are all increased with longer duration of these therapies.

N. Microbiology of LOS. Nearly half of cases of LOS are caused by CONS in the United States. In the NRN 2000 to 2011 study, 20% of cases of LOS were caused by other gram-positive organisms (*S. aureus*, *Enterococcus*, GBS), 19% by gram-negative organisms (*E. coli*, *Klebsiella*, *Pseudomonas*, *Enterobacter*, and *Serratia*), and 6% by fungal species (*Candida albicans* and *Candida parapsilosis*). The distribution of organisms causing LOS may vary significantly at individual centers. Awareness of local variation in the microbiology of LOS is important for determining appropriate empiric antibiotic therapy for the acutely ill infant in whom LOS is suspected.

1. **CONS.** CONS are a heterogeneous group of gram-positive organisms with a structure similar to *S. aureus*, but these organisms lack protein A and have different cell wall components. *Staphylococcus epidermidis* is the primary cause of NICU disease. CONS universally colonize the skin of NICU patients. They are believed to cause bacteremia by first

colonizing the surfaces of central catheters. A polysaccharide surface adhesin (PSA), as well as several other surface components, have been implicated in adherence to and colonization of the catheter surface; subsequent biofilm and slime production inhibit the ability of the host to eliminate the organism. Most CONS are resistant to penicillin, semisynthetic penicillins, and gentamicin, and empiric treatment for LOS in the NICU usually includes vancomycin. CONS disease is rarely fatal even to the VLBW infant and rarely, if ever, causes meningitis or site-specific disease. However, CONS disease can cause systemic instability resulting in temporary cessation of enteral feeding and/or escalation of ventilator support and is associated with prolonged hospitalization and poorer neurodevelopmental outcome.

2. ***S. aureus.*** *S. aureus* is an encapsulated gram-positive organism that elaborates multiple adhesins, virulence-associated enzymes, and toxins to cause a wide range of serious disease, including bacteremia, meningitis, cellulitis, omphalitis, osteomyelitis, and arthritis. *S. aureus* is distinguished from CONS by the production of coagulase and by the presence of protein A, a component of the cell wall that contributes to virulence by binding to the Fc portion of immunoglobulin G (IgG) antibody and blocking opsonization. LOS caused by *S. aureus* can result in significant morbidity. Disease is frequently complicated by focal site infections (soft tissue, bone, and joint infections are commonly observed in neonates) and marked by persistent bacteremia despite antibiotic administration. Joint infections often require open surgical drainage and can lead to joint destruction and permanent disability. The treatment of methicillin-sensitive *S. aureus* (MSSA) requires the use of semisynthetic penicillins such as nafcillin or oxacillin. Rifampin may be added for persistent bacteremia in addition removing potentially infected foreign body in the patient such as an indwelling catheter. Treatment with vancomycin is not recommended for MSSA to prevent emergence of resistance and because semisynthetic penicillins have greater bactericidal activity.

   Methicillin-resistant *S. aureus* (MRSA) is an increasingly recognized pathogen in NICUs. A multicenter study of hospitalized newborns at 328 U.S. centers from 1997 to 2012 found *S. aureus* infection occurred in approximately 5 per 1,000 infants, with one-quarter to one-third due to MRSA. An NRN study of infants born with BW 400 to 1,500 g from 2006 to 2008 found 3.7% had LOS due to *S. aureus*; roughly one-third of these infections were due to MRSA. Mortality was considerable, occurring in approximately 25% of infants infected with either MSSA or MRSA. Resistance to semisynthetic penicillins is mediated by chromosomal acquisition of the *mecA* gene, found on different types of staphylococcal chromosomal cassette *mec* (SCC*mecA*) elements. The *mecA* gene encodes a modified penicillin-binding protein (PBP) with a low affinity for methicillin. Once acquired, the modified PBP replaces similar proteins on the bacterial cell membrane and results in resistance to all β-lactam antibiotics. The emergence of MRSA infections in NICUs appears to track the increase in these infections in both general hospital settings and in the community. MRSA isolates can be grouped

as hospital-associated MRSA (HA-MRSA) or community-associated MRSA (CA-MRSA) in origin. Uniform resistance to all common antibiotics except for vancomycin characterizes HA-MRSA and most HA-MRSA carry SCC*mec* type II or III. Community-acquired isolates are usually resistant only to β-lactam antibiotics and erythromycin and usually carry SCC*mec* type IV or V. Distinguishing between the two types of organisms can be important for determining the source of epidemic outbreaks of MRSA disease within individual units as well as for developing effective infection control measures. Whatever the source of the organism, however, it can be rapidly spread within the NICU by nosocomial transmission on the hands of caregivers. Infection control measures including identification of colonized infants by routine surveillance and cohorting and isolation of colonized infants may be required to prevent spread and persistence of the organism. At our center, we administer nasal mupirocin to MRSA-colonized infants to decrease colonization burden, if the infant requires respiratory support or central venous access. Term infants and preterm infants older than 2 months of age can be treated with chlorhexidine baths to decrease (or prevent) MRSA colonization. MRSA infections usually require treatment with **vancomycin**. As with MSSA, MRSA infections can be complicated by deep tissue involvement and persistent bacteremia that may require surgical debridement for resolution. Although it cannot be used as a single agent, rifampin can be a helpful adjunctive therapy for persistent MRSA infection. Consultation with an infectious disease specialist is recommended regarding the utility of adding newer gram-positive antibiotics (the oxazolidinone antibiotic linezolid or the lipopeptide antibiotic daptomycin) to eradicate persistent MRSA bacteremia.

3. **Enterococci.** Formerly categorized as members of group D streptococci, both *Enterococcus faecalis* and *Enterococcus faecium* cause LOS in premature infants. These organisms are associated with indwelling catheters; they are encapsulated organisms that produce both biofilm and slime and can adhere to and persist on catheter surfaces as described in the preceding text for CONS. Although disease can be complicated by meningitis and is sometimes associated with NEC, enterococcal LOS is associated with low overall mortality. Enterococci are intrinsically resistant to cephalosporins and may be resistant to penicillin G and ampicillin; treatment requires the synergistic effect of an aminoglycoside with ampicillin or vancomycin. Vancomycin-resistant enterococci (VRE) present a significant problem in adult intensive care settings, and outbreaks have occurred in NICUs as well. Linezolid, daptomycin, and quinupristin/dalfopristin (Synercid) have variable activity against VRE. Linezolid is approved for use in neonates and is effective against vancomycin-resistant *E. faecalis* and *E. faecium*. VRE of *faecium* origin can be treated with quinupristin/dalfopristin, but this combination is not effective against *E. faecalis*. Treatment decisions should be made in consultation with infectious diseases experts. VRE outbreaks may also require the institution of infection control measures (surveillance to identify colonized infants, isolation and cohorting of those colonized) to control spread and persistence of the organism.

4. **Gram-negative organisms.** LOS caused by gram-negative organisms is complicated by a higher mortality rates in the reported cohorts compared to gram-positive sepsis. *E. coli* was discussed under EOS (see section I.J.2).

a. *Pseudomonas aeruginosa.* Although responsible for <5% of LOS in NRN cohorts of low BW infants, mortality associated with *P. aeruginosa* sepsis in such infants is high (approximately 50% to 75% in reported cohorts). A number of bacterial factors, including LPS, mucoid capsule, adhesins, invasins, and toxins (notably exotoxin A), contribute to its extreme virulence in premature infants as well as in debilitated adults and burn victims. Both LPS and the mucoid capsule help the organism avoid opsonization and secreted proteases inactivate complement, cytokines, and immunoglobulin. The lipid A moiety of LPS (endotoxin) causes the typical aspects of gram-negative septicemia (i.e., hypotension, DIC). Exotoxin A is antigenically distinct from diphtheria toxin but acts by the same mechanism: adenovirus death protein (ADP)-ribosylation of eukaryotic elongation factor 2 results in inhibition of protein synthesis and cell death. *P. aeruginosa* is present in the intestinal tract of approximately 5% of healthy adults but colonizes premature infants at much higher rates due to nosocomial acquisition of the bacteria. Selection of the bacteria, likely due to the resistance of *Pseudomonas* to most common antibiotics, also plays a role in colonization; prolonged exposure to IV antibiotics is a risk factor for LOS with *Pseudomonas*. *Pseudomonas* can be found in environmental reservoirs in intensive care units (ICUs) (i.e., sinks, respiratory equipment), and outbreaks of nosocomial disease have been linked to both environmental sources and spread by the hands of health care workers. Treatment requires a combination of two agents active against *Pseudomonas*, such as ceftazidime, piperacillin/tazobactam, gentamicin, or tobramycin. Generally, a β-lactam–based antibiotic combined with an aminoglycoside is preferred; however, both extended-spectrum β-lactamases (ESBL) and constitutive AmpC-type β-lactamases are reported in pseudomonal species (see subsequent text), and treatment must be guided by isolate antibiotic sensitivity testing. A survey of neonatologists' practices in the treatment of LOS reveals that the most common antibiotics empirically used are vancomycin and gentamicin. When an infant presents as severely ill or when the infant becomes acutely sicker during or after standard antibiotic treatment, consideration should be given to empiric coverage for *Pseudomonas* until blood culture results are available.

b. *Enterobacter* spp. Like *E. coli*, *Enterobacter* spp. are LPS-containing, gram-negative rods that are normal constituents of colonic flora that can cause overwhelming sepsis in low BW infants. The most common isolates are *Enterobacter cloacae* and *Enterobacter aerogenes*. *Enterobacter sakazakii* has received publicity due to outbreaks of disease caused by contamination of powdered infant formulas with this organism. *Enterobacter* spp. account for <5% of total LOS in NRN data, but there are multiple reports of epidemic outbreaks of cephalosporin-resistant *Enterobacter* in NICUs. *Enterobacter* spp. contain chromosomally encoded, inducible β-lactamases (AmpC-encoded cephalosporinases), and treatment with third-generation

cephalosporins, even if the initial isolate appears to be sensitive, can result in the emergence of cephalosporin-resistant organisms. In addition, stably derepressed, high-level constitutive AmpC-producing strains of *Enterobacter*, *Citrobacter*, and *Serratia* have been reported. The fourth-generation cephalosporin cefepime is relatively stable against AmpC-type β-lactamases. ESBLs (discussed in the subsequent text) have also been reported in *Enterobacter* spp. Given the increasing concern about cephalosporin resistance among infectious disease experts, cefepime or meropenem and gentamicin is usually recommended for treatment of infections caused by *Enterobacter* spp. Infection control measures and restriction of cephalosporin use can be effective in controlling outbreaks of resistant organisms.

O. Symptoms and evaluation of LOS. Lethargy, an increase in the number or severity of apneic spells, feeding intolerance, temperature instability, and/or an increase in ventilator support all may be early signs of LOS—or may be part of the variability in the course of the VLBW infant. The difficulty in distinguishing between these two in part explains the frequency of evaluation for LOS; in one NICHD study, 62% of VLBW infants had at least one blood culture drawn after day of life 3. With mild symptoms and a low suspicion for the presence of sepsis, it is reasonable to screen infants with laboratory tests such as CBC with differential and CRP to determine if blood culture and empiric antibiotics are warranted. Normal ranges for such tests may vary; very low and very high WBC, low ANC, and persistently elevated CRP are associated with infection. Acute changes from prior documented values for such tests may be most informative for an individual infant. If laboratory tests are abnormal or the infant's status worsens, empiric antibiotic therapy should be administered. If the suspicion for LOS is low, and/or the clinical status is nonsevere, it is common practice to obtain a blood cultures only. Ideally, however, urine and CSF culture should also be obtained before initiation antibiotic therapy, both to guide empiric therapy and to ensure proper attribution and follow-up studies (such as renal imaging if a UTI is present). A study of late-onset infection in VLBW infants underscores the importance of **performing an LP in the evaluation of LOS** in this population. Two-thirds of a cohort of >9,000 infants had one or more blood cultures drawn after 72 hours of life; one-third had an LP. Culture-proven meningitis was diagnosed in 134 infants (5% of those on whom an LP was performed) and in 45 out of 134 cases, the coincident blood culture was negative. Urine cultures should also be considered prior to beginning empiric antibiotic therapy, particularly for older infants without central venous access. Urine cultures should be obtained by catheterization or ultrasound-guided suprapubic aspirate (SPA) in VLBW infants; cultures of urine obtained by other means are likely to contain contaminant species. A true UTI is defined as growth of a single pathogen at >10,000 CFU/mL from a catheterized sample.

If a previously well, convalescing premature infant presents primarily with increased apnea with or without upper respiratory infection (URI) symptoms, additional consideration should be given to a viral source of infection. Tracheal or nasopharyngeal aspirate should be sent for rapid analysis and culture to rule out respiratory syncytial virus (RSV), parainfluenzae,

influenzae A and B, and emerging infections such as SARS-CoV-2 as appropriate. Additionally, urine for cytomegalovirus (CMV) detection should be considered among preterm infants being fed with mother's milk, as breastmilk-acquired postnatal CMV infection can present with sepsis-like syndrome.

P. Treatment of LOS. Table 49.1 lists suggested antibiotic regimens for selected organisms. A study of **central line removal** in culture-proven LOS demonstrated that bacteremic infants experience fewer complications of infection if central lines are removed promptly upon identification of a positive culture. This is particularly true for infections caused by *S. aureus* and gram-negative organisms.

ESBLs are plasmid-encoded bacterial enzymes that confer resistance to a variety of penicillins and cephalosporins. ESBLs are distinguished from the generally chromosomally encoded AmpC-type enzymes by sensitivity to clavulanate. Nosocomial gram-negative pathogens that commonly colonize and cause disease in VLBW infants (such as *E. coli*, *Enterobacter*, *Klebsiella*, *Pseudomonas*, and *Serratia*) are increasingly found to harbor these resistance enzymes. ESBL organisms have become a significant problem in adult ICUs. Multiple U.S. and international reports document an increasing impact of ESBL-producing organisms in NICUs. Risk factors for acquiring ESBL organisms include low gestational age and use of third-generation cephalosporins. Current recommendations to control outbreaks of these organisms include restriction of third-generation cephalosporin use and the same infection control measures (routine surveillance for colonization, cohorting, and isolation of colonized infants) as are needed for control of MRSA. Treatment of ESBL infections should ideally include consultation with infectious disease specialists; carbapenems, cefepime, and piperacillin/tazobactam are currently most effective, with increasing rates of coresistance reported for aminoglycosides and fluoroquinolones.

Carbapenemase-producing organisms and other multidrug-resistant organisms (MDROs) have been reported in hospital settings. Carbapenem resistance can occur in gram-negative organisms either by the acquisition of specific enzymes or by reduced carbapenem influx caused by the loss of outer membrane protein porins in ESBL organisms. In the United States, most carbapenemase-producing organisms contain the transposon-mediated *Klebsiella pneumoniae* carbapenemase (KPC), but other enzymes such as the New Delhi metallo-β-lactamase (NDM), the Verona integron-encoded metallo-β-lactamase (VIM), imipenemase (IMP), and oxacillinase-48-like (OXA-48-like) enzymes are common outside the United States and are included in CDC surveillance. Early recognition of these organisms is critical, both for proper individual treatment and to prevent nosocomial spread. Laboratory standards for identification of carbapenem-resistant *Enterobacteriaceae* (CRE) organisms include reduced susceptibility to meropenem, ertapenem, doripenem, or imipenem and resistance to all third-generation cephalosporins. Current treatment of infections with most carbapenemase-producing organisms may require the use of the polymyxin B, an antibiotic with significant toxicity. Recent reports of hospital-acquired infections by extensively drug-resistant *Acinetobacter baumannii* raise the specter of infection with organisms for which no effective treatment exists,

underscoring the importance of good infection control practices and responsible use of antibiotics in all intensive care settings.

Q. Prevention of LOS. In addition to significant mortality, LOS is associated with prolonged hospitalization, adverse neurodevelopmental performance in childhood and overall poorer outcome in VLBW infants compared to those that remain uninfected. A number of strategies to lower rates of LOS have been studied. These include administration of specific medications and biologics for infection prophylaxis, antibiotic restriction and surveillance policies to prevent antibiotic-resistant infections, and "bundled" implementation of multiple care practices to prevent central line–associated bloodstream infections (CLABSI).

1. **IVIG.** Multiple studies have been conducted using prophylactic administration of IVIG to address the relative deficiency of immunoglobulin in low BW infants and prevent LOS. A meta-analysis of these demonstrated no significant decrease in mortality or other serious outcomes and is generally not recommended.
2. **G-CSF.** G-CSF has been shown to resolve preeclampsia-associated neutropenia and may thereby decrease the rate of LOS in this population of infants. One trial of GM-CSF in premature neonates with the clinical diagnosis of early-onset disease did not improve mortality but was associated with acquiring fewer nosocomial infections over the subsequent 2 weeks.
3. **Prophylactic vancomycin.** A meta-analysis of several trials of low-dose vancomycin administration to VLBW infants demonstrated that the administration of prophylactic vancomycin reduced the incidence of both total LOS- and CONS-associated infections but did not improve mortality or length of hospitalization. Prophylactic vancomycin IV lock solution has been studied with some success in decreasing CONS infection. Antibiotic-impregnated catheters are not currently available for VLBW infants. There is concern that widespread use of vancomycin in these ways will lead to the increased emergence of vancomycin-resistant organisms.
4. **Probiotics.** Multiple clinical trials across the world have evaluated the administration of probiotic formulations in the prevention of both LOS and NEC. Two recent network meta-analysis of 45 and 63 randomized controlled trials in preterm infants both concluded that probiotic administration significantly reduced the risk of death or NEC. Among the most effective were combination probiotics that included both *Lactobacillus* or *Bifidobacterium* spp. However, results for prevention of sepsis were inconsistent between the two studies: One study that did not specify the definition of sepsis as an outcome found a reduction with *Lactobacillus* spp. plus prebiotic compared to placebo, and the other defined sepsis as culture-confirmed sepsis and found no significant effect. Some experts feel this evidence is strong enough to offer probiotic formulations to all preterm infants without further placebo-controlled trials. Others argue that the lack of standardized, regulated probiotic products and the relative lack of data among ELBW infants suggest that further study is required.

5. **Lactoferrin.** Lactoferrin is the major whey protein in both human and cow's milk. Present in high concentration in human colostrum, lactoferrin is important to innate immune defense against microbial pathogens, acting by sequestering iron and by impacting microbial membrane integrity. One randomized placebo-controlled trial of oral administration of bovine lactoferrin with or without a *Lactobacillus* probiotic preparation demonstrated a 70% reduction in the incidence of LOS among VLBW infants. However, a larger trial of 2,203 very preterm infants randomized to enteral bovine lactoferrin or placebo found no significant difference in the outcomes of culture-proven or suspected late-onset infection. Questions regarding different dosing regimens and differential effect based on neonatal diet are being explored, but until future studies establish efficacy, lactoferrin supplementation is not recommended for LOS prevention.
6. **Establishment of early enteral feedings** in VLBW infants may have the greatest effect on reducing LOS by reducing exposure to parenteral nutrition and allowing for decreased use of central catheters. **Breast milk** feeding may also help decrease nosocomial infection rates among VLBW infants, both by its numerous infection-protective properties (i.e., secretory immunoglobulin A, lactoferrin, lysozyme) and by aiding in the establishment of enteral feeds. Systematic review of studies of the human milk feeding and risk of LOS have not been able to rigorously establish that human milk prevents LOS among VLBW infants, but multiple small studies support the role of human milk in preventing NEC.
7. **Antibiotic stewardship.** Antibiotic stewardship is defined by the CDC as "the effort to measure and improve how antibiotics are prescribed by clinicians and used by patients." Aimed at minimizing selection of resistant bacteria, antibiotic stewardship also reduces patient exposure to unnecessary or suboptimal antibiotics. Core elements of antibiotic stewardship are provided by CDC (https://www.cdc.gov/antibiotic-use/core-elements/hospital.html). Strategies for antibiotics stewardship in NICUs require local input to build on existing evidence for optimal antibiotic use. Strategies include rigorous implementation of infection control measures, written protocols for infection diagnosis and management, building a multidisciplinary team to monitor choice and duration of antibiotic prescription, and measuring antibiotic use and patient outcomes over time. Limitation of the use of broad-spectrum antibiotics in neonatal, pediatric, and adult ICUs has been inconsistently associated with decrease rates of patient colonization with antibiotic-resistant organisms. Cycling of antibiotics used for empiric treatment has not been successful in preventing neonatal LOS or impacting colonization patterns. **However, the widespread emergence of MRSA, VRE, and multidrug-resistant gram-negative organisms has led to an increased awareness of the risk of empiric use of vancomycin and third-generation cephalosporins among infectious diseases experts.** Some studies suggest that substitution of oxacillin for vancomycin in the empiric treatment of LOS is not likely to cause significant morbidity in VLBW infants because of the low virulence of the CONS and may decrease the acquisition and spread of VRE and other antibiotic-resistant organisms. Empiric use of oxacillin may be best coupled with routine NICU surveillance for MRSA colonization.

8. **Surveillance practices.** A concern over emergence of MRSA, VRE, and multidrug-resistant gram-negative organisms has led to increased interest in the effect of ongoing surveillance to detect neonatal colonization. Multiple reports document the combined use of bacterial surveillance cultures, cohorting, isolation, and, in some cases, attempts at decolonization to control the outbreaks of infection with specific pathogens within NICUs. The impact of ongoing, longitudinal surveillance practices is less certain. We have shown that ongoing use of a weekly MRSA surveillance program can help prevent patient-to-patient spread of MRSA but will not completely eliminated introduction of MRSA into the NICU likely due to the prevalence of this pathogen in the general population. Surveillance may aid in the choice of empiric antibiotics for risk of LOS. Surveillance programs must be accompanied by strict hand hygiene practices for optimal impact, including reinforcement of hand-washing policies; routine use of waterless hand disinfectants; and restriction of artificial fingernails, natural nails over 1/4-inch length, nail polish; and wearing of rings, watches, and bracelets in the NICU setting.
9. **Implementation of recommended best practices to prevent CLABSI.** Many bloodstream infections that occur in VLBW infants are associated with the presence of central venous catheters. CLABSI are defined as culture-confirmed bloodstream infections occurring in the presence of a central catheter for which there is no other obvious source of infection (i.e., perinatal exposures in EOS or perforated bowel in NEC). The recognition of significant inter-NICU variation in the incidence of these infections has led to efforts to define optimal care practices associated with lower rates of infection.

   Multiple resources are now available to guide optimal care practices for the prevention of CLABSI. The basic components of CLABSI prevention bundles are shown in Table 49.5. The California Perinatal Quality Care Collaborative (CPQCC) summarizes and provides critical review of evidence-based practices for neonatal infection prevention in their toolkit, **"Neonatal Hospital Acquired Infection Prevention,"** available at https://www.cpqcc.org/content/neonatal-hospital-acquired-infection-prevention.

II. ANAEROBIC BACTERIAL INFECTIONS.

Anaerobic bacteria comprise a significant portion of the oral, vaginal, and gastrointestinal flora. Although many anaerobes are of low virulence, a few anaerobic organisms can cause both EOS and LOS. These organisms include *Bacteroides* spp. (primarily *B. fragilis*), *Peptostreptococcus*, and *Clostridium perfringens*. NEC and/or bowel perforation can be complicated by anaerobic sepsis alone or in a polymicrobial infection. In addition to bacteremia, *B. fragilis* can cause abdominal abscesses, meningitis, omphalitis, cellulitis at the site of fetal scalp monitors, endocarditis, osteomyelitis, and arthritis in the neonate.

A. **Treatment of anaerobic infections.** Bacteremia and/or meningitis are treated with IV antibiotics; abscesses and other focal infections often require surgical drainage. *B. fragilis* is a gram-negative rod, and although

Table 49.5. Components of Neonatal CLABSI Prevention

Hand Hygiene
■ Before and after any patient contact
■ Before and after donning gloves
■ Before central line placement or adjustment
Central Line Care Practices
■ Maximal barrier precautions/sterile procedure for insertion
■ Formalized daily use and dressing maintenance procedures
■ Preparation of parenteral fluids in pharmacy under laminar flow hood
■ Standards for timing of administration set changes
■ Daily review of central line necessity
Diagnostic Criteria and Reporting Practices
■ Optimize practices for obtaining and interpreting blood culture results
■ Collect accurate data to determine CLABSI per 1,000 line days
■ Communicate CLABSI data and trends to local caregivers
■ Benchmark local data against appropriate national standards

CLABSI, central line–associated bloodstream infections.

Source: Data from Bowles S, Pettit J, Mickas N, et al. Neonatal Hospital-Acquired Infection Prevention. https://www.cpqcc.org/sites/default/files/2007HAIToolkit.pdf and O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. The Hospital Infection Control Practices Advisory Committee, Center for Disease Control and Prevention, U.S. *Pediatrics* 2002;110(5):e51.

oral *Bacteroides* spp. are sensitive to penicillin, *B. fragilis* usually requires treatment with drugs such as metronidazole, clindamycin, cefoxitin, or imipenem. Occasional strains of *B. fragilis* are also resistant to cefoxitin and/or imipenem; as many as one-fourth of all strain in the United States are now resistant to clindamycin. Most other cephalosporins and vancomycin are ineffective against *B. fragilis*. *Peptostreptococcus* and *Clostridia* are gram-positive organisms that are sensitive to penicillin G. NEC and intestinal perforations are treated with anaerobic coverage for the spectrum of organisms that can complicate these illnesses. Common regimens include ampicillin, gentamicin with clindamycin/metronidazole for anaerobic coverage, or piperacillin-tazobactam either alone or with an aminoglycoside. Ongoing studies are evaluating the safety of one regimen over others.

B. Neonatal tetanus. This syndrome is caused by the effect of a neurotoxin produced by the anaerobic bacterium *Clostridium tetani*. Infection can occur by invasion of the umbilical cord due to unsanitary childbirth or cord care practices. It has historically been a significant cause of neonatal mortality in low- and middle-income countries (LMIC). An estimated 787,000 deaths due to neonatal tetanus occurred worldwide in 1988. The World Health Organization (WHO) has set multiple target dates for neonatal tetanus worldwide elimination since 1989. Elimination has been achieved in many LMIC, but neonatal tetanus persists in remote and poverty-ridden regions, associated with lack of adequate maternal tetanus toxoid immunization and unsanitary delivery settings. WHO and CDC estimate 25,000 deaths occurred worldwide from neonatal tetanus in 2018. This disease is rare in the United States due to maternal immunization and infection control practices; 3 cases were reported to the CDC from 2009 to 2017. Infected neonates develop symptoms 4 to 14 days after infection marked by hypertonia and muscle spasms including trismus and consequent inability to feed. Treatment consists of the administration of tetanus immunoglobulin (TIG) (500 U intramuscular) and penicillin G (100,000 U/kg/day divided every 4 to 6 hours) or metronidazole (30 mg/kg/day divided every 6 hours) as well as supportive care with mechanical ventilation, sedatives, and muscle relaxants. IVIG may be given if TIG is not available. Neonatal tetanus does not result in immunity to tetanus, and infants require standard tetanus immunizations after recovery.

III. FUNGAL INFECTIONS

A. Mucocutaneous candidiasis. Fungal infections in the well-term infant are generally limited to mucocutaneous disease involving *C. albicans*. *Candida* spp. are normal commensal flora beyond the neonatal period and rarely cause serious disease in the immunocompetent host. Immaturity of host defenses and colonization with *Candida* before complete establishment of normal intestinal flora probably contribute to the pathogenicity of *Candida* in the neonate. Oral and gastrointestinal colonization with *Candida* occurs before the development of oral candidiasis (thrush) or diaper dermatitis. *Candida* can be acquired through the birth canal or through the hands or breast of the mother. Nosocomial transmission in the nursery setting has been documented, such as transmission from feeding bottles and pacifiers.

Oral candidiasis in the young infant is treated with a nonabsorbable oral antifungal medication, which has the advantages of little systemic toxicity and concomitant treatment of the intestinal tract. **Nystatin** oral suspension (100,000 U/mL) is standard treatment (1 mL is applied to each side of the mouth every 6 hours for a minimum of 10 to 14 days). Ideally, treatment is continued for several days after lesions resolve. Fluconazole (6 mg/kg IV or orally [PO] once followed by 3 mg/kg IV/PO each day) can be used for severe oral candidiasis if nystatin oral therapy is not effective. Systemic **fluconazole** is also highly effective in treating chronic mucocutaneous candidiasis in the immunocompromised host. Infants with chronic, severe thrush refractory to treatment should be evaluated for an underlying congenital or acquired immunodeficiency.

Oral candidiasis in the **breastfed infant** is often associated with superficial or ductal candidiasis in the mother's breast. Concurrent treatment of both the mother and infant is necessary to eliminate continual cross-infection. Breastfeeding of term infants can continue during treatment. Mothers with breast ductal candidiasis who are providing expressed breast milk for VLBW infants should be advised to withhold expressed milk until treatment has been instituted. *Candida* can be difficult to detect in breast milk because lactoferrin inhibits the growth of *Candida* in culture. Freezing does not eliminate *Candida* from expressed breast milk.

Candidal diaper dermatitis is effectively treated with topical agents such as 2% nystatin ointment, 2% miconazole ointment, or 1% clotrimazole cream. Concomitant treatment with oral nystatin to eliminate intestinal colonization is often recommended but not well studied. It is reasonable to use simultaneous oral and topical therapy for refractory candidal diaper dermatitis.

B. Systemic candidiasis. Systemic candidiasis is a serious form of nosocomial infection in preterm infants. LOS data among a cohort of 5,100 ELBW infants cared for at NRN centers from 2006 to 2011 found that 2% developed fungal infection. Among infected infants, fungal species were isolated in 6% of all LOS cases, with *Candida* spp. responsible for 86% of these cases. Nearly 40% of infants with fungal infection died. Invasive candidiasis is associated with overall poorer neurodevelopmental outcomes and higher rates of threshold retinopathy of prematurity, compared to matched control infants. Gastrointestinal tract colonization of the low BW infants often precedes invasive infection, and **risk factors for colonization and invasive disease** are similar. The most significant epidemiologic factors specific to *Candida* LOS in the NICHD cohort studies were ELBW status, presence of central catheter, delay in enteral feeding, and days of broad-spectrum antibiotic exposure. Other clinical factors included in a recent clinical predictive model for invasive candidiasis among ELBW infants include the presence of candidal diaper dermatitis, vaginal delivery, lower gestational age, and significant hypoglycemia and thrombocytopenia. The use of H_2 blockers or systemic steroids have also been identified as independent risk factors for the development of invasive fungal infection.

1. Microbiology. Disseminated candidiasis is primarily caused by *C. albicans* and *C. parapsilosis* in preterm infants, but infection with *Candida tropicalis*, *Candida lusitaniae*, *Candida guilliermondii*, *Candida glabrata*, and *Candida krusei* are reported less frequently in neonates. The pathogenicity of *C. albicans* is associated with the variable production of a number of toxins, including an endotoxin. *C. albicans* can be acquired perinatally as well as postnatally. *C. parapsilosis* has emerged as the second most common cause of disseminated neonatal candidiasis in recent years. Studies suggest that *C. parapsilosis* is primarily a nosocomial pathogen in that it is acquired at a later age than *C. albicans* and is associated with colonization of health care workers' hands. In NICHD studies, fungal species (primarily *C. albicans* vs. *C. parapsilosis*) did not independently predict death or later neurodevelopmental impairment, and a delay in removal of central catheters was associated with higher mortality rates from *Candida* LOS regardless of species. *Candida auris*

has emerged as a new pathogen that is often multidrug resistant, specifically to azoles, difficult to identify using standard laboratory methods and is associated high mortality. Neonatal cases are reported internationally with management including combination therapy with micafungin and amphotericin B.

2. **Clinical manifestations.** Candidiasis due to *in utero* infection can occur. Congenital cutaneous candidiasis can present with severe, widespread, and desquamating skin involvement. Pulmonary candidiasis can occur in isolation or with disseminated infection and presents as a severe pneumonia. Most cases of systemic candidiasis, however, present as LOS in preterm infants, most in association with prior antibiotic administration. The initial clinical features of **late-onset invasive candidiasis** are often nonspecific and can include lethargy, increased apnea or need for increased respiratory support, poor perfusion, feeding intolerance, and hyperglycemia. Both the total WBC and the differential can be normal early in the course of infection, and although thrombocytopenia is a consistent feature, it is not universally found at presentation. The clinical picture is initially difficult to distinguish from sepsis caused by CONS infection and contrasts with the abrupt onset of septic shock that often accompanies LOS caused by gram-negative organisms. Candidemia can be complicated by meningitis and brain abscess as well as end-organ involvement of the kidneys, heart, joints, and eyes (endophthalmitis). The fatality rate of disseminated candidiasis is high relative to that found in CONS infections and increases in the presence of CNS involvement.

3. **Diagnosis.** *Candida* can be cultured from standard pediatric blood culture systems; the time to identification of a positive culture is usually by 48 hours, although late identification (beyond 72 hours) does occur more frequently than with bacterial species. Specialized fungal isolator tubes can aid in the identification of fungal infection if it is suspected by allowing for direct culture on selective media but are not necessary to identify candidemia. Both fungal culture and fungal staining (KOH preparation) of urine obtained by SPA can be helpful in making the diagnosis of systemic candidiasis. Specimens obtained by bag urine collection or bladder catheterization are difficult to interpret because they can be readily contaminated with colonizing species. We have obtained urine by SPA from VLBW infants under bedside ultrasound guidance for maximal safety. Before the initiation of antifungal therapy, CSF should be obtained for cell count and fungal culture if infant condition allows.

4. **Treatment.** Systemic candidiasis is treated with **amphotericin B**, 1 mg/kg/day for 14 days after a documented negative blood culture, if there is no evidence of meningitis or other end-organ infection. Otherwise, recommended length of treatment for neonatal candidemia involving the CNS or other end-organ focus is 3 weeks for longer, pending resolution of specific end-organ infection. Consultation with infectious disease specialists is advised in cases of disseminated infection. All common strains of *Candida* other than some strains of *C. lusitaniae*,

C. glabrata, and *C. krusei* are sensitive to amphotericin. This medication is associated with a variety of dose-dependent immediate and delayed toxicities in older children and adults and can cause phlebitis at the site of infusion. Febrile reactions to the infusion do not usually occur in the low BW infant (although renal and electrolyte disturbances can occur), and we start infants at the higher 1 mg/kg dose from the beginning of treatment. The medication is given over 2 hours to minimize the risk of seizures and arrhythmias during the infusion. When infection is cleared from blood, urine, and/or CSF, treatment can be transitioned to fluconazole 12 mg/kg/day in cases of susceptible isolates. Fluconazole is safe for use in infants but should not be used until speciation is completed because *C. krusei* and *C. glabrata* are frequently resistant to fluconazole. There is increased experience in VLBW babies with liposomal preparations of amphotericin B; due to concerns regarding urinary tract and CNS infection and overall outcomes, use of liposomal amphotericin is currently not recommended in neonates. CNS disease can be treated with nonliposomal amphotericin deoxycholate alone; an additional second agent, generally an **echinocandin or fluconazole should be added only if initial therapy with amphotericin is not effective**. Flucytosine achieves good CNS penetration but is only available for enteral administration, and bone marrow and liver toxicity limit the drug's utility.

Removal of central catheters in place when candidemia is identified is essential to the eradication of the infection. Delayed catheter removal is associated with persistent candidemia and increased mortality.

Further evaluation of the infant with invasive candidiasis should include brain, kidney, liver, and spleen ultrasonography to rule out fungal abscess formation and ophthalmologic examination to rule out endophthalmitis. In infants who are persistently fungemic despite catheter removal and appropriate therapy, an echocardiogram to rule out endocarditis or vegetation formation is warranted.

5. **Prevention.** Minimizing use of broad-spectrum antibiotics and H_2 blockers may be helpful in preventing disseminated candidiasis. The CDC recommends changing infusions of lipid suspensions every 12 hours to minimize microbial contamination; solutions of parenteral nutrition and lipid mixtures should be changed every 24 hours. Several randomized placebo-controlled trials of **prophylactic fluconazole administration** to prevent invasive fungal infection in VLBW infants have been published since 2001. All the trials demonstrated decreased rates of colonization with fungal species, and most also demonstrated decreased rates of invasive fungal infection. Initial concerns that widespread implementation of a fluconazole prophylaxis regimen would result in colonization or infection with less fluconazole-sensitive *Candida* spp. have not been born out. One study of the impact of fluconazole prophylaxis on long-term neurodevelopmental outcome revealed no safety concerns. However, there is no evidence that fluconazole prophylaxis impacts overall mortality or neurodevelopmental outcome. A randomized placebo-controlled trial of 361 infants with BW $<$750 g treated with fluconazole prophylaxis for 42 days demonstrated a statistically significant decrease in invasive fungal disease (from 9% in the placebo

group to 3% in the treatment group) but no impact on the combined outcome of death or candidiasis and no impact on neurodevelopmental outcome. In light of these findings, individual NICUs should balance the potentially severe consequences of invasive fungal infection (in NRN studies of ELBW infants born from 2004 to 2007, nearly three-quarters of those with LOS fungal sepsis died or survived with significant neurodevelopmental impairment) as well as the frequency of LOS fungal infection in an individual NICU in making a decision to implement a fluconazole prophylaxis policy. Targeted use of fluconazole prophylaxis in infants with multiple risk factors—for example, those with BW <1,000 g receiving long-term broad-spectrum antibiotics—may be the optimal course rather than use determined by a BW alone.

IV. FOCAL BACTERIAL INFECTIONS

A. Skin infections. The newborn may develop a variety of rashes associated with both systemic and focal bacterial disease. Responsible organisms include all of the usual causes of EOS (GBS, enteric gram-negative rods, and anaerobes) as well as gram-positive organisms that specifically colonize the skin—staphylococci and other streptococci. Colonization of the newborn skin occurs with organisms acquired from vaginal flora as well as from the environment. **Sepsis** can be accompanied by skin manifestations such as maculopapular rashes, erythema multiforme, and petechiae or purpura. **Localized infections** can arise in any site of traumatized skin: in the scalp at lesions caused by intrapartum fetal monitors or blood gas samples, in the penis and surrounding tissues due to circumcision, in the extremities at sites of venipuncture or IV placement, and in the umbilical stump (omphalitis). Generalized pustular skin infections can occur due to *S. aureus*, occasionally in epidemic fashion; focal abscesses can be caused by MRSA.

1. **Cellulitis** usually occurs at traumatized skin sites as noted in the preceding text. Localized erythema and/or drainage in a term infant (e.g., at a scalp electrode site) can be treated with careful washing and local antisepsis with antibiotic ointment (bacitracin or mupirocin ointment) and close monitoring. Cellulitis at sites of IV access or venipuncture in premature infants must be addressed in a more aggressive fashion due to the risk of local and systemic spread, particularly in the VLBW infant. If the premature infant with a localized cellulitis is well appearing, a CBC and blood culture should be obtained and IV antibiotics administered to provide coverage primarily for skin flora (i.e., oxacillin or nafcillin and gentamicin). If MRSA is a concern, vancomycin should be substituted for nafcillin. If blood cultures are negative, the infant can be treated for a total of 5 to 7 days with resolution of the cellulitis. If an organism grows from the blood culture, an LP should be performed to rule out meningitis and careful physical examination should be performed to rule out accompanying osteomyelitis or septic arthritis. Therapy is guided by the organism identified (see Table 49.1).
2. **Pustulosis.** Infectious pustulosis is usually caused by *S. aureus* and must be distinguished from the benign neonatal rash erythema toxicum

and transient pustular melanosis. The pustules are most commonly found in the axillae, groin, and periumbilical area; both erythema toxicum and transient pustular melanosis have a more generalized distribution. Lesions can be unroofed after cleansing in sterile fashion with povidone-iodine or 4% chlorhexidine, and contents aspirated and analyzed by Gram stain and culture. Gram stain of infectious pustules will reveal neutrophils and gram-positive cocci, whereas Wright stain of erythema toxicum lesions will reveal predominantly eosinophils and no (or a few contaminating) organisms. Gram stain of transient pustular melanosis lesions will reveal neutrophils but no organisms. Cultures of the benign rashes will be sterile or grow contaminating organisms such as *S. epidermidis*. Treatment of pustulosis caused by *S. aureus* is tailored to the degree of involvement and condition of the infant. A few lesions in a healthy term infant may be treated with topical mupirocin and oral therapy with medications such as amoxicillin/clavulanate, dicloxacillin, clindamycin, or cephalexin depending on organism antibiotic sensitivity. More extensive lesions, systemic illness, or pustulosis occurring in the premature infant requires IV therapy with nafcillin or oxacillin.

Some strains of *S. aureus* produce toxins that can cause **bullous lesions or scalded skin syndrome**. The cutaneous changes are due to local and systemic spread of toxin. Although blood cultures may be negative, IV antibiotics should be given (nafcillin or oxacillin) until the progression of disease stops and skin lesions are healing.

Pediatricians who diagnose infectious pustulosis in an infant younger than 2 weeks of age should report the case to the birth hospital; **epidemic outbreaks due to nosocomial acquisition in newborn nurseries** are often recognized in this way because the rash may not occur until after hospital discharge. This has become particularly important with the emergence of MRSA infections among infants <1 month in the community. When such outbreaks are recognized in the nursery or NICU, hospital infection control experts should be consulted. Appropriate steps may include surveillance cultures of staff members and newborns and cohorting of colonized infants.

3. **Omphalitis.** Omphalitis is characterized by erythema and/or induration of the periumbilical area with purulent discharge from the umbilical stump. The infection can progress to widespread abdominal wall cellulitis or necrotizing fasciitis; complications such as peritonitis, umbilical arteritis or phlebitis, hepatic vein thrombosis, and hepatic abscess have all been described. Responsible organisms include both gram-positive and gram-negative species. Treatment consists of a full sepsis evaluation (CBC, blood culture, LP) and empiric IV therapy with oxacillin or nafcillin and gentamicin. With serious disease progression, broader spectrum gram-negative coverage with a cephalosporin or piperacillin/tazobactam should be considered. As noted in section II.B, invasion of the umbilical stump by *C. tetani* under conditions of poor sanitation can result in neonatal tetanus in the infant of an unimmunized mother. A Cochrane review of studies that investigated application of antiseptics such as chlorhexidine to the umbilical cord versus leaving it dry did not note a difference in outcomes of omphalitis and neonatal mortality in

high-income setting but reported a significant reduction in these outcomes in LMIC.

B. Conjunctivitis (ophthalmia neonatorum). This condition refers to inflammation of the conjunctiva within the first month of life. Causative agents include topical medications (chemical conjunctivitis), bacteria, and herpes simplex viruses. Chemical conjunctivitis is most commonly seen with silver nitrate eye prophylaxis, requires no specific treatment, and usually resolves within 48 hours. Bacterial causes include *Neisseria gonorrhoeae*; *Chlamydia trachomatis*; as well as staphylococci, streptococci, and gram-negative organisms. In the United States, where routine birth prophylaxis against ophthalmia neonatorum is practiced, the incidence of this disease is very low. In developing countries, in the absence of prophylaxis, ophthalmia neonatorum remains a major cause of blindness.

1. **Prophylaxis against infectious conjunctivitis.** One percent silver nitrate solution (1 to 2 drops to each eye), 0.5% erythromycin ophthalmic ointment or 1% tetracycline ointment or 1% chloramphenicol ointment (1-cm strip to each eye), and 2.5% povidone-iodine solution (water-based solution, 1 drop to each eye) administered within 1 hour of birth are all effective in the prevention of ophthalmia neonatorum. In a trial comparing the use of these three agents conducted in Kenya, povidone-iodine was shown to be slightly more effective against both *C. trachomatis* and other causes of infectious conjunctivitis, and equally effective against *N. gonorrhoeae* and *S. aureus*. Povidone-iodine was associated with less noninfectious conjunctivitis and is less costly than the other two agents; in addition, this agent is not associated with the development of bacterial resistance. However, an ophthalmic preparation of povidone-iodine solution is not currently available in the United States. In our institution, where most mothers receive prenatal care and the incidences of chlamydia and gonorrhea are low, we use erythromycin ointment. Silver nitrate or povidone-iodine is the preferred agent in areas where the incidence of penicillinase-producing *N. gonorrhoeae* is high.

2. ***N. gonorrhoeae.*** Pregnant women should be screened for *N. gonorrhoeae* as part of routine prenatal care. High-risk women or women without prenatal care should be screened at delivery. If a mother is known to have untreated *N. gonorrhoeae* infection, the infant should receive **ceftriaxone 25 to 50 mg/kg IV or IM (not to exceed 125 mg)**.

   Gonococcal conjunctivitis presents with chemosis, lid edema, and purulent exudate beginning 1 to 4 days after birth. Clouding of the cornea or panophthalmitis can occur. Gram stain and culture of conjunctival scrapings will confirm the diagnosis. The treatment of infants with uncomplicated gonococcal conjunctivitis requires only a single dose of ceftriaxone (25 to 50 mg/kg IV or IM, not to exceed 125 mg). Additional topical treatment is unnecessary. However, infants with gonococcal conjunctivitis should be hospitalized and screened for invasive disease (i.e., sepsis, meningitis, arthritis). Scalp abscesses can result from internal fetal monitoring. Treatment of these complications is ceftriaxone (25 to 50 mg/kg/day IV or IM every 24 hours) or cefotaxime (25 mg/kg IV or IM every 12 hours) for 7 days (10 to 14 days

for meningitis). If cefotaxime is unavailable and ceftriaxone is contraindicated due to hyperbilirubinemia or concomitant treatment with calcium-containing IV fluids, cefepime may be considered; consultation with an infectious diseases specialist is suggested. The infant and mother should be screened for coincident chlamydial infection.

3. ***C. trachomatis.*** Pregnant women should be screened for ***C. trachomatis*** as part of routine prenatal care. Prophylaxis for infants born to mothers with untreated chlamydial infection is not indicated. Chlamydial conjunctivitis is the most commonly identified cause of infectious conjunctivitis in the United States. It presents with variable degrees of inflammation, yellow discharge, and eyelid swelling 5 to 14 days after birth. Conjunctival scarring can occur, although the cornea is usually not involved. DNA hybridization tests or shell vial cultures are used to detect *Chlamydia* in conjunctival specimens. NAATs are commercially available and more sensitive than direct hybridization or culture methods and have largely replaced other methods in clinical practice. NAATs can be used for conjunctival specimens only with local verification of clinical laboratory standards because they are not currently U.S. Food and Drug Administration (FDA) approved for this indication. Chlamydial conjunctivitis is treated with oral **erythromycin base or ethylsuccinate 50 mg/kg/day divided into four doses for 14 days**, or with **azithromycin 20 mg/kg/day in a single dose for 3 days**. Topical treatment alone is not adequate and is unnecessary when systemic therapy is given. An association of erythromycin and azithromycin therapy with infantile hypertrophic pyloric stenosis has been reported in infants younger than 6 weeks. Infants should be monitored for this condition. The efficacy of treatment is approximately 80%, and infants must be evaluated for treatment failure and the need for a second course of treatment. Infants should also be evaluated for the concomitant presence of chlamydial pneumonia. The treatment for pneumonia is the same as for conjunctivitis, in addition to necessary supportive respiratory care.

4. **Other bacterial conjunctivitis.** Other causes are generally diagnosed by culture of eye exudate. *S. aureus*, *E. coli*, and *Haemophilus influenzae* can cause conjunctivitis that is usually easily treated with local ophthalmic ointments (erythromycin or gentamicin) without complication. Very severe cases caused by *H. influenzae* may require parenteral treatment and evaluation for sepsis and meningitis. *P. aeruginosa* can cause a rare and devastating form of conjunctivitis that requires parenteral treatment.

C. Pneumonia. The diagnosis of **neonatal pneumonia** is challenging. It is difficult to distinguish primary (occurring from birth) neonatal bacterial pneumonia clinically from sepsis with respiratory compromise, or radiographically from other causes of respiratory distress (hyaline membrane disease, retained fetal lung fluid, meconium aspiration, amniotic fluid aspiration). Persistent focal opacifications on chest radiograph due to neonatal pneumonia are uncommon, and their presence should prompt some consideration of noninfectious causes of focal lung opacification (such as congenital cystic lesions or pulmonary sequestration). The causes of neonatal bacterial pneumonia are the same as for EOS, and antibiotic treatment

is generally the same as for sepsis. The infant's baseline risk of infection, radiographic and laboratory studies, and, most important, the clinical progression must all be taken into account when making the diagnosis of neonatal pneumonia.

The diagnosis of **nosocomial, or ventilator-associated pneumonia** in neonates who are ventilator dependent due to chronic lung disease or other illness, is equally challenging. Culture of tracheal secretions in infants who are chronically ventilated can yield a variety of organisms, including all the causes of EOS and LOS as well as (often antibiotic resistant) gram-negative organisms that are endemic within a particular NICU. A distinction must be made between colonization of the airway and true tracheitis or pneumonia. Culture results must be taken together with the infant's respiratory and systemic condition as well as radiographic and laboratory studies when making the diagnosis of nosocomial pneumonia.

Ureaplasma urealyticum deserves mention with respect to chronically ventilated infants. This mycoplasmal organism frequently colonizes the vagina of pregnant women and has been associated with chorioamnionitis, spontaneous abortion and premature delivery, and infection of the premature infant. Infection with *Ureaplasma* has been studied as a contributing factor to the development of chronic lung disease, but the role of the organism and the value of diagnosis and treatment are unclear and controversial. *Ureaplasma* requires special culture conditions and will grow within 2 to 4 days. Polymerase chain reaction (PCR)-based diagnostics have been developed but are not widely available. It will not be identified on routine bacterial culture. A randomized placebo-controlled trial including 121 infants born 24 to 28 weeks' gestation evaluated the impact of azithromycin prophylaxis; azithromycin eradicated *Ureaplasma* from infants colonized with the organism. At 22- to 26-month follow-up, there was no difference in death or respiratory morbidity and no difference in death or neurodevelopmental impairment between infants receiving azithromycin or placebo. There is no current evidence to support the use of *Ureaplasma* treatment to prevent bronchopulmonary dysplasia.

D. UTI. UTIs may occur secondary to bacteremia, or bacteremia may occur secondary to primary UTI. UTI is a common cause of infection among febrile infants younger than 3 months of age. The incidence is highest among uncircumcised males. Among community infants who present with febrile UTI, the prevalence of high-grade (grade 5) vesicoureteral reflux (VUR) diagnosed on subsequent vesicourethrocytogram (VCUG) is approximately 1%. The incidence of UTI among VLBW infants in the NICU is much less well documented. The most common causative organisms are gram negative, such as *E. coli*, but enterococci and staphylococci can also cause UTI, especially among VLBW NICU infants. Culture of urine is not routinely recommended as part of the evaluation for EOS but is an essential part of the evaluation for LOS (see section I.N). The most common presenting symptoms in term and older preterm infants are fever, lethargy, and poor feeding; younger preterm infants will present as for LOS. Diagnosis is made by urinalysis and urine culture. Culture of urine obtained from a bag collection or diaper is of little value because it will commonly be contaminated with skin and fecal flora. Specimens should be obtained by bladder

catheterization or SPA with sterile technique. Ultrasound guidance can be useful in performing SPA in the VLBW infant. Empiric treatment in term and preterm infants is as for LOS (see section I.P); antibiotic choice and treatment duration is guided by blood, urine, and CSF culture results. If the urine culture **alone** is positive in a term infant, treatment is completed with oral therapy once the infant is afebrile. Treatment duration in the absence of a positive blood or CSF culture is 10 to 14 days.

The AAP recommends that infants with UTI undergo renal ultrasound after a first episode of UTI. VCUG imaging to identify any underlying anatomic or functional abnormalities (i.e., VUR) that may have contributed to the development of the UTI is recommended if the renal ultrasound is abnormal, or after a second episode of UTI. Traditionally, infants have received UTI prophylaxis with amoxicillin (10 to 20 mg/kg once per day) after completing UTI treatment until imaging studies are performed and have continued with prophylaxis if VUR is documented. Several recent meta-analyses have found little to no value in antibiotic prophylaxis for low-grade VUR, although it remains widely used and is recommended only for high-grade (grade 5) VUR.

E. Osteomyelitis and septic arthritis. These focal infections are rare in newborns and may result from hematogenous seeding in the setting of bacteremia, or direct extension from a skin source of infection. The most common organisms are *S. aureus*, GBS, and gram-negative organisms including *N. gonorrhoeae*. Symptoms include localized erythema, swelling, and apparent pain or lack of spontaneous movement of the involved extremity. The hip, knee, and wrist are commonly involved in septic arthritis, and the femur, humerus, tibia, radius, and maxilla are the most common bone sites of infection. The evaluation should be as for sepsis, including blood, urine, and CSF culture, and culture of any purulent skin lesions. Needle aspiration of an infected joint is sometimes possible, and plain film and ultrasound can aid in diagnosis. Empiric treatment is with nafcillin or oxacillin and gentamicin, and/or vancomycin if MRSA is a concern, and is later tailored to any identified organisms. Joint infections commonly require surgical drainage; material can be sent for Gram stain and culture at surgery. Duration of therapy is 3 to 4 weeks. Significant disability can result from joint or growth plate damage.

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50 Congenital Toxoplasmosis

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KEY POINTS

- Toxoplasmosis can be acquired via foodborne, animal-to-human, or mother-to-child transmission. Less commonly, infection may be acquired from infected donor in the setting of organ transplantation or blood transfusion.
- In the United States, congenital infection occurs in about 1/1,000 to 1/10,000 live births (approximately 500 to 5,000 cases per year).
- The risk of intrauterine infection increases with gestational age, but the effects on the fetus are more severe when fetal infection occurs earlier in gestation.
- Congenital toxoplasmosis typically follows acute primary infection during pregnancy or through reactivation of latent infection in immunocompromised mothers.
- Congenital toxoplasmosis requires prolonged treatment for 1 year to improve developmental outcomes and reduce neurologic and ocular sequalae.

I. EPIDEMIOLOGY.

Toxoplasma gondii, an obligate intracellular protozoan parasite, is an important human pathogen, especially for the fetus, newborn, and immunocompromised individuals.

A. Transmission.

T. gondii exists in three infectious forms: tachyzoite, bradyzoites (tissue cysts), and oocysts. The tachyzoite is the actively replicating form that is responsible for symptoms during acute infection. Following acute infection, latent bradyzoite forms persist asymptomatically in tissues, with risk for future reactivation. The definitive host of *T. gondii* is the cat, in which infection is typically asymptomatic. Intermediate hosts include all warm-blooded animals and humans. Tissue cysts, which are infectious, form in the intermediate host, particularly in brain, eye, and muscle. Cats are typically infected by ingesting cysts from an infected intermediate host, ultimately shedding oocysts from their intestinal lumen into the environment. Cats may shed up to 10 million oocysts a day for >2 weeks following an initial infection, and oocysts remain infective in soil for up to 18 months. Other animals can become infected by ingesting these oocysts.

Humans acquire *T. gondii* infection through ingestion of infected oocysts from the environment (contaminated food or water), ingestion

of tissue cysts present in raw or undercooked meat (most common in developed world), from an infected organ donor in the setting of organ transplantation, and transplacentally (congenital infection). Rarely, toxoplasmosis is transmitted by blood transfusion. Risk factors associated with acute infection in the United States include consumption of raw ground beef or lamb; locally produced, cured, dried, or smoked meat; working with meat; and drinking unpasteurized goat's milk. Raw oysters and clams have also been associated with transmission. Untreated water has been reported to be the source of major outbreaks around the world. The prevalence of *T. gondii* infection varies broadly among different countries and geographic areas and increases with age. In the United States, those aged 70 to 79 years are up to 5 times more likely to be seropositive for *T. gondii*, compared to individuals 18 to 29 years of age. The *T. gondii* seroprevalence has decreased steadily over the last two decades in the United States, from 16% in 1988–1994 to 10.1% in 2009–2010. Worldwide, 10% to 80% of women of childbearing age possess *T. gondii* immunoglobulin G (IgG). Women without preexisting antibodies, including most American women, are at risk for acute toxoplasmosis during pregnancy.

The risk of seroconversion during pregnancy also varies by geographic location. Rates range from 1.5% in France, a high-prevalence country, to 0.17% in Norway. Incidence of maternal seroconversion during pregnancy in the United States is estimated to be <1 in 1,000. Prompt treatment of acute toxoplasmosis during pregnancy appears to reduce both the rate of mother-to-child transmission and the likelihood of fetal loss or severe neurologic and ocular sequelae.

B. Incidence. The reported incidence of congenital toxoplasmosis in the United States has decreased during the last 20 years from a high of 20 per 10,000 to 1 per 10,000. In the United States, an estimated 500 to 5,000 infants are born each year with congenital toxoplasmosis.

II. PATHOPHYSIOLOGY

A. Postnatal infection. Immunocompetent children and adults are susceptible to acute primary toxoplasmosis. Both humoral and cell-mediated immunity are important in the control of infection. The majority of *T. gondii* infections in immunocompetent hosts are asymptomatic. When present, symptoms are typically mild and may include lymphadenopathy, malaise, fever, and headache. Severe manifestations of infection such as encephalitis, myocarditis, pneumonia, and hepatitis are less common in individuals with intact adaptive immunity. Chorioretinitis has also been reported in postnatally acquired cases. In immunocompetent hosts, infection with *T. gondii* imparts lifelong protection.

B. Congenital infection. Congenital infection is most commonly acquired as a result of acute maternal toxoplasmosis during pregnancy or within 3 months prior to conception. Less commonly, congenital toxoplasmosis may result from reactivation disease in an immunocompromised mother. Circulating maternal parasitemia leads to placental invasion and subsequent passage of *T. gondii* into the fetal circulation and tissues.

The risk of intrauterine infection increases with gestational age. One analysis demonstrated the risk of transmission to the fetus to be 6% at 13 weeks, 40% at 26 weeks, and 72% at 36 weeks, although the vast majority of these mothers (>94%) received antiparasitic treatment. As with many other congenital infections, the earlier in gestation that infection occurs, the more profound the potential impact on the developing fetus. For example, only 9% of infants have clinically symptomatic disease when maternal seroconversion occurs at 36 weeks of gestation, compared to 61% of infants at 13 weeks' gestation. Infection early in pregnancy may result in intrauterine fetal demise and spontaneous abortion. Nearly all infants infected during the third trimester will be asymptomatic, accounting for 67% to 80% of prenatally infected infants.

Immunocompromised pregnant patients (i.e., those with uncontrolled HIV infection, hematologic malignancy, or on immunosuppressive therapies) previously infected with *T. gondii* may be unable to suppress parasite replication. In such cases, fetal infection may occur following reactivation of latent bradyzoites with resultant circulating parasitemia.

III. MATERNAL/FETAL INFECTION

A. Clinical manifestations

1. Maternal infection is most commonly asymptomatic (>90%). Symptoms may include fatigue, painless lymphadenopathy, and chorioretinitis.
2. Fetal findings on ultrasound (US) include intrauterine growth restriction, hydrops fetalis, echogenic bowel, hepatosplenomegaly, ascites, hydrocephalus, pericardial and/or pleural effusions, and calcifications of the brain, spleen, and liver.

B. Diagnosis

1. Recommended maternal tests

a. Screening: serum immunoglobulin M (IgM) and IgG

i. Detection and quantification of antibodies in pregnant women can determine the presence and timing of infection. Serology performed earlier in pregnancy (i.e., first trimester) is more helpful in determining if infection was acquired during pregnancy than serology drawn after 18 weeks' gestation.

ii. Toxoplasma IgG and IgM: Initial testing may be performed at a nonreference commercial lab. Negative results or positive IgG and negative IgM (indicative of prior infection) reasonably exclude infection during the current pregnancy if performed prior to the third trimester. A positive or equivocal IgM should be confirmed at a reference laboratory (e.g., the Palo Alto Medical Foundation Toxoplasma Serology Laboratory [http://www.pamf.org/serology]).

iii. Toxoplasma-specific IgM may present within 2 weeks of infection and peaks at 1 month. It typically becomes negative within 6 to 9 months but can persist for more than a year. A reference lab can help determine if a patient with a positive IgM acquired infection recently or in the distant past.

b. Confirmatory testing of a positive or equivocal IgM test at a reference laboratory: IgG, IgM, immunoglobulin A (IgA), and immunoglobulin E (IgE). A series of IgG tests can help differentiate acute versus remote infection:

i. **Toxoplasma IgG avidity test used in conjunction with differential agglutination (AC/HS) test.** High avidity antibodies develop at least 12 to 16 weeks after infection. If positive during the first months of pregnancy, these antibodies indicate that infection occurred prior to conception. AC/HS compares IgG titers for sera against formalin (HS) versus acetone (AC) fixed tachyzoites. AC antigens detect acute IgG antibodies formed only during the acute stage of infection.

ii. **IgA and IgE antibodies** become undetectable more rapidly following acute infection, compared to IgM.

2. **Fetal testing**

a. US is recommended monthly in women suspected of having acute toxoplasmosis that acquired during or just before gestation.

b. Polymerase chain reaction (PCR) of amniotic fluid is recommended to diagnose fetal infection in the following cases: if acute infection or infection acquired during pregnancy cannot be excluded; if there is evidence of fetal abnormality on US; or if a pregnant woman is significantly immunocompromised with risk of reactivation. The optimal time for performance of an amniotic fluid PCR is at >18 weeks' gestation. Gestational age at the time of maternal primary infection significantly influences the sensitivity and negative predictive value (NPV) of molecular testing. Sensitivity of PCR testing is highest when maternal infection occurs between 17 and 21 weeks' gestation (93% sensitive) as opposed to earlier. High parasite DNA levels can be found in cases in which infection occurred earlier in gestation or sequelae are more severe. Because the accuracy range is wide and parasite transmission from the mother to the fetus may be delayed, a negative amniotic fluid PCR does not fully exclude fetal infection unless maternal infection occurred very early in gestation (<7 weeks [100% NPV]).

C. Treatment. If maternal toxoplasmosis is confirmed or suspected to have occurred at <18 weeks' gestation, treatment with spiramycin is recommended to reduce the likelihood of mother-to-child transmission. If fetal infection is highly likely (infection >18 weeks' gestation) or appears to have already occurred (positive amniotic fluid PCR or consistent fetal US findings), treatment with pyrimethamine, sulfadiazine, and folinic acid is recommended in an effort to prevent and/or treat fetal infection.

1. **Spiramycin** may prevent placental transmission of *T. gondii* but is insufficient for fetal infection because it does not cross the placenta. There is some controversy to its efficacy because no clearly designed prospective trials have been performed. Spiramycin is a macrolide antibiotic that appears to reduce or delay vertical transmission to the fetus through high placental drug levels. Spiramycin should be continued until delivery in patients with negative amniotic fluid PCR because of the theoretical risk of fetal transmission occurring later in pregnancy. Spiramycin is available in the United States as an investigational new drug through the U.S. Food and Drug Administration.

2. **Pyrimethamine, sulfadiazine, and folinic acid.** Combination therapy is recommended to treat fetal infection and/or prevent transmission to the fetus when maternal infection occurs at ≥18 weeks' gestation. Pyrimethamine has teratogenic potential and should not be used prior to 18 weeks' gestation. Patients should have complete blood count (CBC) monitoring during therapy due to its potential for bone marrow suppression.
3. For women with infection acquired ≥6 months before gestation, no treatment is recommended, with exception of women who are severely immunosuppressed and at risk for reactivation.

IV. NEONATAL INFECTION

A. Clinical manifestations. There are four recognized patterns of presentation for congenital toxoplasmosis.

1. **Subclinical/asymptomatic infection.** Most infants with congenital toxoplasmosis (70% to 90%) are asymptomatic at birth. If left untreated, however, a majority will develop visual or central nervous system (CNS) deficits, including hearing impairment, learning disabilities, or intellectual disabilities over months to years.
2. **Neonatal symptomatic disease.** Signs of congenital disease at birth include maculopapular rash, lymphadenopathy, hepatosplenomegaly, jaundice, pneumonitis, diarrhea, hypothermia, petechiae, and thrombocytopenia. CNS disease symptoms include cerebral calcifications, hydrocephalus, seizures, cerebrospinal fluid (CSF) abnormalities, meningoencephalitis, and chorioretinitis.
3. **Delayed onset** is most often seen with premature infants and occurs within the first 3 months of age. It can behave like neonatal symptomatic disease.
4. **Sequelae or relapse during infancy or childhood of a previously untreated infection.** Chorioretinitis develops in up to 85% of adolescents/young adults with previously unrecognized and untreated congenital infection.

B. Differential diagnosis. The clinical and laboratory findings are shared with other congenital "TORCH" infections caused by rubella, cytomegalovirus, syphilis, neonatal herpes simplex virus, HIV, enterovirus, and lymphocytic choriomeningitis virus (LCMV). Other disorders to be considered include hepatitis B, varicella, bacterial sepsis, hemolytic diseases, metabolic disorders, immune thrombocytopenia, histiocytosis, and congenital leukemia.

C. Diagnosis. Evaluation for congenital toxoplasmosis should occur in neonates with consistent clinical symptoms, following maternal *T. gondii* infection during pregnancy, or in the setting of maternal immunodeficiency and known chronic *T. gondii* infection. Diagnosis may be made by serology, PCR, and pathology (less common). Currently, the vast majority of states in the United States do not screen or report congenital toxoplasmosis.

1. **Toxoplasma serologies.** IgM, IgA, and IgG testing should be performed in a reference laboratory with special expertise in *T. gondii* serologies (i.e., Palo Alto Medical Foundation Toxoplasma Serology Laboratory).

Sabin-Feldman dye test (IgG), IgM immunosorbent agglutination assay (ISAGA), and IgA enzyme-linked immunosorbent assay (ELISA) should be obtained from the infant. In addition, serologic testing should also be performed in the postpartum mother, in an effort to determine if she appears to have been infected during gestation.

a. IgG appears within 1 to 2 weeks of infection, peaks at 1 to 2 months, and persists throughout life. Transplacental IgG antibody disappears by 6 to 12 months of age. A positive IgG at 12 months of age is diagnostic of congenital toxoplasmosis.

b. Positive IgM or IgA antibody at least 10 days after birth is also diagnostic. Data from the Palo Alto Medical Foundation Toxoplasma Serology Laboratory database demonstrated that in infants with untreated congenital toxoplasmosis, IgM was positive 86.6% of the time, IgA 77.4% of the time, and when both IgM and IgA were taken into consideration, 93.3% were positive. In congenital toxoplasmosis, antibody production varies significantly and is affected by treatment.

2. ***T. gondii* PCR.** Molecular testing of blood, CSF, and urine should be performed for all infants with suspected infection. A positive PCR is diagnostic of infection. When CSF PCR results were combined with IgM and IgA antibody results for diagnosis of congenital toxoplasmosis, sensitivity for diagnosis was increased. Ideally, samples should be obtained prior to initiating antiparasitic therapy.
3. **CSF findings.** CSF leukocytosis, elevated protein, and hypoglycorrhachia may be observed. CSF eosinophilia has been described.
4. **Pathologic findings.** *T. gondii*–specific immunoperoxidase staining can be performed on any tissue. Presence of extracellular antigens and surrounding inflammatory response are diagnostic.
5. **Ophthalmology exam** at birth and every 3 months until 18 months of age, followed by screening every 6 to 12 months until 18 years old
6. Screening for hearing loss with auditory brainstem response or otoacoustic emissions by 3 months of age; full audiologic evaluation by 24 months of age
7. Routine labs. Abnormal CBC, liver enzymes, and bilirubin levels can also be seen with disseminated disease.
8. **Brain imaging.** Head computed tomography (CT) scan without contrast is the preferred study. One study reported a clear relationship between the lesions on CT scan, neurologic signs, and the date of maternal infection.

   a. CT or magnetic resonance imaging (MRI) may detect calcifications not seen by ultrasonography. They may be single or multiple. Other abnormalities may be seen.

   b. Hydrocephalus is usually due to periaqueductal obstruction. Massive hydrocephalus may develop rapidly (<1 week).
9. Multidisciplinary consultation may facilitate patient management. Specialty consultation is typically required from the following:

   a. Infectious diseases

   b. Ophthalmology

c. Neurosurgery
d. Neurodevelopmental pediatrics

D. Treatment

1. Medications. For congenital toxoplasmosis, combination therapy for the duration of a year has been associated with decreased incidence of neurologic, cognitive, auditory, and ocular sequelae. Therapy also speeds resolution of acute symptoms. Patients should be weighed weekly and dosing adjusted accordingly. Monitoring for toxicity should occur weekly as well. Treatment in the first year of life is associated with improved clinical outcomes. Infected newborns who are not treated or who receive short courses of treatment have a high risk of developing new chorioretinal lesions later in life, along with other long-term sequelae.
   a. Pyrimethamine 2 mg/kg once daily for 2 days, then 1 mg/kg once daily for 6 months, and then 1 mg/kg three times a week (every other day) to complete 1 year of therapy
   b. Sulfadiazine 50 mg/kg every 12 hours for 1 year
   c. Folinic acid 10 mg three times a week, administered until 1 week after completing pyrimethamine
   d. Prednisone (0.5 mg/kg every 12 hours) may be added if CSF protein exceeds 1 g/dL or active chorioretinitis with lesions very close to macula.
2. Adverse events
   a. Most common adverse effects of pyrimethamine (a dihydrofolate reductase inhibitor) are neutropenia, thrombocytopenia, and anemia. CBC should be monitored weekly. Temporary cessation of pyrimethamine should be considered if absolute neutrophil count (ANC) falls below 500.
   b. Adverse effects of sulfadiazine include hemolysis in infants with glucose-6-phosphate dehydrogenase (G6PD) deficiency, bone marrow suppression, renal failure, and hypersensitivity.
   c. The same antiparasitic treatment regimen is recommended for infants born to mothers coinfected with both HIV and *T. gondii*. However, combining these antiparasitic agents with antiretrovirals such as zidovudine may increase the risk of bone marrow toxicity.
3. Ventricular shunting for hydrocephalus is recommended when necessary.

V. OUTCOMES.

The National Collaborative Congenital Toxoplasmosis (NCCT) study has reported outcomes in a series of children with congenital infection. Prolonged treatment for 1 year has been associated with improved outcomes for many congenitally infected children. All children who died had severe infection at birth.

A. Chorioretinitis. Ninety-one percent of children with asymptomatic or mild neurologic disease at birth did not develop new eye lesions after treatment. Of those with moderate or severe neurologic disease at birth, 64% of children did not develop new or recurrent lesions. With treatment, chorioretinitis usually resolved within 1 to 2 weeks and did not relapse during therapy. Relapse after treatment may occur, often during adolescence. Visual impairment is a prominent sequela, even with treatment, in 85% of patients who had severe disease at birth and 15% of neonates with mild or asymptomatic disease.

B. Neurologic outcomes. All neurologically asymptomatic or mildly affected patients at birth who were treated for 1 year had normal cognitive function, neurologic function, and hearing. More than 72% of those with moderate to severe neurologic disease who were treated for 1 year had normal cognitive or neurologic outcomes, and none had hearing loss.

C. These outcomes are significantly improved as compared to previous studies of untreated patients or patients treated for short duration.

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51 Syphilis

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KEY POINTS

- Prevention of congenital syphilis depends on the identification and adequate treatment of pregnant women with syphilis.
- Trends in congenital syphilis follow trends in primary and secondary syphilis rates among women, which have been rising.
- Women and infants with syphilis should be evaluated for HIV and other sexually transmitted diseases (STDs).
- Reverse screening approaches are increasingly popular but have high false-positive rates and need additional testing to confirm or exclude diagnosis.
- Affected infants can be asymptomatic at birth but present with symptoms later.
- Parenteral penicillin G remains the preferred drug for prevention and treatment of maternal and congenital syphilis.
- Late manifestations of congenital syphilis are preventable with early treatment.

I. INTRODUCTION.

Syphilis is a sexually transmitted infection caused by the spirochete *Treponema pallidum*. Pregnant women with syphilis can transmit it through the placenta to the fetus or at birth to the neonate. Congenital infection can have severe consequences to the fetus and newborn including perinatal death, premature delivery, low birth weight, congenital anomalies, active congenital syphilis, and long-term sequela such as deafness and neurologic impairment. Prevention of congenital syphilis depends on the identification and adequate treatment of pregnant women with syphilis.

II. CLINICAL MANIFESTATIONS

A. Congenital syphilis.

Congenital infection may result in stillbirth, hydrops fetalis, and/or prematurity and can present with a range of symptoms and signs in live births. For reporting purposes, congenital syphilis includes cases of congenitally acquired syphilis among infants and children as well as syphilitic stillbirths.

1. Most affected infants are asymptomatic at birth, but clinical signs usually develop within the first 1 to 3 months of life. Signs of **early congenital syphilis** (younger than 2 years old) include hepatosplenomegaly,

lymphadenopathy, maculopapular copper rash on hands and feet, edema, condylomata lata, watery nasal discharge (snuffles), pneumonia, jaundice, hemolytic anemia, thrombocytopenia, and skeletal abnormalities (osteochondritis, periostitis, pseudoparalysis).

2. **Late congenital syphilis** presents in an untreated older child (older than 2 years old) with skeletal stigmata such as frontal bossing, short maxilla, high palatal arch, Hutchinson teeth (peg-shaped central incisors), saddle nose, anterior bowing of shins, and Clutton joints (painless symmetric knee joint swelling). Late manifestations include interstitial keratitis (5 to 20 years) and sensorineural deafness (10 to 40 years). **Neurosyphilis** can present at any stage. Early treatment prevents occurrence of late manifestations of congenital syphilis.
3. **Differential diagnosis.** Symptoms and signs of congenital syphilis in neonates are similar to those of other neonatal infections, including toxoplasmosis, herpes simplex, cytomegalovirus, rubella, and neonatal sepsis. Clinical data from mother, physical findings, and laboratory tests can help to make the diagnosis.

B. Maternal syphilis

1. **Primary stage (primary syphilis)** is manifested by one or more chancres (painless indurated ulcers) at the site of inoculation, typically the genitalia, anus, or mouth, often accompanied by painless regional lymphadenopathy. These highly infectious lesions appear around 3 weeks after exposure and heal spontaneously in a few weeks.
2. **Secondary stage (secondary syphilis)** occurs in around 25% of untreated patients, 3 to 6 weeks after the appearance of the chancre. It is characterized by a generalized polymorphic maculopapular rash, involving the palms and soles and sparing the face. Sore throat, fever, headache, diffuse lymphadenopathy, myalgias, arthralgias, alopecia, condylomata lata, and mucous membrane plaques may also occur. The symptoms completely resolve without treatment in 3 to 12 weeks. A latent period follows. Most women present at this stage.
3. **Latent syphilis** is defined as the ensuing period when patients are positive by serologic testing with no clinical manifestations of disease. **Early latent syphilis** refers to the period within a year of infection. **Late latent syphilis** refers to the period past 1 year of initial infection (or if the timing of infection is unknown).
4. **Tertiary stage (tertiary syphilis)** usually occurs 4 to 30 years after the secondary stage in about one-third of untreated patients and is characterized by gummata (benign but tissue destructive lesions), cardiovascular syphilis, especially inflammation of the great vessels, or neurosyphilis. These lesions are thought to be due to a pronounced immunologic reaction.
5. **Neurosyphilis** may occur at any stage of the disease especially in patients with HIV. Manifestations include syphilitic meningitis, uveitis, seizures, optic atrophy, and, later, dementia and posterior column disease (tabes dorsalis).

III. EPIDEMIOLOGY.

Congenital syphilis results from transplacental passage of *T. pallidum* or contact with infectious lesions during birth. Transplacental transmission of *T. pallidum* can occur throughout pregnancy. The risk of transmission to the fetus correlates with the proximity of maternal infection—the more recent the maternal infection, the more likely transmission to the fetus. During primary and secondary syphilis, the likelihood of transmission from an untreated woman to her fetus is extremely high, approaching 100%. After the secondary stage, the likelihood of transmission to the fetus declines steadily until it reaches approximately 10% to 30% in late latency.

Trends in congenital syphilis usually follow trends in primary and secondary syphilis among women, with a lag of 1 to 2 years. Although rates of congenital syphilis declined from 2008 to 2012, cases increased by 87% from 2012 to 2016, from 8.4 to 15.7 cases per 100,000 live births. The highest number of cases (918) in 20 years was reported in 2017. The rise in congenital syphilis cases over this time period mirrors a national increase in syphilis rates among women of reproductive age.

Factors associated with risk for congenital syphilis include lack of prenatal health care, maternal HIV infection, and maternal illicit drug use. Clinical scenarios that contribute to the occurrence of congenital syphilis include lack of prenatal care; no serologic test for syphilis (STS) performed during pregnancy; a negative STS in the first trimester, without repeat testing later in pregnancy; a negative maternal STS around the time of delivery in a woman who was recently infected with syphilis but had not converted her STS yet; laboratory error in reporting STS results; delay in treatment of a pregnant woman identified as having syphilis; and noncompliance with or failure of treatment in an infected pregnant woman.

IV. DIAGNOSTIC TESTS FOR SYPHILIS

A. Confirmed syphilis. Definitive diagnosis is established by demonstration of *T. pallidum* spirochetes by darkfield microscopy, polymerase chain reaction (PCR), or immunohistochemical (IHC) test, or special stains of specimens from lesions, nasal discharge, placenta, umbilical cord, or autopsy material.

B. Probable diagnosis of syphilis (See Table 51.1 for interpretation of STS.)

1. **Nontreponemal tests** include the rapid plasma reagin (RPR) test and the venereal disease research laboratory (VDRL) slide test. These tests measure antibody directed against a lipoidal antigen from *T. pallidum* and/or its interaction with host tissues. These tests give rapid semiquantitative results, measure a baseline titer, and identify recent/new infection and response to treatment. Titers usually rise with each new infection and fall after effective treatment. A sustained fourfold decrease in titer of the nontreponemal test within 6 to 12 months of treatment demonstrates adequate therapy; a similar increase after treatment suggests reinfection. RPR values are usually higher than VDRL and results are not interchangeable—either one should be measured consistently in mother and infant and through the treatment course.

Table 51.1 Interpreting Treponemal and Nontreponemal Tests

Nontreponemal Test (RPR, VDRL)	Treponemal Test (FTA-ABS, TP-PA, TP-EIA, TP-CIA)	Outcome	Additional Evaluation?
Reactive—low titer (<1:8)	Nonreactive	**1.** Likely false positive **2.** Early primary infection **3.** Serofast state from old treated infection (>1–2 years prior)	Retest in 2–4 weeks to see if titers rising.
Nonreactive	Nonreactive	**1.** Likely true negative **2.** Prozone phenomenon	Test RPR/VDRL at further dilutions to rule our prozone.
Reactive—high titer or fourfold increase in titer	Reactive	Likely true positive	Treat; measure RPR/VDRL titers serially to ensure fourfold decrease.
Nonreactive	Reactive	Other spirochetal diseases (Lyme, yaws, pinta) Occasionally, prior treated syphilis	Perform second treponemal test targeting different *Treponema pallidum* antigen.

RPR, rapid plasma reagin; VDRL, venereal disease research laboratory; FTA-ABS, fluorescent treponemal antibody absorption test; TP-PA, *T. pallidum* particle agglutination; TP-EIA, *T. pallidum* enzyme immunoassay; TP-CIA, *T. pallidum* chemiluminescence immunoassay.

Nontreponemal tests are positive in approximately 80% of cases of primary syphilis, nearly 100% of cases of secondary syphilis, and 75% of cases of latent and tertiary syphilis. In secondary syphilis, the RPR or VDRL test result is usually positive in a titer >1:16. In the first attack of primary syphilis, the RPR or VDRL test will usually become nonreactive 1 year after treatment, whereas in secondary syphilis (and most congenital syphilis), the test will usually become nonreactive approximately 2 years after treatment. In latent or tertiary syphilis, the RPR or VDRL test may become nonreactive 4 or 5 years after treatment or may never turn completely nonreactive ("serofast state").

False-negative tests can occur in early primary syphilis and late latent or late congenital syphilis. The prozone phenomenon, another cause of false-negative nontreponemal tests, occurs when a negative or weakly positive reaction occurs due to very high antibody concentrations. In this case, dilution of the serum will result in a positive test.

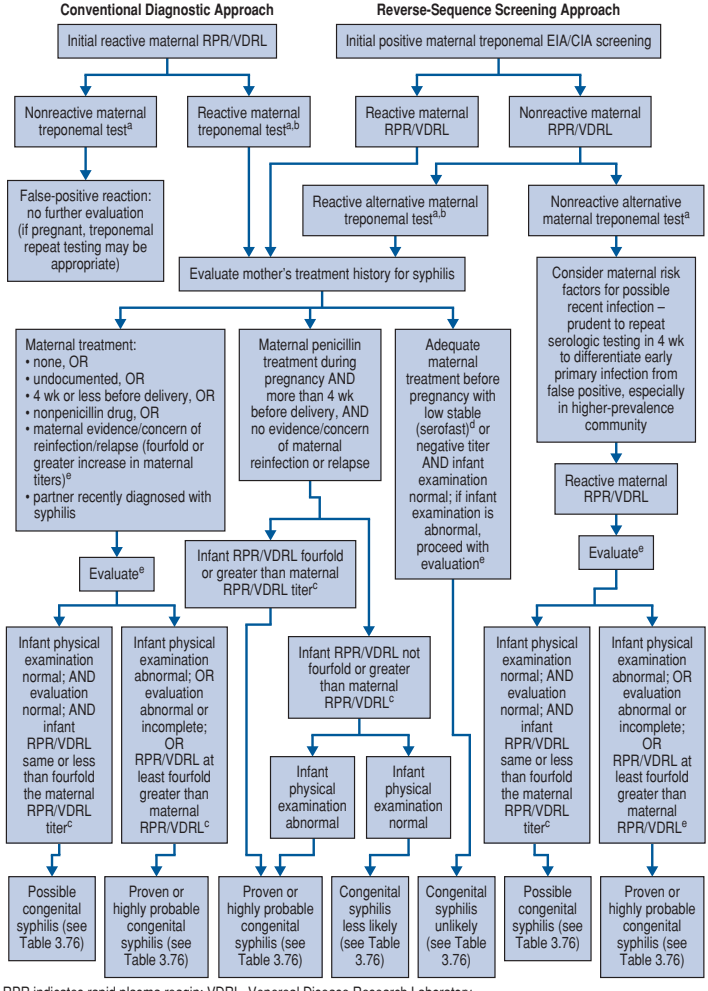
False-positive tests occur in 1% of cases due to causes including pregnancy, autoimmune and connective tissue diseases (systemic lupus erythematosus [SLE]), viral infections (Epstein-Barr virus [EBV], hepatitis, varicella), intravenous (IV) drug use, endocarditis, tuberculosis, malaria, laboratory error, and Wharton jelly contamination. Patients usually have low titers (1:8 or less) and nonreactive treponemal tests.

A reactive nontreponemal test in a patient with classical symptoms indicates a presumptive diagnosis; however, any positive nontreponemal test should be confirmed by a treponemal test to exclude a false-positive test result.

2. **Treponemal tests** include the fluorescent treponemal antibody absorption test (FTA-ABS), the *T. pallidum* particle agglutination (TP-PA) test, the *T. pallidum* enzyme immunoassay (TP-EIA), and the *T. pallidum* chemiluminescence immunoassay (TP-CIA). Treponemal tests correlate poorly with disease activity and remain positive for life in 75% to 85% of patients ("serologic scar"), even after successful therapy; they should not be used to assess treatment response. False-positive treponemal tests occur occasionally, particularly in other spirochetal diseases such as Lyme disease, yaws, pinta, leptospirosis, and rat-bite fever; nontreponemal tests are usually nonreactive in these conditions.

   Traditionally, treponemal tests are used to confirm positive nontreponemal tests. However, several laboratories use a reverse screening approach (TP-EIA or TP-CIA) due to ease of automated testing. TP-EIA and TP-CIA can be associated with high false-positive rates in low-risk populations and especially in pregnant women, and need additional testing. If positive, a nontreponemal test is performed which, if also reactive, confirms syphilis. If the nontreponemal test is negative, a second treponemal test (TP-PA) is performed to resolve the discordant results (Fig. 51.1).

C. Laboratory tests in neurosyphilis. Patients with neurosyphilis may demonstrate increased cerebrospinal fluid (CSF) protein concentration, increased CSF white blood cell (WBC) count, and/or a reactive CSF VDRL test. Suggested parameters for abnormal values include a CSF WBC count of >15 WBC/mm^3 or a CSF protein >120 mg/dL during the first 30 days of life. After the first 30 days of life, a CSF WBC count of >5 WBC/mm^3 or a CSF protein >40 mg/dL is regarded as abnormal. The CSF VDRL is highly specific (a positive CSF VDRL test result is diagnostic) but insensitive (a negative CSF VDRL test result does not exclude neurosyphilis). An exception to high specificity in neonates is that nontreponemal immunoglobulin G (IgG) antibodies may be able to cross the blood–brain barrier and lead to a false-positive CSF VDRL test. The FTA-ABS test is recommended by some experts for CSF testing because it is more sensitive than the VDRL test; however, contamination with blood during the lumbar puncture may result in a false-positive CSF FTA-ABS test result. A negative CSF FTA-ABS test result is good evidence against neurosyphilis. The RPR test should not be used for CSF testing.



RPR indicates rapid plasma reagin; VDRL, Venereal Disease Research Laboratory.
[a] *Treponema pallidum* particle agglutination (TP-PA) (which is the preferred treponemal test), fluorescent treponemal antibody absorption (FTA-ABS), or microhemagglutination test for antibodies to *T pallidum* (MHA-TP).
[b] Test for human immunodeficiency virus (HIV) antibody. Infants of HIV-infected mothers do not require different evaluation or treatment for syphilis.
[c] A fourfold change in titer is the same as a change of 2 dilutions. For example, a titer of 1:64 is fourfold greater than a titer of 1:16, and a titer of 1:4 is fourfold lower than a titer of 1:16. When comparing titers, the same type of nontreponemal test should be used (eg, if the initial test was an RPR, the follow-up test should also be an RPR).
[d] Stable VDRL titers 1:2 or less of RPR 1:4 or less beyond 1 year after successful treatment are considered low serofast.
[e] Complete blood cell (CBC) and platelet count; cerebrospinal fluid (CSF) examination for cell count, protein, and quantitative VDRL; other tests as clinically indicated (eg, chest radiographs, long-bone radiographs, eye examination, liver function tests, neuroimaging, and auditory brainstem response).

Figure 51.1. Algorithms for conventional and reverse-sequence approaches to diagnosis of syphilis. (Republished with permission of American Academy of Pediatrics; American Academy of Pediatrics. Syphilis. In: Kimberlin DW, Barnett ED, Lynfield R, et al, eds. *Red Book: 2021 Report of the Committee on Infectious Disease*. 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021:729–743; permission conveyed through Copyright Clearance Center, Inc.)

V. EVALUATION AND TREATMENT OF CONGENITAL SYPHILIS. No newborn should be discharged from the hospital until the mother's serologic syphilis status has been determined. Routine screening of newborn serum or cord blood in place of screening maternal blood is not recommended because of potential false-negative results.

A. Any infant born to a mother with a reactive nontreponemal test should have the following:

1. Complete physical examination looking for evidence of congenital syphilis
2. Quantitative nontreponemal test (RPR or VDRL). The same test should be performed on infant serum as the mother to compare titers. The infant's titer should begin to fall by 3 months and become nonreactive by 6 months if the antibody is passively acquired. If the baby was infected, the titer will not fall and may rise. The tests may be negative at birth if the infection was acquired late in pregnancy. In this case, repeating the test later will confirm the diagnosis.
3. Treponemal test to confirm diagnosis
4. Pathologic examination of the placenta or umbilical cord using specific fluorescent antitreponemal antibody staining, if available
5. Darkfield microscopic examination or direct fluorescent antibody staining of suspicious lesions or body fluids (e.g., nasal discharge)
6. Any child at risk for congenital syphilis should receive a full evaluation for HIV infection.
7. The diagnosis and treatment approach to infants being evaluated for congenital syphilis depends on (i) identification of maternal syphilis, (ii) adequacy of maternal therapy, (iii) maternal serologic response to therapy, (iv) comparison of maternal and infant serologic titers, and (v) the findings on the infant's physical examination.

B. Evaluation and treatment of infants <1 month

1. The Centers for Disease Control and Prevention (CDC) recommends classifying infants into one of the following four categories:
   a. Proven or highly probable congenital syphilis
      i. Diagnostic criteria
         a) Abnormal physical examination consistent with congenital syphilis OR
         b) Nontreponemal titer that is fourfold higher than the mother's titer, e.g., mother's titer 1:2 or 1:4, neonate 1:8 or 1:16 (Note: The absence of a fourfold or greater titer does not exclude congenital syphilis.) OR
         c) A positive darkfield test or PCR of lesions or body fluid
      ii. Recommended evaluation
         a) CSF analysis for VDRL, cell count, and protein concentration
         b) Complete blood count (CBC) with differential and platelet count
         c) Other tests as clinically indicated, including long-bone radiographs, chest radiograph, liver function tests, neuroimaging, ophthalmologic examination, and auditory brainstem response

iii. Recommended regimens
a) Aqueous crystalline penicillin G 50,000 units/kg per dose every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days
b) Procaine penicillin G 50,000 units/kg per dose IM daily for 10 days

b. Possible congenital syphilis

i. Diagnostic criteria
a) Neonate with normal physical examination AND
b) Serum quantitative nontreponemal serologic titer equal to or less than fourfold the maternal titer AND one of the following:
1) Maternal treatment not given, inadequate, or lacking documentation
2) Mother was treated with nonpenicillin regimen (e.g., erythromycin)
3) Maternal treatment administered <4 weeks before delivery

ii. Recommended evaluation
a) CSF analysis for VDRL, cell count, and protein
b) CBC with differential and platelet count
c) Long-bone radiographs

iii. Recommended regimens
a) Aqueous crystalline penicillin G 50,000 units/kg per dose every 12 hours during the first 7 days of life and every 8 hours thereafter for a total of 10 days
b) Procaine penicillin G 50,000 units/kg per dose intramuscular (IM) daily for 10 days.
c) Benzathine penicillin G 50,000 units/kg per dose IM in a single dose **only** if evaluation completely normal (CBC with differential and platelets, CSF analysis with VDRL, cell count and protein concentration, and long-bone radiographs) and follow-up is certain. If any part of the infant's evaluation is abnormal or not interpretable (e.g., CSF sample contaminated with blood), or if follow-up is not certain, then the full 10-day course of aqueous or procaine penicillin G should be given.

c. Congenital syphilis less likely

i. Diagnostic criteria
a) Neonate with normal physical examination AND
b) Serum quantitative nontreponemal titer equal to or less than fourfold the maternal titer AND
c) Mother was treated during pregnancy with an appropriate penicillin regimen >4 weeks before delivery AND
d) No evidence of maternal reinfection or relapse

ii. Recommended evaluation
a) No evaluation is recommended.

iii. Recommended regimen
a) Benzathine penicillin G 50,000 units/kg per dose IM in a single dose
b) For an infant whose mother's nontreponemal titers have decreased at least fourfold after appropriate therapy for early syphilis or remained stable at low titer (RPR <1:4), an alternative approach

involves not treating the infant but providing close follow-up every 2 to 3 months until the nontreponemal test is nonreactive.

d. Congenital syphilis unlikely

i. Diagnostic criteria

a) **Neonate with** normal physical examination AND

b) Serum quantitative nontreponemal serologic titer equal or less than fourfold the maternal titer AND

c) Adequate maternal treatment before pregnancy AND

d) Maternal nontreponemal titer remained low and stable (serofast) before and during pregnancy and at delivery (VDRL <1:2 or RPR <1:4).

ii. Recommended evaluation

a) No evaluation is recommended.

iii. Recommended regimen

a) No treatment is required; however, some experts recommend a single dose of penicillin G benzathine 50,000 units/kg IM, particularly if follow-up is uncertain.

C. Evaluation and treatment of infants and children older than 1 month. Infants and children identified as having a reactive STS should be examined thoroughly and have maternal serology and treatment records reviewed to determine if the child has congenital or acquired syphilis.

1. Recommended evaluation

a. CSF analysis for VDRL, cell count, and protein concentration

b. CBC with differential and platelet count

c. Other tests as clinically indicated, including long-bone radiographs, chest radiograph, liver function tests, cranial ultrasonography, ophthalmologic examination, and auditory brainstem response

d. Any infant or child at risk for congenital syphilis should receive a full evaluation and testing for HIV infection.

e. If diagnosed as acquired syphilis, the child should be evaluated for possible sexual abuse.

2. Recommended treatment

a. Aqueous crystalline penicillin G 200,000 to 300,000 units/kg/day IV, administered as 50,000 units/kg every 4 to 6 hours for 10 days.

b. If the infant or child has no clinical manifestations of congenital syphilis and the evaluation (including the CSF examination) is normal, treatment with up to 3 weekly doses of penicillin G benzathine, 50,000 units/kg IM can be considered.

c. Some experts also suggest administering a single dose of penicillin G benzathine 50,000 units/kg IM following the 10-day course of IV therapy.

VI. SCREENING AND TREATMENT OF PREGNANT WOMEN FOR SYPHILIS

A. Effective prevention and detection of congenital syphilis depends on the identification of syphilis in pregnant women. Routine serologic screening of pregnant women should occur during the first prenatal visit. The CDC recommends additional testing at 28 weeks' gestation and at delivery for women who are at increased risk or live in communities with an increased prevalence

of syphilis infection. When a woman presents in labor with no history of prenatal care or if results of previous testing are unknown, an STS should be performed at delivery, and the infant should not be discharged until the results are known. In women at very high risk, consideration should be given to a repeat STS 1 month postpartum to capture the rare patient who was infected just before delivery but had not yet seroconverted. All positive nontreponemal STS in pregnant women should be confirmed with a treponemal test. If the treponemal test is negative, a positive nontreponemal test is likely a false positive; repeat treponemal testing in 2 to 4 weeks may be considered in high-risk patients to evaluate for seroconversion.

B. Pregnant women with a reactive nontreponemal STS confirmed by a reactive treponemal STS should be treated regardless of stage of pregnancy unless previous adequate treatment is clearly documented and follow-up nontreponemal titers have declined at least fourfold.

C. Adequate treatment for pregnant women is defined as "completion of a penicillin-based regimen," in accordance with CDC treatment guidelines, appropriate for stage of infection, initiated 30 or more days before delivery.

D. Treatment of pregnant women with syphilis

1. **Primary, secondary, and early latent syphilis (without neurosyphilis).** Benzathine penicillin G 2.4 million units IM in a single dose is the preferred treatment. Some experts recommend a second dose of 2.4 million units IM 1 week after the first dose.
2. **Late latent syphilis and tertiary syphilis (without neurosyphilis).** Benzathine penicillin G benzathine 7.2 million units administered as three doses of 2.4 million units IM at 1-week intervals.
3. **Neurosyphilis.** Aqueous crystalline penicillin G 18 to 24 million units daily administered as 3 to 4 million units IV every 4 hours for 10 to 14 days. If compliance can be assured, an alternative regimen of penicillin G procaine 2.4 million units IM daily plus probenecid 500 mg orally four times a day for 10 to 14 days may be used. At the end of these therapies, some experts recommend penicillin G benzathine 2.4 million units IM weekly for up to 3 weeks.
4. Penicillin-allergic patients. There are no proven alternatives to penicillin for the prevention of congenital syphilis. If an infected pregnant woman has a history of penicillin allergy, she may be skin tested against the major and minor penicillin determinants. If these test results are negative, penicillin may be given under medical supervision. If test results are positive or unavailable, the patient should be desensitized and then given penicillin. Desensitization should be done in consultation with an expert and in a facility where emergency treatment is available.
5. The Jarisch-Herxheimer reaction—fever, chills, headache, myalgias, and exacerbation of cutaneous lesions—may occur after treatment of pregnant women for syphilis. Fetal distress, premature labor, and stillbirth are rare but possible. Patients should be made aware of the possibility of such reactions, but concern about such complications should not delay treatment.

6. Monthly follow-up should be provided to any mother treated for syphilis in pregnancy. A sustained fourfold decrease in nontreponemal titer should be seen with successful treatment.
7. All patients with syphilis should be evaluated for other sexually transmitted diseases (STDs), such as chlamydia, gonorrhea, hepatitis B, and HIV.
8. HIV-infected pregnant women should receive the same treatment as HIV-negative pregnant women, except that treatment for primary and secondary syphilis and early latent syphilis may be extended to 3 weekly doses of benzathine penicillin G 2.4 million units IM per week.

VII. FOLLOW-UP ON INFANTS TREATED FOR CONGENITAL SYPHILIS.

All neonates with reactive nontreponemal tests should receive careful follow-up examinations and nontreponemal titers every 2 to 3 months until the test becomes nonreactive. In the neonate who was not treated due to low likelihood of infection, or infected but adequately treated, nontreponemal antibody titers should decline by age 3 months and be nonreactive by age 6 months. At 6 months, if the nontreponemal test is nonreactive, no further evaluation or treatment is needed. Treated neonates who exhibit persistent or rising nontreponemal test titers at 6 to 12 months should be reevaluated through CSF examination and managed in consultation with an expert. Retreatment with a 10-day course of a penicillin G regimen may be indicated. Neonates whose initial CSF evaluations are abnormal should undergo a repeat lumbar puncture approximately every 6 months until the results are normal. A reactive CSF VDRL test or abnormal CSF indices that persist and cannot be attributed to other ongoing illness requires retreatment for possible neurosyphilis and should be managed in consultation with an expert. Treponemal tests are not used to evaluate response to treatment in congenital syphilis; passively transferred maternal treponemal antibodies can cause persistent seropositivity for up to 15 months.

VIII. INFECTION CONTROL

A. Isolation of hospitalized patient. *Red Book 2018* recommends standard precautions for all patients, including infants with suspected or proven congenital syphilis. Gloves should be worn when caring for patients with congenital, primary, and secondary syphilis with skin and mucous membrane lesions (which can be contagious) until 24 hours of treatment has been completed.

B. Control measures. All people who have had close unprotected contact with a patient with early congenital syphilis (before identification of the disease or during the first 24 hours of therapy) should be examined clinically for the presence of lesions 2 to 3 weeks after contact. Immediate treatment can be considered for high-risk exposures. Serologic testing should be performed and repeated 3 months after contact or sooner if symptoms occur.

C. Assistance and guidance in syphilis testing and treatment are available from the CDC, Atlanta, Georgia, and state health departments.

Suggested Readings

American Academy of Pediatrics. Syphilis. In: Kimberlin DW, Barnett ED, Lynfield R, et al, eds. *Red Book: 2021 Report of the Committee on Infectious Disease*. 32nd ed. Itasca, IL: American Academy of Pediatrics; 2021:729–743.

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52 Tuberculosis

Saki Ikeda and Jeffrey R. Starke

KEY POINTS

- The World Health Organization (WHO) estimates that 1.2 million children developed tuberculosis (TB) disease in 2019, causing an estimated 205,000 deaths (32,000 occurring in HIV-infected children).
- TB infection is determined through use of either the Mantoux tuberculin skin test (TST) or an interferon γ release assay (IGRA).
- True congenital TB with transmission from the mother to the fetus *in utero* is quite rare but can occur in several ways: hematogenous spread through the umbilical vein, aspiration of infected amniotic fluid, or ingestion of other infected materials.
- The clinical signs and symptoms of congenital TB vary in relation to the intensity of transmission as well as the site of disease.

I. EPIDEMIOLOGY AND INCIDENCE. *Mycobacterium tuberculosis* is the etiologic agent that causes tuberculosis (TB). The organism produces a spectrum of clinical entities that have differing diagnostic and management approaches. Prior to any discussion about TB, it is helpful to define these entities (Table 52.1).

Over a quarter of the world's population is infected with *M. tuberculosis*. Each year, at least 10 million people develop TB disease, and 1.5 million people die as a result. The World Health Organization (WHO) estimates that 1.2 million children developed TB disease in 2019, causing 205,000 deaths (32,000 occurring in HIV-infected children).

In the early 20th century, TB was a common entity in the United States. The advent of effective anti-TB medications in the 1950s resulted in a declining TB prevalence until the mid-1980s. At that time, a decline in public health services, the HIV epidemic, an increase in immigration from high-prevalence countries, and increased transmission in congregate settings caused a sudden upsurge in cases (20% increase overall and 40% increase among children). This surge peaked in 1992 at 26,673 reported annual cases. Once increased strategic public health measures were enacted in the early 1990s, the incidence subsequently decreased to 8,920 cases in 2019.

In the United States, most TB-infected patients are found in certain high-risk groups, as listed in Table 52.2. Approximately 70% of TB cases in the United States occur in foreign-born individuals. Foreign-born individuals are screened and treated only for TB disease before they immigrate; treatment of TB infection requires that they enter into care after arrival in the United States, which can be difficult due to lack of insurance and a medical home. Persons traveling to the United States on visitors' visas receive no TB screening. Thus, many foreign-born

Table 52.1. Definitions	
Tuberculosis exposure	Occurs when an individual has had contact with a case of contagious tuberculosis disease in the past 3 months. An exposed individual may or may not have infection or disease.
Tuberculosis infection	Occurs when an individual has a positive tuberculin skin test result (defined in Table 52.2) or a positive interferon γ release assay result (defined in the text), a normal physical exam, and a chest radiograph that is either normal or shows evidence of healed calcifications. An untreated infected individual can develop tuberculosis disease in the near or distant future.
Tuberculosis disease	Occurs when an evident illness (signs, symptoms, and/or radiographic changes) is caused by *Mycobacterium tuberculosis*.
Congenital tuberculosis disease	Occurs when a neonate is infected with *M. tuberculosis in utero* or during delivery and develops disease afterward. This is determined by having a positive acid-fast bacillus stain or culture from the neonate, with exclusion of possible postnatal transmission, and either lesions in the first week of life, primary hepatic complex or caseating hepatic granulomas, or tuberculosis infection of the placenta or maternal genital tract.
Postnatally acquired tuberculosis disease	Occurs when an infant is infected after delivery, either through inhalation of *M. tuberculosis* from a contagious caregiver or ingestion of *M. tuberculosis* via infected breast or cow milk and develops signs, symptoms, and/or radiographic evidence of tuberculosis disease.

Table 52.2. Groups at High Risk for Tuberculosis Infection
Foreign-born person from high-prevalence countries
Persons with a family history of tuberculosis infection or disease
Individuals who travel to high-prevalence countries
Inmates of correctional facilities
Illicit drug users
Migrant families
Homeless persons

women are at risk for developing TB disease after arrival in the United States. For many young women, their first health care visit after arrival is during their pregnancy or at labor and delivery, and this may be the best opportunity to diagnose and manage their TB infection or disease.

II. TRANSMISSION AND PATHOGENESIS. Transmission of *M. tuberculosis* most commonly occurs when an individual expectorates infectious droplet nuclei, which may remain airborne for hours. An individual whose sputum is acid-fast bacillus (AFB) smear positive is the most likely to be infectious. Individuals who are AFB smear negative but culture positive are generally less infectious than those who are AFB smear positive, but many can still transmit the organism. Fomites and other secretions rarely cause transmission.

Infants and children with pulmonary TB usually do not produce a cough effective enough to expectorate the droplet nuclei necessary to spread the disease, and they usually have a low burden of organisms; hence, childhood TB is often called "pauci-bacillary disease." As a result, children rarely infect others. However, adolescents with reactivation pulmonary disease or children who have hallmarks of adult-type disease (cavitary lung lesions with an effective cough) may be contagious. In addition, children with true congenital TB often have a large pulmonary burden of organisms and may transmit infection to health care workers, especially if they are intubated. Within 2 weeks of starting effective treatment, a patient of any age with drug-susceptible TB usually becomes noncontagious, but a patient with multidrug-resistant TB (MDR-TB) may remain infectious for weeks to months after starting treatment.

Once the droplet nuclei are inhaled, *M. tuberculosis* bacilli land in the alveoli where they multiply freely or are consumed by alveolar macrophages. In some individuals, the immune system is able to clear the infection without treatment. In others, *M. tuberculosis* subverts the alveolar macrophages' attempts at its degradation and instead replicates inside macrophages for several weeks. As the bacilli multiply, they frequently are carried into regional lymph nodes by alveolar macrophages and can spread hematogenously to other sites, including but not limited to the vertebrae, peritoneum, meninges, liver, spleen, lymph nodes, and genitourinary tract. Most patients are asymptomatic during this time and usually have no radiologic evidence of disease. The exception to this occurs in infants, who are at much higher risk for progressing rapidly to symptomatic disease due to their immature immune system. Although healthy adults infected with *M. tuberculosis* have a 5% to 10% of developing TB disease within their lifetime, the majority who do so—including pregnant women—develop disease within the first 1 to 2 years after infection. Infants and toddlers who are infected but untreated have a 40% chance of developing disease within 6 to 9 months. The risk to both the mother and the child is greatest when the mother has been infected recently. Any condition that depresses cell-mediated immunity (HIV infection, diabetes mellitus, poor nutritional status, biologic response modifying drugs [such as tumor necrosis factor-α inhibiting drugs] or high-dose corticosteroids) increases the risk of progression from infection to disease in adults and children.

In young children, the organisms tend to spread to the regional hilar and mediastinal lymph nodes, which then enlarge if inflammation is intense. The lymph nodes can compress or erode into the bronchi, frequently resulting in a distal atelectasis or parenchymal infection, causing the so-called "collapse-consolidation" lesion. However, the hallmark of childhood

TB is intrathoracic lymphadenopathy with or without subsequent parenchymal disease.

A. TB infection. TB infection is defined as having evidence of an immune response to *M. tuberculosis*–related antigens. **TB infection is determined through use of either the Mantoux tuberculin skin test (TST) or an interferon-γ release assay (IGRA).**

1. **The TST** is a delayed-type hypersensitivity test to determine if the patient reacts to a purified protein derivative (PPD) of *M. tuberculosis*. The delayed-type hypersensitivity typically develops 3 to 9 weeks after the TB infection occurs; the TST will be negative before this time. The PPD is placed subcutaneously, typically on the left volar forearm. After 48 to 72 hours, the area is examined for any induration and the amount of induration is measured and recorded. A TST is interpreted as positive depending on the measurement of the induration as well as risk factors that the patient may have (Table 52.3).
2. **IGRAs** are blood tests that detect the production of interferon-γ, a chemical routinely released by immune cells as they combat TB organisms. The IGRAs include positive and negative controls, and because there is no "gold standard" for TB infection, their thresholds for positivity have been determined from studies in adults who have culture-positive TB disease. These tests help to determine if someone has been infected with *M. tuberculosis*, but they do not differentiate between infection and disease. There are two IGRAs approved for clinical use in the United States: QuantiFERON-TB Gold Plus test (QIAGEN, Germantown, Maryland) and the T-SPOT.*TB* test (Oxford Immunotec, Abingdon, United Kingdom). Although PPD contains hundreds of mycobacterial antigens, the IGRA tests use only two or three that are specific for *M. tuberculosis*. The IGRAs do not cross-react with *Mycobacterium bovis*-bacille Calmette-Guérin (BCG) (the organism used in TB vaccines) or *Mycobacterium avium* complex, the most common environmental nontuberculous mycobacterium. Because these two organisms are responsible for most false-positive TST results, the IGRAs are more specific than the TST. An additional advantage of the IGRAs is that they require only one provider visit to take blood. However, they require specific laboratory capacities and are more expensive than the TST. Although the IGRAs are more specific for infection by *M. tuberculosis* than TSTs, they appear to offer no increased sensitivity. IGRAs can be used to diagnose TB infection in both adults and children.

III. MATERNAL TB.

There are a handful of large studies in the modern era that examine the impact of pregnancy on TB and of TB on pregnancy; the majority of literature predates the 1960s. Prior to the availability of anti-TB medications, TB disease had a poor prognosis for both the fetus and the mother. Now, with effective therapy, the mother with TB can be cured and the fetus or child spared from disease. Providers should screen all pregnant women for risk factors of TB infection or disease at an early prenatal visit, and questionnaires have been developed to aid this screening. Women belonging to high-risk groups, such as those listed in Table 52.2, or contacts to a current or previous TB case, should be tested immediately with a TST or an IGRA. There is strong evidence that pregnancy does not alter the response to the TST and that the TST does not adversely

Table 52.3. Definitions of Positive Tuberculin Skin Test

≥5 mm Induration	10–14 mm Induration	≥15 mm Induration
Persons living with HIV	Persons who immigrated from a high-prevalence country in the past 5 years	Persons with no risk factors for tuberculosis disease
Recent contacts of contagious tuberculosis disease cases	Injection drug users	
Individuals with chest radiographic changes suggestive of tuberculosis disease	Residents and employees of the following high-risk congregate settings: ■ Prisons/jails ■ Nursing homes/long-term care facilities for the elderly ■ Hospitals and other health care facilities ■ Residential facilities for HIV/AIDS patients ■ Homeless shelters	
Organ transplant or otherwise immunosuppressed patients (receiving the equivalent of 15 mg/day of prednisone or more)	Mycobacteriology laboratory personnel Persons with any of the following high-risk clinical conditions: ■ Silicosis ■ Diabetes mellitus ■ Chronic renal failure ■ Hematologic disorders (e.g., leukemia and lymphoma) ■ Carcinoma of the head, neck, or lung ■ Weight loss (>10% ideal body weight) ■ Any infant, child, or adolescent in contact with a high-risk adult	

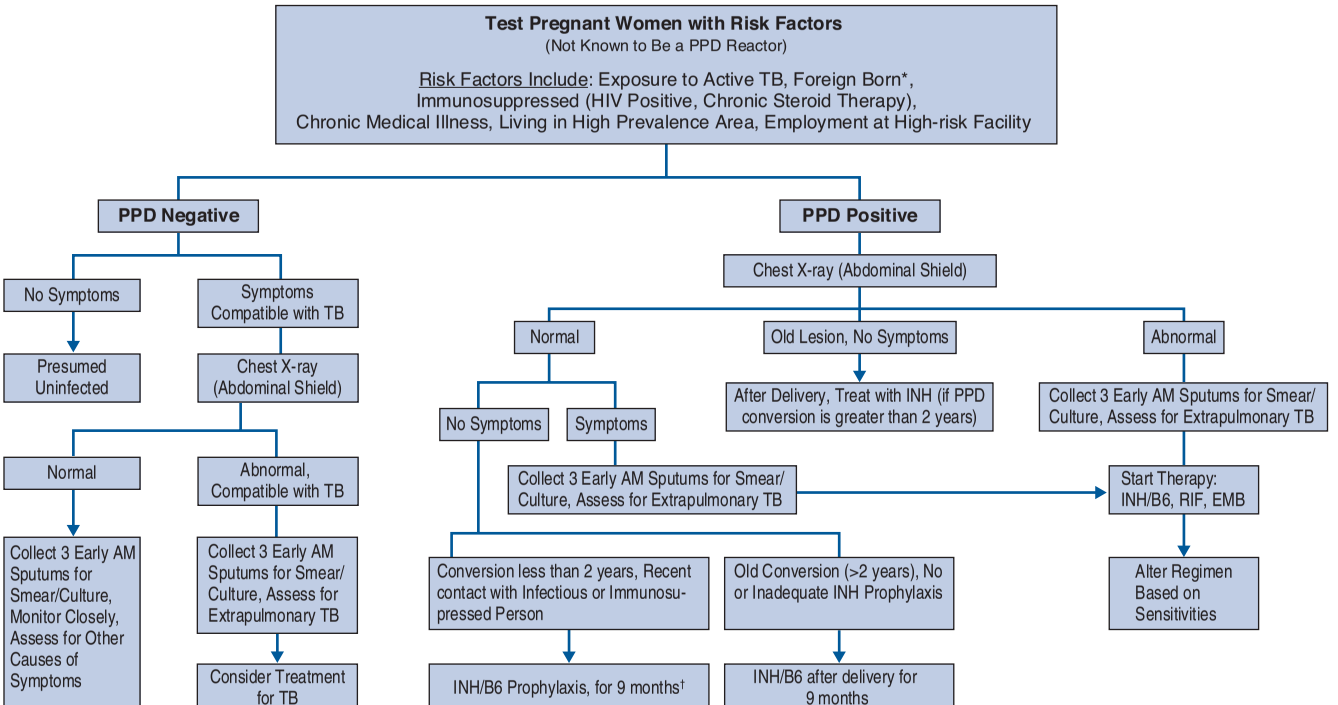
affect the woman or the fetus. Similarly, the IGRA results do not appear to be affected by pregnancy. TB of the female genital tract has been associated with 0.2% to 21% of infertility cases, depending on the local TB rates. This involves the fallopian tubes which is affected in majority of the cases, the ovaries, and the endometrial cavity (50% to 70%). Cervical and vaginal disease are rare. Female genital TB presents clinically as infertility as a result of tubal obstruction or adhesions of the uterine cavity. This may complicate *in vitro* fertilization (IVF), and screening for TB should be considered when a woman from a high–TB-burden country or with other risk factors requires IVF.

A. Management of maternal TB infection. If a pregnant woman has a positive TST as defined in Table 52.2, or a positive IGRA, she should undergo an evaluation for TB disease, which includes a complete medical history and physical exam and a chest radiograph with abdominal shielding. The chest radiograph should not be deferred until after delivery because the fetus can be protected and the outcome for the mother and the baby usually is worse if TB disease goes undetected during the pregnancy. Once TB disease is excluded, the timing of treatment of TB infection in the mother is considered. If the mother likely has been infected recently, or is immunocompromised in any way, treatment of the mother's TB infection should be started during the pregnancy. If the woman does not belong to these highest risk groups, some experts recommend that her treatment wait until after the child is delivered. The most common treatment of TB infection for the pregnant woman has been 300 mg of isoniazid (INH) taken daily. INH is known to cause a peripheral neuropathy due to depletion of vitamin B_6 (pyridoxine), and pregnant women taking INH should also be given this vitamin.

1. **When the pregnant woman has TB infection**, it is recommended that the remainder of the household and extended family be investigated for TB infection and disease. The purpose is to find, diagnose, and treat a potentially infectious individual that the child could be exposed to after delivery, thereby minimizing risk of transmission of the organism to the infant and others. However, if this has not occurred by the time of delivery, the child's discharge to home should not be held up while this is occurring unless a symptomatic family member is identified. Although the local health departments are typically responsible for contact tracing when a case of TB disease is found, due to inadequate resources, most do not provide this service when the pregnant woman has only TB infection, and this investigation is left to other health care providers. When the mother is undergoing treatment for TB infection and no current case of TB disease is found, her infant does not need to be treated for TB infection or disease.

B. Management of maternal pulmonary TB disease (Fig. 52.1)

1. **Symptoms.** If a pregnant woman is found to have a positive TST or IGRA, the clinical evaluation for TB disease should include a history and thorough physical examination. Patients with pulmonary TB usually complain of some combination of fever, cough, weight loss, fatigue, or, less frequently, hemoptysis. However, pregnant women can have relatively fewer symptoms than might be suggested by the extent of disease in the chest radiograph. Extrapulmonary TB can occur almost anywhere in the body, but the most common sites are the cervical or supraclavicular lymph nodes, bones and joints, peritoneum, meninges, or genitourinary system.



†Although there are no known teratogenic effects of isoniazid, some experts recommend waiting until the 2nd trimester before initiating treatment for tuberculosis infection.

Figure 52.1. Diagnosis and treatment of tuberculosis in the pregnant woman. PPD, purified protein derivative; TB, tuberculosis; INH, isoniazid; RIF, rifampin; EMB, ethambutol.

The most common "symptom" of female genitourinary TB is difficulty conceiving, but abnormal patterns of menstrual bleeding also occur commonly. Extrapulmonary TB rates are increased in HIV-coinfected patients. Maternal TB disease portends negative effects on the fetus. Mothers with untreated TB disease are more likely to have infants who are premature or are small for gestational age. They are also more likely to have stillbirths.

2. **Radiographic findings.** A chest radiograph, performed with abdominal shielding to protect the fetus, should be obtained for every pregnant woman with untreated TB infection to rule out pulmonary TB disease even if she is asymptomatic. Radiographic findings consistent with TB disease include focal or multinodular infiltrates, cavitation, decreased expansion of the upper lobes of the lung, and hilar or mediastinal adenopathy. Although most adults with pulmonary TB have lesions in the apices of the upper lobes, pregnant women have an increased tendency to have lesions in other lung areas, presenting with a somewhat "atypical" radiographic picture.

3. **Culture.** Any pregnant woman suspected of having pulmonary TB disease will need microbiologic evaluation, which usually consists of three early morning sputum samples that are stained for acid-fast bacteria, tested with a nucleic acid amplification test, such as PCR, and cultured for mycobacteria. Due to the slow growth of the *M. tuberculosis*, up to 6 weeks may be required to detect the organism on solid media, and conventional drug susceptibility testing can take several weeks longer. If liquid media are used, as is common in modern laboratories, the organism is more often detected within 2 to 3 weeks. If extrapulmonary disease is suspected, appropriate samples, including tissue biopsy of the affected sites if no secretion or excretion is available, should be obtained and sent for AFB stain and mycobacterial culture. In most centers, a molecular diagnostic technique is available to assist with diagnosis. Xpert MTB/RIF Ultra (Cepheid, Sunnydale, California) is a nested real-time PCR that tests for *M. tuberculosis* DNA as well as the genetic material that confers resistance to the first-line drug rifampin (RIF). Xpert MTB/RIF Ultra is less sensitive than culture but yields results within 2 to 3 hours. The sensitivity improves in instances of AFB smear–positive disease. In addition, the U.S. Centers for Disease Control and Prevention (CDC) TB laboratory performs rapid molecular testing for drug resistance for the first-line and many second-line drugs on isolates of *M. tuberculosis* complex. These molecular tests may have false-negative or false-positive tests, and the data should be interpreted in the clinical context and confirmed using culture methods for drug susceptibility testing.

4. **Treatment**

   a. Nonpregnant adults. When TB disease is suspected in nonpregnant adults, initial therapy consists of four drugs: RIF, INH, pyrazinamide (PZA), and ethambutol (EMB), or so-called RIPE therapy. If the patient is found to have drug-susceptible disease, EMB can be removed from the regimen at that time. The other drugs are continued for 2 months as an induction period. After 2 months, PZA is then removed from the regimen, but INH and RIF are continued for another 4 months in a continuation phase. This gives a total length of therapy of 6 months. If there are cavitary lesion in the lungs, therapy is usually extended to

9 months. If drug resistance is found, it is recommended that an expert in TB treatment be consulted. If there are extrapulmonary manifestations or the patient does not respond quickly to standard treatment, the treatment course may need to be prolonged. All TB disease treatment regimens should be administered via directly observed therapy (DOT), an intervention where medications are administered to the patient by a health care professional or trained third-party member, often a local health department employee, who observes either in-person or via video and documents that the patient ingests each dose of medication.

b. Pregnant women. Treatment in pregnant women differs in that the initial regimen often includes only RIF, INH, and EMB. PZA is sometimes excluded because there is a smaller amount of data on PZA's safety during pregnancy, but most TB experts include PZA in the initial regimen, and the WHO recommends its use in pregnancy. Pyridoxine is added to prevent the peripheral neuropathy associated with INH use during pregnancy, as mentioned earlier. The first-line drugs are considered safe for the fetus, and the risks of poorly treated disease far outweigh the risks of treatment. Anti-TB drugs that are usually contraindicated for pregnant women include kanamycin, amikacin, and capreomycin (hearing loss); the fluoroquinolones are not routinely given to pregnant women because of inadequate safety data but may be used for suspected drug resistance or if one or more of the primary drugs cannot be tolerated. If drug resistance is found that requires use of medications with unknown or adverse fetal effects, consultation with a TB expert is recommended.

c. Other considerations. Anti-TB medications are present in small amounts in breast milk, on average about 5% to 10% of serum concentrations. Treatment of TB infection or disease in the mother is not a contraindication to breastfeeding. Because breast milk also has very low concentrations of pyridoxine, it is recommended to give pyridoxine to any breastfeeding infant who is also taking INH or whose mother is taking the drug.

Pregnant women with pulmonary TB disease may be contagious via the airborne route. While hospitalized, all patients suspected of having pulmonary TB disease should be placed initially in airborne isolation in a negative air pressure room. All staff should wear fit-tested N95 respirator masks. Most hospitals will require that a patient remain in isolation until there have been three consecutive negative early morning AFB sputum smears. If a patient is found to have MDR-TB, the patient should be isolated for the entire hospital stay.

In all instances of ***suspected*** TB disease, the local health department should be notified promptly to start contact tracing aimed at finding newly infected individuals as well as others who may have TB disease so that they can be treated and stop transmission to others.

IV. TUBERCULOSIS OF THE FETUS OR NEWBORN

A. Congenital tuberculosis

1. **Pathogenesis.** True congenital TB with transmission from the mother to the fetus *in utero* is quite rare but can occur in several ways: hematogenous spread through the umbilical vein, aspiration of infected amniotic fluid, or ingestion of other infected materials. If the mother has TB disease or is

infected during pregnancy, the organisms may disseminate hematogenously to the placenta and, from there, may spread to the fetus via the umbilical vein. However, placental infection does not guarantee transmission to the fetus; likewise, the absence of organisms in the placenta does not ensure that the child remains uninfected. The usual deposits of hematogenous spread follow the path of the umbilical vein. The liver is frequently infected, where a primary focus develops within periportal lymph nodes. The organisms may spread beyond the liver and into the main systemic circulation by the patent foramen ovale or into the pulmonary circulation via the right ventricle. Multiple sites may be seeded initially or seeded secondarily to the initial hepatic or pulmonary foci. The definitive lesion of congenital TB is the hepatic primary complex with caseating hepatic granulomas. Congenital TB may disseminate to include bone marrow infiltration; osteomyelitis; mesenteric lymphadenitis; and tubercles and granulomas of the adrenal glands, GI tract, spleen, kidneys, meninges, and skin.

If the placenta develops a caseous lesion that ruptures into the amniotic fluid, the primary foci may be found in the lungs or in the gastrointestinal tract. The disease can secondarily disseminate to other organ systems. Rarely, the dissemination can be swift and massive, and the child will present with a sepsis-like syndrome. The fetus can inhale or ingest the organisms that can spread to the middle ear and cause disease via the eustachian tube as the fetus swallows.

2. **Symptoms.** The clinical signs and symptoms of congenital TB vary in relation to the intensity of transmission as well as the site of disease. Occasionally, symptoms are noted at birth, but they more commonly begin at 1 to 3 weeks of life because the organisms are obligate aerobes and thrive best in the oxygen-rich postnatal environment. The initial presentation can be similar to sepsis or a congenital infection and should be suspected if an ill neonate does not respond to empiric antimicrobials and has an otherwise unrevealing evaluation. Hepatosplenomegaly and respiratory distress are the two most common signs and symptoms, followed by fever.
3. **Radiographic findings.** Chest radiography is usually abnormal, with half of neonates having a miliary disease pattern (but this pattern may not develop for several days to weeks of illness). Other neonates have adenopathy and parenchymal infiltrates.
4. **Additional considerations.** Because the two available types of testing for TB infection—TST and IGRAs—depend on a fully functioning immune system, they are frequently negative in neonates and infants with TB infection or disease. Negative tests of infection should never be considered to rule out TB infection or disease in a neonate or infant undergoing evaluation for these conditions.

   All neonates suspected of having congenital TB should be placed in airborne isolation while the evaluation is in process because confirmed cases often have extensive pulmonary involvement; there have been case reports of transmission of *M. tuberculosis* from a congenitally infected patient to a health care worker, but not directly to other neonates, with the exception of transmission due to contaminated respiratory equipment. The congenitally infected neonate's family members should also be screened with radiography because they may have subclinical but radiographic signs of TB disease that has not yet been diagnosed.

Investigation of congenital TB should include assessment of the mother's risk factors for TB, and suspicion should be high if the mother has had an otherwise unexplained pneumonia, bronchitis, meningeal disease, difficulty getting pregnant, unusual pattern of uterine bleeding, or endometritis before, during, or after pregnancy. The placenta should be examined by a pathologist and should be cultured for *M. tuberculosis*. If the placenta is not available, the mother should be examined and consideration be given to performing a uterine dilation and curettage because endometrial specimens often yield positive culture results. The infant should be evaluated for microbiologic confirmation of disease by AFB smear and culture of body fluids or tissues, including gastric aspirates, middle ear fluid, bone marrow, tissue biopsy, and tracheal aspirates. The cerebrospinal fluid (CSF) should also be examined because TB meningitis occurs in one-third of congenital TB cases.

V. POSTNATAL TRANSMISSION OF *MYCOBACTERIUM TUBERCULOSIS*.

Persons with TB infection are not contagious, so there is no risk to the infant if the mother has TB infection without disease. Occasionally, an infant will be exposed postnatally to a visitor or caregiver with TB disease, including the child's mother, another household contact, or even a nursery worker. Recommended management in these scenarios includes evaluating the neonate for clinical evidence of TB disease with a physical examination and chest radiography (posteroanterior and lateral views). Infants with postnatal acquisition of *M. tuberculosis* frequently have the same symptoms as congenitally infected neonates. However, they typically present later, at the age of 1 to 6 months, and lack the primary hepatic focus seen in congenital TB. If an infant has evidence of TB disease, the same clinical evaluation, isolation precautions, and treatment as used for suspected congenital TB should occur.

VI. TREATMENT OF NEONATAL TB DISEASE.

Once the diagnosis of congenital or postnatal TB is *suspected*, treatment should be initiated promptly. Due to the rarity of these conditions, the data regarding the pharmacokinetics of anti-TB drugs in neonates are limited. RIF, INH, PZA, and either an EMB or an aminoglycoside such as amikacin comprise the initial suggested regimen. Neonates and infants have a high risk of developing disseminated disease or meningitis, so amikacin is often used instead of EMB due to its bactericidal activity and better central nervous system (CNS) penetration across inflamed meninges. If the infant cannot tolerate oral medications, RIF, amikacin, and levofloxacin can be given intravenously; an expert in managing TB should be consulted in such cases. If the organism is susceptible to first-line medications, the initial four-drug regimen should be continued for the first 2 months of therapy, followed by treatment with INH and RIF for an additional 7 to 10 months, a total duration of treatment of 9 to 12 months. If TB meningitis is suspected, amikacin should be substituted for EMB and 2 mg/kg/day of prednisone (or equivalent corticosteroid) should be administered for the first 4 to 6 weeks with a slow taper to prevent development of hydrocephalus or infarcts caused by vasculitis. Neonatal TB always should be managed with the help of an expert in TB.

A. Prognosis. The prognosis of neonatal TB disease—particularly true congenital TB—is guarded, and the mortality rate, even with effective treatment, is

25% to 50%. The diagnosis and institution of effective treatment are often delayed because congenital TB is rare, the clinical onset often occurs several weeks after birth, the mother's TB disease has not been diagnosed, and confirming the disease in the neonate and the mother can be difficult. Pulmonary damage in the infant can be extensive resulting in atelectasis or a bronchiolitis obliterans–like picture. Infants often suffer from growth delay, even when usually adequate calories are taken, because of the energy requirements created by the disease. Electrolyte disturbances are common, particularly hyponatremia caused by the inappropriate secretion of antidiuretic hormone or renal salt wasting. A variety of neurologic complications can occur when TB meningitis is present, including hearing loss, visual impairments, global developmental delay, seizures, hemiparesis, and cognitive abnormalities.

VII. MANAGEMENT OF AN EXPOSED NEONATE. The American Academy of Pediatrics' 2018 *Red Book* includes recommendations for the management of a neonate or infant exposed to a contact with TB infection or TB disease and are as follows:

A. Mother (or household contact) has evidence of TB infection and a normal chest radiograph findings. If the mother or household contact is asymptomatic, no separation is required. The mother usually is a candidate for treatment of TB infection after the initial postpartum period. The newborn infant needs no special evaluation or therapy. Because of the young infant's exquisite susceptibility, and because the mother's positive TST or IGRA result could be a marker of an unrecognized case of contagious TB within the household, other household members should have a TST or an IGRA and further evaluation if positive; however, this evaluation should not delay the infant's discharge from the hospital. The mother can breastfeed her child.

B. Mother (or household contact) has clinical signs and symptoms and/or abnormal findings on chest radiograph consistent with TB disease. Cases of suspected or proven TB disease in mothers (or household contacts) should be reported immediately to the local health department, and investigation of all household members should start as soon as possible. If the mother has possible TB disease, the infant should be evaluated for congenital TB, and the mother should be tested for HIV infection. If the mother has an abnormal chest radiograph, she and the infant should be separated until she has been evaluated, and if TB disease is suspected, until she and her infant are receiving appropriate anti-TB therapy. Once the infant is receiving INH, separation is not necessary unless the mother (or household contact) has possible MDR-TB disease or has poor adherence to treatment, and DOT is not possible. If the mother is suspected of having MDR-TB disease, an expert in TB disease treatment should be consulted. When the mother and child are together, the mother should wear a mask and must be willing to adhere to all appropriate infection-control measures. Usually, contact between a potentially contagious mother and her infant should be brief and occur in a very well-ventilated room. Women with drug-susceptible TB disease who have been treated appropriately for 2 or more weeks and who are not considered contagious can breastfeed.

Once congenital TB is excluded, INH is given until the infant is 3 or 4 months of age (some experts recommend 6 months of age), when a TST

should be performed. If the TST result is positive, the infant should be reassessed for TB disease. If TB disease is excluded in an infant with a positive TST result, INH alone should be continued for a total of 9 months. The infant should be evaluated monthly during treatment for signs of illness or poor growth. If the TST result is negative at 3 to 4 months of age and the mother (or household contact) has good adherence and response to treatment and is no longer contagious, INH should be discontinued.

C. Mother (or household contact) has a positive TST or IGRA and abnormal findings on chest radiography but no evidence of TB disease. If the chest radiograph of the mother (or household contact) appears abnormal but is not suggestive of TB disease and the history, physical examination, and sputum smear indicate no evidence of TB disease, the infant can be assumed to be at low risk for *M. tuberculosis* infection and need not be separated from the mother (or the household contact). The mother and her infant should receive follow-up care, and the mother should be treated for TB infection. Other household members should have a TST or IGRA and further evaluation.

VIII. BCG. BCG vaccines are among the oldest vaccines worldwide. They are attenuated strains of *M. bovis*, a close relative of *M. tuberculosis*. The original BCG strain created at the Pasteur Institute has been lost, but early on, it was sent to several different laboratories which have each maintained their own strain. As a result of the different methods or propagation used at these laboratories, there are many BCG strains that differ significantly in important properties. The preponderance of evidence indicates that BCG vaccination prevents 60% to 90% of disseminated TB disease and TB meningitis in infants and young children. There is inconsistent evidence that the vaccine prevents pulmonary disease in older persons. The BCG vaccines remain in use in most high-burden countries.

Within the United States, the use of BCG vaccine is limited. The CDC currently recommends considering BCG vaccination for children with a negative TST who cannot be separated from an untreated or "ineffectively treated" adult with TB disease, or an MDR-TB case, as defined by resistance to at least INH and RIF.

The vaccine is typically given intradermally and produces a pustule at the injection site before leading to a permanent scar. Possible adverse reactions include local ulceration and regional lymphadenitis. These adverse events are not necessarily immediate. In normal hosts, these events may take weeks to months to develop and resolve. In immunocompromised hosts, the lesions may take years to develop and resolve. Severely immunocompromised individuals can develop disseminated disease from the BCG vaccine. As a result, BCG is not recommended for HIV-infected or exposed children; patients with congenital immunodeficiency or malignancy; or patients on immune-modulating drugs such as corticosteroids, chemotherapy, or radiation. All adverse events should be reported to the vaccine manufacturer.

It should be noted that after BCG immunization, the child may develop a positive reaction to a TST. Some studies have shown that the majority of children who received a BCG vaccine in infancy will have a negative TST at 5 to 10 years of age. However, the BCG vaccines do not induce a positive IGRA test result (Tables 52.4 and 52.5).

Table 52.4. Commonly Used Medications for Treatment of Tuberculosis Disease

Drug and Dosage Forms	Activity	Dosage	Maximum Dose	Pregnancy Category	Side Effects	Other
Isoniazid (INH) **Scored tablets:** **100 mg** **300 mg** **Intravenous solution**	Bactericidal	10–15 mg/kg/day Or 20–30 mg/kg/dose twice weekly after 2 months of treatment	300 mg	C	Peripheral neuropathy Mild transaminitis Hepatitis Hypersensitivity	Requires pyridoxine supplementation (25–50 mg/day) if the patient has any of the following: **1.** Breastfed, pregnant, or lactating **2.** Nutritional deficiencies **3.** Symptomatic HIV infection **4.** Meat- and milk-deficient diet
Rifampin (RIF) **Capsules:** **150 mg** **300 mg** **Intravenous solution**	Bactericidal	15–20 mg/kg/day (same dose when given twice weekly)	600 mg	C	Vomiting Hepatitis Influenza-like reaction Thrombocytopenia Pruritus	Discolors urine and other secretions an orange color Causes oral contraceptives to be ineffective

Pyrazinamide (PZA) **Scored tablets:** **500 mg**	Bactericidal	30–40 mg/kg/day Or 50 mg/kg/dose twice weekly	2 g	C	Hepatitis Hyperuricemia Arthralgia GI upset	Hyperuricemia and arthralgias most prominent in adolescents and adults
Ethambutol (EMB) **Tablets:** **100 mg** **400 mg**	Bacteriostatic (except at high doses)	15–25 mg/kg/day	2.5 g	C	Optic neuritis Decreased red-green color discrimination GI disturbances Hypersensitivity	Does not cross blood–brain barrier well, thus not recommended for TB meningitis treatment
Amikacin **Intravenous solution**	Bactericidal	15–30 mg/kg IV or IM	1 g	D —	Auditory and vestibular toxicities Nephrotoxicity	Can be used in place of ethambutol in TB meningitis treatment

GI, gastrointestinal; TB, tuberculosis; IV, intravenous; IM, intramuscular.

Table 52.5. Key Summary Points

Tuberculosis in the United States is most common among people born or with frequent travel to high-prevalence countries.
The presenting signs and symptoms of neonatal tuberculosis include a sepsis-like episode that does not respond to empiric antibiotics or a presentation consistent with congenital infection for which no other cause can be found.
Diagnostic criteria for congenital tuberculosis: **1.** Proved tuberculous lesions such as positive stain or culture **2.** One of the following: a. Lesions in the first week of life b. Primary hepatic complex or caseating hepatic granulomas c. Tuberculosis infection of the placenta or maternal genital tract d. Exclusion of the possibility of postnatal transmission
All neonates suspected of having congenital tuberculosis should be put in airborne isolation, and all visitors should be screened for tuberculosis disease.
The health department should be notified of all suspected tuberculosis disease cases in order to start a contact investigation.
The neonate with possible congenital tuberculosis should be evaluated for disseminated disease and meningitis.
Treatment should always include the following: ■ Rifampin ■ Isoniazid ■ Pyrazinamide ■ An aminoglycoside should be used if tuberculous meningitis is suspected. If CSF evaluation is negative for meningitis, then ethambutol can be used. ■ Pyridoxine should be added if the patient is exclusively taking breast milk.
Therapy should be tailored based on the patient or the mother's drug susceptibility testing.
All treatment should be administered by directly observed therapy (DOT).

CSF, cerebrospinal fluid.

Suggested Readings

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53 Lyme Disease

Michael E. Russo

KEY POINTS

- No evidence of a congenital Lyme disease syndrome
- No evidence that *Borrelia burgdorferi* is transmitted in human milk
- Pregnant individuals who develop Lyme disease should be treated.
- Prevention of Lyme disease is best by avoiding tick-infested areas, use of tick repellents, and surveillance for tick attachment with immediate removal.

I. LYME DISEASE. Lyme disease is the most commonly reported vector-borne disease in the United States. The causative organism in North America is the spirochete *Borrelia burgdorferi* sensu stricto, which is transmitted to humans through the bite of *Ixodes* ticks. In the United States, the cases of Lyme disease correlate with the distribution of the tick vector and major reservoirs: *Ixodes scapularis* and the white-footed mouse in the East and Midwest and *Ixodes pacificus* and the western gray squirrel in the West. Most cases in the United States are clustered along the Atlantic coast from Maine through Virginia and in the Midwest in Wisconsin and Minnesota. Rare cases occur sporadically from Northern California into the Pacific Northwest. Lyme disease also occurs in Eastern Canada, and parts of Europe, China, Japan, and Russia. In Eurasia, there are two additional genotypes (*Borrelia afzelii* and *Borrelia garinii*) that cause Lyme disease but with a variation in the clinical presentation. In the United States, humans are most likely to be infected in the summer months of June through August. Ticks must be attached for at least 36 to 48 hours to transmit infection. The incubation period from tick bite to the appearance of skin lesions ranges from 3 to 30 days with a median of 11 days.

The clinical manifestations of Lyme disease are generally divided into three stages: early localized, early disseminated, and late disseminated disease. In the **early localized** stage, an annular, erythematous, nonpruritic lesion known as *erythema migrans* presents at the site of a tick bite, usually within 1 to 2 weeks. Over several days, the lesion enlarges to 5 cm or more in diameter and occasionally develops central clearing providing the classic "bulls-eye" appearance. The early localized stage may present with or without constitutional symptoms such as fever, malaise, headache, myalgia, and arthralgia. Patients with **early disseminated** disease, may present with multiple erythema migrans lesions due to spirochetemia, weeks after the initial tick bite. These lesions are typically smaller than the primary solitary lesion seen in early localized disease. Other manifestations of early disseminated disease (occurring weeks to months

after the initial infection) may include neurologic involvement (lymphocytic meningitis, cranial nerve palsy—especially cranial nerve VII—or peripheral radiculopathy) and carditis (atrioventricular block and myocardial dysfunction). Patients may also have mild constitutional symptoms during this stage. **Late disseminated** disease occurs months to years after the onset of infection and manifests primarily as an intermittent relapsing monoarticular arthritis of large joints, particularly the knee.

Postnatal infections in infants are exceedingly rare, likely given the lack of exposure to ticks as well as the frequent care that would allow ticks to be identified and removed before transmission can occur.

Early case reports raised concerns about a potential congenital Lyme disease syndrome analogous to that seen with other spirochetal infections such as syphilis. However, multiple prospective and retrospective epidemiologic studies and surveys in endemic regions have not supported an association between maternal infection and adverse fetal or neonatal outcomes. Of note, *I. scapularis* can transmit *Babesia microti* which can on rare occasion affect the fetus; there have been about 10 cases reported of congenital babesiosis presenting in the first 1 to 2 months of life.

There is no evidence that *B. burgdorferi* is transmitted in human milk or any other bodily fluid.

II. DIAGNOSIS. Early Lyme disease is a clinical diagnosis made on the recognition of the classic erythema migrans lesion in patients living in or visiting an endemic area. Individuals frequently have not yet developed an immunoglobulin M (IgM) response, and thus, serologic testing usually does not play a role at this stage unless testing acute and convalescent samples to confirm atypical cases.

Serologic testing is only indicated when there is a recent history of living or traveling to an endemic Lyme disease area and symptoms are consistent with either early or late disseminated disease as described earlier. Standard serologic testing in these scenarios entails a two-tier algorithm using an initial enzyme immunosorbent assay (EIA) to detect IgM and/or immunoglobulin G (IgG) antibodies followed by a confirmatory Western blot if the EIA is positive. False-positive serologic tests from infection/colonization with cross-reacting microbes or autoimmune diseases are common. Additionally, both IgM and IgG responses from resolved infections can linger for months to decades. Modified two-step algorithms using two EIA's with different targets in combination with one another have been developed, but the utility of these compared to the traditional algorithm is still an area on ongoing study. Polymerase chain reaction (PCR) for detection of *B. burgdorferi* has extremely limited utility outside of testing synovial fluid in certain cases of Lyme arthritis where the diagnosis is uncertain despite positive serologic testing.

III. TREATMENT OF MOTHERS AND THE NEWBORN. Patients diagnosed with Lyme disease during pregnancy should be treated in accordance with consensus guidelines, most recently updated in 2020, from the Infectious Diseases Society of America (IDSA), the American Academy of Neurology (AAN), and the American College of Rheumatology (ACR). The specific agents used

and their duration vary depending on the age of the patient and the clinical manifestation and are outside the scope of this chapter. The treatment regimens are the same for pregnant persons as for nonpregnant persons except that doxycycline is contraindicated. In the rare case in which an infant is postnatally infected, the treatment would generally be the same as for other children aside from any age or condition-specific contraindications to ceftriaxone or long durations of doxycycline. Of note, in 2018, the American Academy of Pediatrics concluded that prior concerns about adverse effects of doxycycline on dentition have not borne out and recommended that doxycycline may be used younger than 8 years of age for any indication for durations ≤21 days.

A. Isolation. Standard isolation precautions are recommended.

B. Newborn of mother with confirmed Lyme disease in pregnancy. Mothers should be reassured that Lyme disease does not appear to affect neonates, whether or not the mother was treated. The infant does not require any specific evaluation or treatment. If the infant has findings concerning for a congenital infection, investigations should be directed toward other common causes.

C. Prevention of Lyme disease. Prevention rests on avoidance of tick-infested areas, use of appropriate repellents, and careful examination for and removal of ticks as soon as possible after attachment. A single dose of doxycycline for prophylaxis after a high-risk bite (the tick can be identified as an *Ixodes* species, the bite occurred in an endemic area, and it has been attached ≥36 hours) can be considered within 72 hours of tick removal. A detailed discussion of prevention strategies and prophylaxis can be found in the aforementioned IDSA/AAN/ACR 2020 guidelines. Screening of pregnant women whether living in endemic or nonendemic areas is not recommended.

Suggested Readings

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54 Intracranial Hemorrhage and White Matter Injury/Periventricular Leukomalacia

Janet S. Soul

KEY POINTS

- Serial cranial ultrasound (CUS) studies are best for detecting and managing germinal matrix/intraventricular hemorrhage (IVH) and its complications (especially progressive ventricular dilation) and periventricular leukomalacia (PVL), and brain magnetic resonance imaging (MRI) at term age may provide additional prognostic information for preterm neonates.
- Newborns with large IVH are at risk for developing progressive ventricular dilation, which should be monitored carefully with serial measurements of ventricular size by CUS and treated with lumbar punctures (LPs) and/or surgical interventions to reduce cerebrospinal fluid (CSF) volume and ideally to prevent ventriculoperitoneal (VP) shunt placement and improve long-term outcome.
- Seizures may occur but are often subclinical; therefore, continuous video electroencephalogram (cvEEG) monitoring should be obtained for newborns with large intraventricular, parenchymal, subarachnoid, or subdural hemorrhage (SDH).
- A large intracranial hemorrhage (ICH) of any type is an emergency that requires prompt stabilization with volume replacement, pressors and respiratory support, as needed, and urgent neuroimaging (ideally MRI or CUS) and neurosurgical consultation, and avoidance of LP until neuroimaging is obtained.
- Due to radiation exposure, computed tomography (CT) scanning should be reserved for **urgent** situations in which MRI or ultrasound (US) is not available.

OVERVIEW

The incidence of intracranial hemorrhage (ICH) varies from 2% to >30% in newborns, depending on gestational age (GA) at birth and the type of ICH. Bleeding within the skull can occur in the following locations:

1. External to the brain into the epidural, subdural, or subarachnoid spaces
2. Into the parenchyma of the cerebrum or cerebellum
3. Into the ventricles from the subependymal germinal matrix or choroid plexus (Table 54.1)

The incidence, pathogenesis, clinical presentation, diagnosis, management, and prognosis of ICH varies according to the ICH location and size and the newborn's GA. There is often a combination of two or more types of ICH because an ICH in one location often extends into an adjacent compartment; for example, extension of a parenchymal hemorrhage into the subarachnoid space or ventricles, such as a thalamic hemorrhagic infarction with associated intraventricular hemorrhage (IVH).

Diagnosis usually depends on clinical suspicion when a newborn presents with typical neurologic signs, such as seizures, irritability, depressed level of consciousness, and/or focal neurologic deficits referable to either the cerebrum or brainstem. Diagnosis is confirmed with an appropriate neuroimaging study. Magnetic resonance imaging (MRI) is the optimal imaging modality for almost all types of ICH, but cranial ultrasound (CUS) is typically preferred for premature newborns and critically ill newborns who are not stable for transport to MRI. When MRI is obtained, susceptibility-weighted imaging (SWI) is a sequence used to identify ICH, and magnetic resonance angiography (MRA) and magnetic resonance venography (MRV) are also

Table 54.1. Neonatal Intracranial Hemorrhage (ICH) by Location (Primary [1°], Secondary [2°])

Type (Location) of Hemorrhage	Principal Source of ICH	Relative Incidence in PT versus T
1. Subdural and epidural hemorrhage	1° > 2°	T > PT
2. Subarachnoid hemorrhage (SAH)	2° > 1°*	Unknown*
3. Intraparenchymal hemorrhage		
Cerebral	2° > 1°	PT > T
Cerebellar	2° > 1°	PT > T
4. Germinal matrix/intraventricular hemorrhage	1° > 2°	PT > T

*True incidence unknown, small 1° SAH may be more common than is recognized in both preterm (PT) and term (T) newborns.

occasionally used to investigate vascular contributions to ICH. To avoid exposure of newborns to the ionizing radiation associated with computed tomography (CT), CT scan should be used only for emergent imaging studies when neither MRI nor CUS is available or possible. The American Academy of Neurology (AAN) practice parameter states that all newborns with a birth GA of <30 weeks should undergo routine CUS between 7 and 14 days and optimally repeated between 36 and 40 weeks' postmenstrual age. The American Academy of Pediatrics (AAP) guidelines published in 2020 recommends a CUS by 7 to 10 days for all neonates ≤30 weeks and those >30 weeks with factors that put them at increased risk of brain injury and note that earlier screening may be needed if there are signs of significant brain injury. For those <30 weeks, they recommend repeat CUS at 4 to 6 weeks of age and at term equivalent age or before hospital discharge.

Management varies according to the size and location of the ICH and the presenting neurologic signs. In general, only very large hemorrhages with clinical signs require surgical intervention for removal of the ICH itself. With a large ICH, pressor support or volume replacement (with normal saline, albumin, or packed red blood cells) may be required because of significant blood loss. More commonly, management is focused on treating complications of ICH such as seizures or posthemorrhagic hydrocephalus (PHH). Although a large ICH is more likely to result in greater morbidity or mortality than a small one, the presence and severity of parenchymal injury is usually the most important predictor of neurologic outcome.

Table 54.1 illustrates neonatal ICH by location, and whether each ICH type is predominantly primary or secondary source of bleeding, and the relative incidence in preterm or term newborns.

I. SUBDURAL HEMORRHAGE AND EPIDURAL HEMORRHAGE

A. Etiology and pathogenesis. The pathogenesis of subdural hemorrhage (SDH) relates to rupture of the draining veins and sinuses of the brain that occupy the subdural space. Vertical molding, fronto-occipital elongation, and torsional forces acting on the head during delivery may provoke laceration of dural leaflets of either the tentorium cerebelli or the falx cerebri.[1] These lacerations can result in rupture of the vein of Galen, inferior sagittal sinus, straight sinus and/or transverse sinus, and usually result in posterior fossa SDH. Breech presentation also predisposes to occipital osteodiastasis, a depressed fracture of the occipital bone or bones, which may lead to direct laceration of the cerebellum or rupture of the occipital sinus. Clinically significant SDH in the posterior fossa can result from trauma in the full-term newborn but occurs infrequently. Small, clinically inconsequential SDH ("parturitional SDH") is fairly common in uncomplicated deliveries. The true incidence in apparently well newborns is unclear. A supratentorial SDH usually results from rupture of bridging, superficial veins over the cerebral convexity. Other risk factors for SDH include factors that increase the likelihood of significant forces on the newborn's head, such as large head size, rigid pelvis (e.g., in a primiparous or older multiparous mother), nonvertex presentation (breech, face, etc.), very rapid or prolonged labor or delivery, difficult instrumented delivery, or, rarely, a bleeding diathesis. Postnatally, SDH and epidural hemorrhage (EH) are almost always due to

direct head trauma or shaking; hence, nonaccidental injury needs to be suspected in cases of acute presentation of SDH or EH beyond the perinatal period. However, care should be taken not to confuse an old chronic effusion from a birth-related ICH with an acute postnatally acquired ICH. Careful interpretation of neuroimaging studies, particularly MRI, should help distinguish very acute SDH or EH from chronic effusion.

B. Clinical presentation. When the accumulation of blood is rapid and large, as occurs with rupture of large veins or sinuses, the presentation follows shortly after birth and evolves rapidly. This is particularly true in infratentorial SDH where compression of the brainstem may result in nuchal rigidity or opisthotonus, obtundation or coma, apnea, other abnormal respiratory patterns, and unreactive pupils and/or abnormal extraocular movements. With increased intracranial pressure (ICP), there may be a bulging fontanelle and/or widely split sutures. With large hemorrhage, there may be systemic signs of hypovolemia and anemia. When the sources of hemorrhage are small veins, there may be few clinical signs for up to a week, at which time either the hematoma attains a critical size, imposes on the brain parenchyma, and produces neurologic signs or hydrocephalus develops. Seizures may occur in neonates with SDH, particularly over the cerebral convexity. With cerebral convexity SDH, there may also be subtle focal cerebral signs and mild disturbances of consciousness, such as irritability. Subarachnoid hemorrhage (SAH) probably coexists in the majority of cases of neonatal SDH in the supratentorial compartment, as demonstrated by a cerebrospinal fluid (CSF) exam. Finally, a chronic subdural effusion may gradually develop over months, presenting as abnormally rapid head growth, with the occipitofrontal circumference (OFC) crossing percentiles in the first weeks to months after birth.

C. Diagnosis. The diagnosis should be suspected on the basis of history and clinical signs and confirmed with a neuroimaging study. MRI is the study of choice for diagnosing SDH or EH, but CT may be used for acute emergencies if MRI cannot be obtained quickly, e.g., an unstable newborn with elevated ICP who may require neurosurgical intervention. Although CUS may be valuable in evaluating the sick newborn at the bedside, **imaging of structures adjacent to bone (i.e., the subdural space) is often inadequate by CUS**. MRI has proven to be quite sensitive to small hemorrhage and can help establish timing of ICH. MRI is also superior for detecting other lesions, such as contusion, thromboembolic infarction, or hypoxic-ischemic injury that may result from severe hypovolemia/anemia or other risk factors for parenchymal lesions. **When there is clinical suspicion of a large SDH, a lumbar puncture (LP) should not be performed until after neuroimaging is obtained.** An LP may be contraindicated if there is a large hemorrhage within the posterior fossa or supratentorial compartment. If a small SDH is found, an LP should be performed to rule out infection in the newborn with seizures, depressed mental status, or other systemic signs of illness because small SDH are usually clinically silent.

D. Management and prognosis. Most newborns with SDH do not require surgical intervention and can be managed with supportive care and treatment of any accompanying seizures. Newborns with rapid evolution of a large infratentorial SDH require prompt stabilization with volume replacement

(fluid and/or blood products), pressors, and respiratory support, as needed. An urgent head CT and neurosurgical consultation should be obtained in any newborn with signs of progressive brainstem dysfunction (i.e., coma, apnea, cranial nerve dysfunction), opisthotonus, or tense, bulging fontanelle. Open surgical evacuation of the clot is the usual management for the minority of newborns with large SDH in any location accompanied by such severe neurologic abnormalities or obstructive hydrocephalus. When the clinical picture is stable and no deterioration in neurologic function or unmanageable increase in ICP exists, the management of posterior fossa SDH should focus on supportive care and serial fast MRI (or CT if MRI unavailable) examinations instead of surgical intervention. Laboratory testing to rule out sepsis or a bleeding diathesis should be considered with large SDH, particularly if there is no history of trauma or other risk factor for large SDH. The newborn should be monitored for the development of hydrocephalus, which can occur in a delayed fashion following SDH. Finally, chronic subdural effusions may occur rarely and can present weeks to months later with abnormally increased head growth. The outcome for newborns with nonsurgical SDH is usually good, provided there is no other significant neurologic injury or disease. The prognosis is also good for cases in which prompt surgical evacuation of the hematoma is successful and there is no other parenchymal injury.

E. EH. EH is uncommon in newborns compared with older infants and children. EH appears to be correlated with trauma (e.g., difficult instrumented delivery), and a large cephalohematoma or skull fracture was found in about half the reported cases of EH. Removal or aspiration of the hemorrhage was performed in the majority of reported cases, and the prognosis was quite good except when other ICH or parenchymal pathology was present. It is likely that the majority of cases of clinically silent EH are not reported and do not require surgical intervention. Similar to SDH, a small EH should still be monitored carefully with serial imaging—preferably MRI—to ensure there is no progressive enlargement of the EH or other hemorrhage or brain injury.

II. SUBARACHNOID HEMORRHAGE

A. Etiology and pathogenesis. SAH is a common form of ICH among newborns, although the true incidence of small SAH remains unknown. Primary SAH (i.e., SAH not due to extension from ICH in an adjacent compartment) is probably frequent but clinically insignificant. In these cases, SAH may go unrecognized because of a lack of clinical signs. For example, hemorrhagic or xanthochromic CSF may be the only indication of such a hemorrhage in newborns who undergo a CSF exam to rule out sepsis. Small SAH probably results from the normal "trauma" associated with the birth process. The source of bleeding is usually ruptured bridging veins of the subarachnoid space or ruptured small leptomeningeal vessels. In contrast, a subpial hemorrhage is a focal subtype of SAH that occurs mostly in term newborns and is likely caused by local trauma resulting in venous compression or occlusion, often associated with forceps or vacuum-assisted delivery. Neonatal SAH is quite different from SAH in adults, where the

source of bleeding is usually arterial and therefore produces a much more emergent clinical syndrome. Isolated SAH should be distinguished from subarachnoid extension of blood from a germinal matrix hemorrhage (GMH)/IVH, which occurs most commonly in the preterm newborn. SAH may also result from extension of SDH or a cerebral contusion (parenchymal hemorrhage).

B. Clinical presentation. As with other forms of ICH, clinical suspicion of SAH may arise because of blood loss or neurologic dysfunction. Only rarely is the blood volume loss large enough to provoke catastrophic results. More often, neurologic signs manifest as seizures, irritability, or other mild alteration of mental status, particularly with SAH or subpial hemorrhage occurring over the cerebral convexities. Small SAH may not result in any overt clinical signs except seizures in an otherwise well-appearing baby. In these circumstances, the seizures may be misdiagnosed as abnormal movements or other clinical events.

C. Diagnosis. Seizures, irritability, lethargy, or focal neurologic signs should prompt investigation to determine whether there is a SAH (or other ICH). The diagnosis is best established with a brain MRI scan, or by LP, to confirm or diagnose small SAH. CT scans may be adequate to diagnose SAH but as in the case of SDH/EH, an MRI is preferred to avoid radiation from CT and for optimal visualization of any other parenchymal pathology. For example, SAH may occur in the setting of hypoxic-ischemic brain injury or meningoencephalitis, pathologies that are better detected by MRI than CT or CUS. CUS is not sensitive for the detection of small SAH, so it should be used only if the patient is too unstable for transport to MRI/CT.

D. Management and prognosis. Management of SAH usually requires only symptomatic therapy, such as anticonvulsant therapy for seizures (see Chapter 56) and nasogastric feeds or intravenous fluids if the newborn is too lethargic to feed orally. The majority of newborns with small SAH do well with no recognized sequelae. In rare cases, a very large SAH will cause a catastrophic presentation with profound depression of mental status, seizures, and/or brainstem signs. In such cases, blood transfusions and cardiovascular support should be provided as needed, and neurosurgical intervention may be required. It is important to establish by MRI whether there is coexisting hypoxic-ischemic brain injury or other significant neuropathology that would result in a poor neurologic prognosis despite a surgical procedure. Occasionally, hydrocephalus will develop after a moderate-to-large SAH, and thus, follow-up CUS scans should be performed in such newborns, particularly if there are signs of increased ICP or abnormally rapid head growth.

III. INTRAPARENCHYMAL HEMORRHAGE

A. Etiology and pathogenesis

1. **Primary cerebral hemorrhage** is uncommon in both term and preterm newborns, whereas cerebellar hemorrhage is found in 5% to 10% of autopsy specimens in the premature newborn. A primary intracerebral hemorrhage may occur rarely from rupture of an arteriovenous malformation or aneurysm, from a coagulation disturbance (e.g., hemophilia,

thrombocytopenia), or from an unknown cause. More commonly, cerebral intraparenchymal hemorrhage (IPH) occurs as a secondary event, particularly hemorrhage into a region of hypoxic-ischemic brain injury. From the venous side of the cerebral circulation, IPH may occur as a result of venous infarction (as venous infarctions are typically hemorrhagic) either in relation to a large GMH/IVH (preterm > term; see section IV) or as a result of sinus venous thrombosis (term > preterm). From the arterial side, bleeding may occur secondarily into an arterial embolic infarction (rare) or into areas of hypoxic-ischemic brain injury from global hypoxia-ischemia (term > preterm). Occasionally, there may be hemorrhage that occurs secondarily within an area of necrotic periventricular leukomalacia (PVL) (preterm > term). An IPH may occur in newborns undergoing extracorporeal membrane oxygenation (ECMO) therapy. Finally, cerebral IPH may result from an extension of a large ICH in another compartment, such as large SAH or SDH, as occurs on rare occasion with significant trauma or coagulation disturbance, and it may sometimes be difficult to identify the original source of hemorrhage.

2. **Intracerebellar hemorrhage** occurs more commonly in preterm than term newborns and may be missed by routine CUS because the reported incidence is higher in neuropathologic than clinical studies. The use of mastoid and posterior fontanelle views during CUS examination increases the likelihood of detection of cerebellar hemorrhage (and posterior fossa SAH). MRI is even more sensitive than CUS for the detection of small posterior fossa IPH, SAH, or SDH. It is difficult to determine the original source of cerebellar hemorrhage; hence, the proportion of primary versus secondary cerebellar hemorrhage is unclear. Intracerebellar IPH may be a primary hemorrhage or may result from venous hemorrhagic infarction or from extension of GMH/IVH or SAH (preterm > term). Small foci of cerebellar hemorrhage of unclear pathogenesis may be detected by MRI more often than by CUS. Cerebellar IPH can rarely occur as an extension of large SAH/SDH in the posterior fossa related to a trauma (term > preterm).

B. Clinical presentation. The presentation of IPH is similar to that of SDH, where the clinical syndrome depends on the size and location of the IPH. In the preterm newborn, IPH is often clinically silent in either intracranial fossa, unless the hemorrhage is quite large. In the term newborn, intracerebral hemorrhage typically presents with focal neurologic signs such as seizures, asymmetry of tone/movements, or gaze preference, along with irritability or depressed level of consciousness. A large cerebellar hemorrhage (± SDH/SAH) presents as described in section I earlier and should be managed as for a large posterior fossa SDH.

C. Diagnosis. MRI with SWI is the best imaging modality for IPH, but CUS may be used in the preterm newborn or when rapid bedside imaging is necessary. CT can be used for urgent evaluation when MRI is not available quickly, but the radiation exposure of CT should be avoided when possible. Notably, CT is insensitive for detection of small posterior fossa ICH because of artifact from surrounding skull bones. MRI is superior for demonstrating the extent and age of the hemorrhage and the presence of any other parenchymal abnormality. In addition, MRA/MRV may be useful

to demonstrate a vascular anomaly or sinus venous thrombosis. Thus, MRI is more likely than CT or CUS to establish the etiology of the IPH and to determine accurately the long-term prognosis for the term newborn. For the preterm newborn, CUS views through the mastoid and posterior fontanelle improve the detection of hemorrhage in the posterior fossa.

D. Management. Acute management of IPH is similar to that for SDH and SAH, where most small hemorrhages require only symptomatic treatment and support, whereas a large IPH with severe neurologic compromise should prompt neurosurgical intervention. It is important to diagnose and treat any coexisting pathology, such as infection or sinus venous thrombosis because these underlying conditions may cause further injury that can have a greater impact on long-term outcome than the IPH itself. A large IPH, especially in association with IVH or SAH/SDH, may cause hydrocephalus, and thus head growth and neurologic status should be monitored for days to weeks following IPH. Follow-up imaging by MRI and/or CUS should be obtained in the case of large IPH, both to establish the severity and extent of injury and to rule out hydrocephalus or remaining vascular malformation.

E. Prognosis. The long-term prognosis largely relates to location and size of the IPH and GA of the newborn. A small IPH may have relatively few or no long-term neurologic consequences. A large cerebral IPH may result in epilepsy, hemiparesis or other type of cerebral palsy (CP), feeding difficulties, and cognitive impairments ranging from learning disabilities to significant intellectual disability, depending on the location and size of parenchymal injury. Focal cerebellar hemorrhage in the term newborn often has a relatively good prognosis, although it may result in cerebellar signs of ataxia, hypotonia, tremor, nystagmus, and mild cognitive deficits. There may be only minor deficits from small, unilateral cerebellar IPH in either preterm or term newborns. In contrast, an extensive cerebellar IPH that destroys a significant portion of the cerebellum (i.e., significant bilateral cerebellar injury) in a preterm newborn may result in severe cognitive and motor disability.

IV. GERMINAL MATRIX HEMORRHAGE/INTRAVENTRICULAR HEMORRHAGE

A. Etiology and pathogenesis. GMH/IVH is found principally in the preterm newborn, where the incidence is currently 15% to 20% in those born at <32 weeks' GA but is uncommon in the term newborn. The etiology and pathogenesis are different for term and preterm newborns.

1. **In the term newborn**, primary IVH typically originates in the choroid plexus or in association with venous (± sinus) thrombosis and thalamic infarction and less commonly in the small remnant of the subependymal germinal matrix. The pathogenesis of IVH in the term newborn is likely to be related to perinatal asphyxia, venous thrombosis, trauma (i.e., from a difficult delivery), and/or other risk factors. One study suggested that IVH might occur secondary to venous hemorrhagic infarction in the thalamus in 63% of otherwise healthy term newborns with clinically significant IVH. In such cases, there may be thrombosis of the internal

cerebral veins, but occasionally, there may be more extensive sinovenous thrombosis.

2. **In the preterm newborn, GMH/IVH originates from the fragile involuting vessels of the subependymal germinal matrix, located in the caudothalamic groove.** There are numerous perinatal risk factors that contribute to the pathogenesis of IVH, including maternal factors such as infection/inflammation and hemorrhage, lack of antenatal steroids, external factors such as mode of delivery or neonatal transport to another hospital, and increasingly recognized genetic factors that predispose some newborns to IVH.[1] These intravascular, vascular, and extravascular risk factors all contribute to the pathogenesis of GMH/IVH, although the intravascular risk factors are probably the most important and are also the factors most amenable to preventive efforts (Table 54.2).

   a. The intravascular risk factors predisposing to GMH/IVH include ischemia/reperfusion, increases in cerebral blood flow (CBF), fluctuating CBF, and increases in cerebral venous pressure. Fetal head compression during labor and delivery likely results in significantly increased venous pressure. Indeed, a higher incidence of GMH/IVH is found in preterm newborns with a longer duration of labor and in those delivered vaginally compared with those delivered via cesarean section. Ischemia/reperfusion occurs commonly when hypotension is corrected. This scenario often occurs shortly after birth when a premature newborn may have hypovolemia or hypotension that is treated with infusion of colloid,

Table 54.2. Factors in the Pathogenesis of Germinal Matrix Hemorrhage/Intraventricular Hemorrhage[1]

Intravascular factors	Ischemia/reperfusion (e.g., volume infusion after hypotension)
	Fluctuating CBF (e.g., with mechanical ventilation)
	Increase in cerebral venous pressure (e.g., with high intrathoracic pressure, usually from ventilator)
	Increase in CBF (e.g., with hypertension, anemia, hypercarbia)
	Platelet dysfunction and coagulation disturbances
Vascular factors	Tenuous, involuting capillaries with large luminal diameter
Extravascular factors	Deficient vascular support
	Excessive fibrinolytic activity

CBF, cerebral blood flow.

normal saline, or hyperosmolar solutions such as sodium bicarbonate, especially if infused rapidly. Indeed, studies of the beagle puppy model showed that ischemia/reperfusion (hypotension precipitated by blood removal followed by volume infusion) reliably produces GMH/IVH. Brief fluctuations in CBF have been demonstrated to be associated with GMH/IVH in preterm newborns. In a seminal study from 1983, newborns with large fluctuations in CBF velocity by Doppler ultrasound (US) were much more likely to develop GMH/IVH than newborns with a stable pattern of CBF velocity. The large fluctuations typically occurred in newborns breathing out of synchrony with the ventilator, but such fluctuations have also been observed in newborns with large patent ductus arteriosus (PDA) or hypotension, for example. Increases in cerebral venous pressure are also thought to contribute to GMH/IVH. Sources of such increases include ventilatory strategies where intrathoracic pressure is high (e.g., high continuous positive airway pressure), pneumothorax, and tracheal suctioning. With all of these intravascular factors related to changes in cerebral arterial and venous blood flow, the role of a **pressure-passive cerebral circulation** is likely important. Several studies have shown that preterm newborns, particularly asphyxiated newborns, have an impaired ability to regulate CBF in response to blood pressure changes (hence "pressure passive"). A pressure-passive cerebral circulation has been shown to occur frequently but fluctuates over time in critically ill preterm newborns.[2] Impaired cerebral autoregulation puts the newborn at increased risk for rupture of the fragile germinal matrix vessels in the face of significant increases in cerebral arterial or venous pressure and particularly when ischemia precedes such increased pressure. Sustained increases in CBF can be caused by seizures, hypercarbia, anemia, and hypoglycemia, which result in a compensatory increase in CBF, and contribute to the risk of developing GMH/IVH. Finally, impaired coagulation and platelet dysfunction are also intravascular factors that can contribute to the pathogenesis or severity of GMH/IVH.

b. Vascular factors that contribute to GMH/IVH include the fragile nature of the involuting vessels of the germinal matrix. There is no muscularis mucosa and little adventitia, and the vessels have relatively large diameter and thin walls, all factors which make the vessels particularly susceptible to rupture.

c. Extravascular risk factors for GMH/IVH include deficient extravascular support with minimal astrocytic fibrillary development and deficient glial fibrillary acidic protein to support the fragile capillaries of the germinal matrix. There is also likely excessive fibrinolytic activity related to the extracellular proteolytic system in the subependymal matrix of preterm newborns.

B. Pathogenesis of complications of GMH/IVH. The two major complications of GMH/IVH are **periventricular hemorrhagic infarction (PVHI)** and **posthemorrhagic ventricular dilation (PVD). The risk of both complications increases with increasing size of IVH, occurring mostly with grade 3 IVH** (Table 54.3). The pathogenesis of these two complications are discussed here.

1. **PVHI** was originally considered an extension of a large IVH and is still referred to as a grade 4 IVH by many clinicians and in much of

Table 54.3. Grading of Germinal Matrix Hemorrhage (GMH)/Intraventricular Hemorrhage (IVH)[1]

Grading System	Severity of GMH/IVH	Description of Findings
Papile	I	Isolated GMH (no IVH)
	II	IVH without ventricular dilatation
	III	IVH with ventricular dilatation
	IV	IVH with parenchymal hemorrhage
Volpe	I	GMH with no or minimal IVH (<10% ventricular volume)
	II	IVH occupying 10%–50% of ventricular area on parasagittal view
	III	IVH occupying >50% of ventricular area on parasagittal view, usually distends lateral ventricle (*at time of IVH diagnosis*)
	Separate notation	Periventricular echodensity (location and extent)

the literature. Although this designation is still used, neuropathologic studies have shown that the finding of a large, often unilateral or asymmetric, hemorrhagic lesion dorsolateral to the lateral ventricle **is not an extension of the original IVH but is a venous hemorrhagic infarction that is separate from the IVH**. Neuropathologic studies demonstrate the fan-shaped appearance of a typical hemorrhagic venous infarction in the distribution of the medullary veins that drain into the terminal vein, resulting from obstruction of flow in the terminal vein by the large ipsilateral IVH. Evidence supporting venous obstruction underlying the pathogenesis of PVHI includes the observation that PVHI occurs on the side of the larger IVH, and Doppler US studies demonstrated markedly decreased or absent flow in the terminal vein on the side of the large IVH. Further neuropathologic evidence that PVHI is a separate lesion from the original IVH is that the ependymal lining of the lateral ventricle separating IVH and PVHI sometimes remains intact, demonstrating that the IVH did not "extend" into the adjacent cerebral parenchyma. Hence, PVHI is a complication of large IVH, which is why some authors refer to it as a separate lesion rather than denoting PVHI to be a "higher" grade of IVH (i.e., a grade 4 IVH).

2. **Progressive PVD or PHH (terminology varies)** may occur days to weeks following the onset of GMH/IVH. Not all ventricular dilation progresses to established hydrocephalus that requires treatment; hence, the terms are used with slightly different meanings (see section IV.C.3

for clinical course of PVD). The pathogenesis of *progressive PVD* may relate in part to impaired CSF resorption and/or obstruction of the aqueduct or the foramina of Luschka or Magendie by particulate clot. However, other mechanisms likely play a more important role in the pathogenesis of PVD. High levels of TGF-β1 are found in the CSF following IVH, particularly in newborns with PVD; TGF-β1 upregulates genes for extracellular matrix proteins that elaborate a "scar" which may obstruct CSF flow and/or CSF reabsorption. In addition, restricted arterial pulsations (e.g., due to decreased intracranial compliance) have been proposed to underlie chronic hydrocephalus in hydrodynamic models of hydrocephalus. The **pathogenesis of the brain injury resulting from PVD** is probably related in large part to regional hypoxia-ischemia and mechanical distension of the periventricular white matter based on numerous animal and human studies. In addition, the presence of non–protein-bound iron in the CSF of newborns with PVD may lead to the generation of reactive oxygen species that in turn contribute to the injury of immature oligodendrocytes in the white matter. The brain injury associated with PVD/PHH is principally a bilateral cerebral white matter injury (WMI) similar to PVL with regard to both its neuropathology and long-term outcome.

C. Clinical presentation

1. **GMH/IVH in the preterm newborn is usually clinically silent** and thus is detected only when a routine CUS is performed. The vast majority of these hemorrhages occur within 72 hours after birth, hence the common recommendation to obtain routine CUS within 3 to 4 days after birth for newborns with a GA <32 weeks. Newborns with very large IVH (often bilateral) may present with full fontanelle, anemia, decreased levels of consciousness and spontaneous movements, hypotonia, abnormal eye movements, or skew deviation. Rarely, a newborn will present with a rapid and severe neurologic deterioration with full or tense fontanelle, obtundation or coma, severe hypotonia and lack of spontaneous movements, and generalized tonic posturing thought to be seizure but does not have an electrographic correlate by electroencephalogram.
2. **The term newborn with IVH typically presents with signs such as seizures, apnea, irritability or lethargy, vomiting with dehydration, or a full fontanelle.** Ventriculomegaly is often present at the time of IVH diagnosis in a term newborn. IVH may be initially clinically silent such that a newborn may be discharged home after birth and then present within the first week or so after birth with the earlier-listed clinical signs.
3. **PVD may develop over days to weeks following IVH** and may present with splitting of sutures, decreased level of consciousness, increased apnea or worsening respiratory status, feeding difficulties, and eventually abnormally rapid head growth (crossing percentiles on the growth chart), bulging fontanelle, or impaired upgaze or sunsetting sign. However, PVD is often relatively asymptomatic in preterm newborns because ICP is often normal in this population, particularly with slowly progressive dilation, and the signs of PVD are largely nonspecific. Thus, serial CUS scans are critical for diagnosis of PVD in preterm newborns

with known IVH. One retrospective study of newborns with birth weight <1,500 g who developed IVH and survived at least 14 days showed that 50% of such newborns will not show ventricular dilation, 25% will develop nonprogressive ventricular dilation (or stable ventriculomegaly), and the remaining 25% will develop PVD. The incidence of PVD increases with increasing severity of GMH/IVH; it is uncommon with grades 1 to 2 IVH (up to 12%) but occurs in up to 75% of newborns with grade 3 IVH ± PVHI (see Table 54.3). The incidence of PVD is also higher with younger GA. Ventricular enlargement may increase rapidly (over a few days) or slowly (over weeks). About 40% of newborns with PVD will have spontaneous resolution of PVD without any treatment. The remaining 60% generally require medical and/or surgical therapy of whom ~15% do not survive.

D. Diagnosis

1. **The diagnosis of GMH/IVH in the premature newborn is almost invariably made by real-time portable CUS.** The threshold for obtaining screening CUS varies from 30 to 32 weeks' GA among different institutions. A CUS may be considered in newborns born at >32 weeks' GA who have risk factors such as perinatal asphyxia or tension pneumothorax or who present with abnormal neurologic signs as described earlier. Many centers perform routine CUS studies on or around days 7, 30, and 60 (and/or just prior to discharge) for newborns born at <30 to 32 weeks' GA (or birth weight <1,500 g). For unstable newborns in whom the CUS may change management, a CUS should be obtained in the first few days after birth. In a very sick, very low birth weight newborn, a first CUS might be needed within 24 hours of birth because a large IVH with additional intracranial pathology (e.g., PVHI) may be an important factor in considering goals of care. Also, a large IVH in very sick, very preterm newborns will require earlier follow-up CUS studies to determine whether there is rapidly progressive ventricular dilation, which occurs more frequently in the smaller more preterm newborns. Newborns with GMH/IVH require more frequent CUS than newborns without GMH/IVH to monitor for complications such as PVD and PVHI and for other lesions such as PVL (see section V) or cerebellar hemorrhage. In addition, any preterm newborn who develops new neurologic signs or a significant risk factor for IVH (such as pneumothorax, sepsis, sudden hypotension, or volume loss of any etiology) later in the neonatal intensive care unit (NICU) course should undergo CUS.
2. **Grading of GMH/IVH is important for determining management and prognosis.** Two systems are widely used for grading GMH/IVH as outlined in Table 54.3. Grading of GMH/IVH should be assigned based on the earliest CUS obtained when the IVH itself is of maximal size. Notably, enlarged ventricles observed days to weeks following a grade 1 or 2 GMH/IVH does **not** make the IVH a grade 3 IVH. In this case, the ventricular enlargement ("dilation") usually represents either PVD or ventriculomegaly secondary to parenchymal volume loss. Given the variability in grading systems and in CUS interpretation, a detailed description of the CUS findings is more informative than only assigning

a grade of GMH/IVH. Specifically, the description should include the following:

a. Presence or absence of hemorrhage in the germinal matrix

b. Laterality (or bilaterality) of the hemorrhage

c. Presence or absence of hemorrhage in each ventricle, including volume of hemorrhage in relation to ventricle size

d. Presence or absence of echogenicity (blood or other abnormality) in cerebral parenchyma, including location and size of echogenicity

e. Presence or absence of ventricular dilation, with measurements of ventricles if enlarged

f. Presence or absence of any other ICH (e.g., SAH) or parenchymal abnormalities (cerebral or cerebellar)

3. **In the term newborn, IVH is usually diagnosed when a CUS or MRI is performed because of seizures, apnea, or abnormal mental status.** A CUS is sufficient to detect IVH, but brain MRI is superior for the demonstration of other lesions that may be associated with IVH in full-term newborns, such as hypoxic-ischemic brain injury or thalamic hemorrhagic infarction, with or without sinus venous thrombosis, particularly when diffusion-weighted, susceptibility-weighted, and MRV sequences are included (see Table 54.3).

E. Prevention. **Prevention of GMH/IVH should be the primary goal**; the decreased incidence of GMH/IVH since the 1980s is likely related to numerous improvements in maternal and neonatal care, although the incidence has only modestly declined further in the last decade.[3] Although antenatal administration of **glucocorticoids** has clearly been shown to decrease the incidence of GMH/IVH, antenatal phenobarbital, vitamin K, and magnesium sulfate have not been conclusively demonstrated to prevent GMH/IVH. Postnatal prevention of GMH/IVH should be directed toward minimizing risk factors outlined earlier in section IV.A. In particular, infusions of colloid or hyperosmolar solutions should be given slowly when possible, and all efforts should be directed toward avoiding hypotension and large fluctuations or sustained increases in arterial blood pressure or cerebral venous pressure. Prophylactic ibuprofen and indomethacin given to close PDA have both been associated with reduced severe IVH and PVHI in some studies, but no difference was shown in long-term neurologic outcome, and the routine use of these medications solely for prevention of IVH remains controversial. Elimination of CBF fluctuation related to mechanical ventilation may be achieved by administration of sedative medication. This recommendation is based on the randomized trial that showed a marked reduction in the incidence of GMH/IVH in premature newborns with fluctuating CBF who were chemically paralyzed for the first 72 hours after birth, compared with newborns who were not. Paralytic medications are not typically used because of the many risks associated with this intervention but sedation should be provided as needed. Some NICUs have instituted a bundle of care practices to prevent IVH and minimize brain injury, with several publications showing that these quality improvement efforts can be successful.

F. Management. **Management of GMH/IVH in the premature newborn largely consists of supportive care** and monitoring for and treating complications of GMH/IVH. The size of GMH/IVH can sometimes increase

over the first few days; thus, appropriate early care may prevent enlargement of the IVH. Supportive care should be directed toward maintaining stable cerebral perfusion by maintaining normal blood pressure, circulating volume, glucose, electrolytes, and blood gases. Transfusions of packed red blood cells may be required in cases of large IVH to restore normal blood volume and hematocrit. Thrombocytopenia or coagulation disturbances should be corrected.

1. **Management of IVH in the term newborn is directed at supportive care of the newborn and treatment of seizures during the acute phase.** However, as symptomatic IVH in this group of newborns is frequently large, PVD develops in many and **may require serial LPs and/or eventual surgical management in up to 50% of such newborns**. In contrast, small IVH may occur in neonates with congenital heart disease or those treated with ECMO, often detected by screening CUS (similar to preterm neonates); therefore, the risk of PVD is low in this subgroup of neonates.

2. **Management of PVD consists of careful monitoring of ventricle size by serial CUS and appropriate intervention when needed to reduce CSF accumulation, such as LPs to remove CSF and/or surgical interventions to remove CSF or divert CSF flow** (Fig. 54.1).

   About half of newborns with IVH will have no PVD, mostly those with grades 1 to 2 IVH. In cases of **slowly progressive PVD** over weeks, close monitoring of clinical status (particularly OFC, fontanelle, and sutures) and ventricle size (by serial CUS) may be sufficient. In as many as 25% of neonates, the very slow enlargement of ventricles with subsequent stabilization represents the gradual development of atrophic ventriculomegaly from PVL rather than excess CSF accumulation. **It is critical to use serial CUS to determine which newborns have progressive dilation requiring therapy versus which have stable ventriculomegaly.**

   a. When serial CUS show persistent PVD, intervention is usually required, particularly if the newborn shows clinical signs related to the PVD (e.g., worsening clinical status, bulging fontanelle, widening sutures, abnormally rapid increase in OFC). Many centers will initiate intervention based on enlarging ventricles without clinical signs, as described in detail in the following text. Note that the data are unclear regarding the exact threshold for initiating intervention or the best management strategy that will improve long-term neurologic outcome. Many different strategies and treatments have been tested, as described in the following text.

   The goals of therapy are to reduce the CSF volume of dilated ventricles and to remove blood products, both of which may contribute to the pathogenesis of brain injury (see section IV.B.2) and prevent need for a permanent shunt. Many clinical research studies have shown that CSF removal improves cerebral perfusion, oxidative metabolism, and neurophysiologic function in newborns with PVD. However, many intervention studies and trials have been ineffective, or have not shown improved long-term outcome or avoidance of ventriculoperitoneal (VP) shunt, despite apparent improvement in short-term outcome measures.

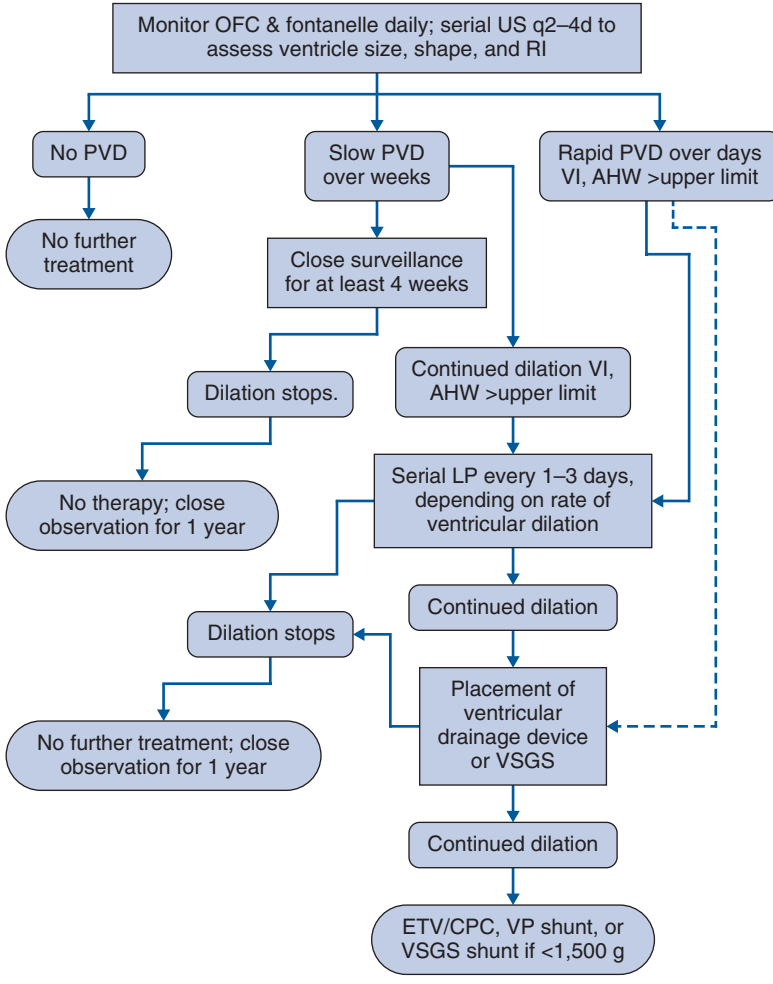

Figure 54.1. Suggested algorithm for management of posthemorrhagic ventricular dilation (PVD) following intraventricular hemorrhage (IVH). OFC, occipital-frontal circumference; US, ultrasound; RI, resistive index; VI, ventricular index; AHW, anterior horn width; LP, lumbar puncture; VSGS, ventriculosubgaleal shunt; ETV/CPC, endoscopic third ventriculostomy combined with choroid plexus cauterization; VP, ventriculoperitoneal.

For example, acetazolamide and furosemide are carbonic anhydrase inhibitors that can be used to decrease CSF production, so were tested in a clinical trial. Although there was a small decrease in the rate of VP shunt placement or death, there appeared to be a worse long-term neurologic outcome. Additionally, their combined use often produces electrolyte disturbances and nephrocalcinosis requiring treatment. For these

reasons, the use of acetazolamide and furosemide together has fallen out of favor, and these agents are rarely used.

Fibrinolytic therapy alone did not prevent PVD in five separate studies of different fibrinolytic agents. However, a pilot trial of continuous DRainage, Irrigation and Fibrinolytic Therapy (called "DRIFT") in 24 newborns with PVD showed a promising reduction in the incidence of shunt surgery, mortality, and disability compared with historical controls. That said, when this very intensive, high-risk therapy was tested in a larger multicenter trial, the adverse effects appeared to outweigh the benefit. Of 34 newborns treated with DRIFT in this second trial, 2 died and 13 received a VP shunt, whereas of the 36 newborns treated with standard therapy (lumbar or ventricular taps), 5 died and 14 underwent a shunt placement. Notably, 12 of 34 patients treated with DRIFT had a secondary IVH, which occurred in only 3 of 36 in the standard therapy group. Analysis of the 2-year outcome data showed that DRIFT reduced the incidence of severe cognitive disability in a subset of newborns. Because the overall risks of the therapy were greater than in the pilot trial, and the therapy is very challenging to implement and perform safely, this therapy has not been widely adopted.

Evidence from numerous animal studies and some human data suggest that earlier treatment of PVD can improve neurologic outcome. For example, a retrospective study of 73 newborns with treated PVD suggested that treatment initiated before the ventricular index (VI) reached the 97th percentile + 4 mm resulted in improved long-term neurologic outcome. Human clinical trials of interventions such as serial LPs or fibrinolytic agents prior to publication of this study showed mixed effects on neurologic outcome, likely related in part to the numerous covariates affecting long-term outcome, such as preexisting brain injury prior to onset of PVD. However, these trials may also have been unsuccessful in demonstrating benefit because neonates were typically randomized once the VI reached the 97th percentile + 4 mm (Fig. 54.2), potentially too late to alter the course of PVD or reduce brain injury.

Clinical trials have also been challenging to conduct because of need for multicenter design, difficulties enrolling subjects, and traditional physician preferences for management. These issues were demonstrated by a multicenter trial that randomized neonates to early versus late ventricular intervention (Early vs. Late Ventricular Intervention Study [ELVIS]; ISRCTN 43171322), where the enrollment period was 2006 to 2016 and results published in 2019. For this trial, preterm neonates were randomized to be treated for PVD either in the early intervention group: ventricular measurements reached anterior horn width (AHW) >6 mm and VI >97th percentile (+2 standard deviation [SD]), or the later intervention group: AHW >10 mm and VI >97th percentile +4 mm (see Fig. 54.2 for measures). Although the early intervention group underwent more LPs and reservoirs, beginning at a median 1 day after randomization (vs. 6 days for the later intervention group), there was no significant difference in the primary outcome measures of VP shunt placement or death. The neurodevelopmental outcome by Bayley exam at 2 years also showed no significant difference between treatment groups, published in 2020. The authors noted that the predictors of

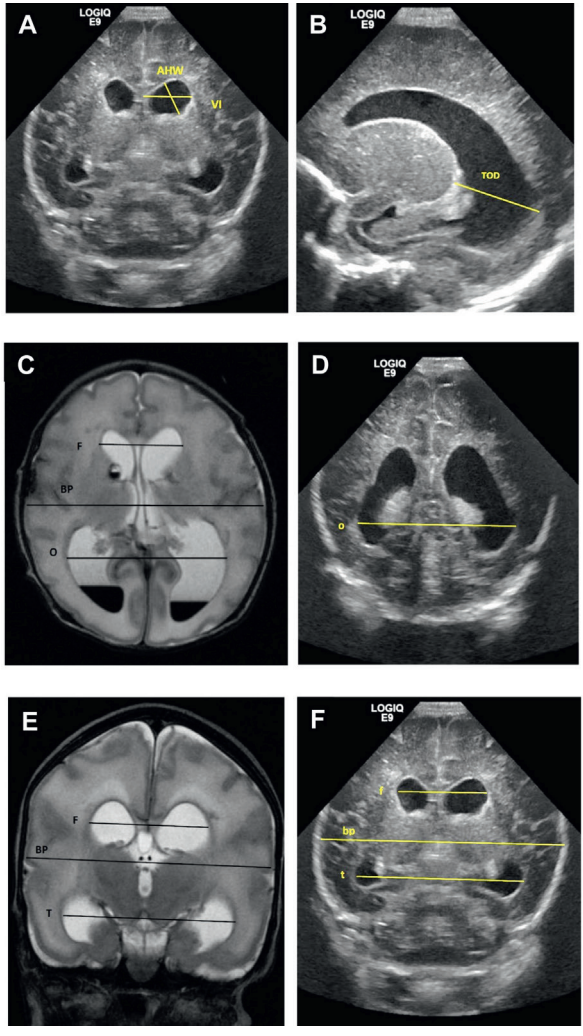

Figure 54.2. Demonstration of different ventricular measures and ratios. Images from cranial ultrasound (CUS) and brain magnetic resonance imaging (MRI) of 1-week-old male infant born at 30 weeks of gestation. **A and F:** Coronal CUS at level of foramen of Monro. **B:** Parasagittal CUS. **C:** Axial view of T2 MRI. **D:** Coronal CUS at level of occipital horn. **E:** Coronal view of T2 MRI. MRI dimensions are in capital letters: BP, biparietal; F, bifrontal horn; O, bioccipital horn; T, bitemporal horn. CUS dimensions are in small letters: bp, biparietal; f, bifrontal horn; o, bioccipital horn; t, bitemporal horn. Evans ratio = F / BP by MRI or f / bp by CUS. Frontal and temporal horn ratio = (F + T / 2) / BP by MRI or (f + t / 2) / bp by CUS. Frontal and occipital horn ratio (FOHR) = (F + O / 2) / BP by MRI or (f + o / 2) / bp by CUS. AHW, anterior horn width; VI, ventricular index; TOD, thalamo-occipital distance. (Reprinted from El-Dib M, Limbrick DD Jr, Inder T, et al. Management of post-hemorrhagic ventricular dilatation in the infant born preterm. *J Pediatr* 2020;226:16.e3–27.e3. Copyright © 2020 Elsevier. With permission.)

worse outcome included severity of IVH and extensive cerebellar hemorrhage; thus, they performed a post hoc analysis adjusting for birth GA, IVH severity, and cerebellar hemorrhage. With this analysis, they found that early intervention reduced the risk of death/disability, with an odds ratio of 0.24 (95% confidence interval, 0.07 to 0.87; $P = .03$). They also analyzed developmental outcome with respect to whether or not a VP shunt was placed, for both early and later intervention groups. This analysis showed that neonates in the later intervention group who required a VP shunt had a significantly lower Bayley cognitive and motor score compared with those without VP shunt, whereas there was no difference for the early group with or without VP shunt. Thus, despite the failure to show a difference in the primary outcome of the ELVIS, the post hoc analyses suggested that earlier intervention conferred a benefit on long-term neurodevelopmental outcome, similar to much of the experimental data.

An observational cohort study conducted concurrently with the ELVIS compared neonates treated with early approach (EA) at Dutch centers with neonates treated with a late approach (LA) at a Canadian center. The EA again required LPs or reservoir when ventricular measurements reached AHW >6 mm and/or VI >+2 SD, then permanent neurosurgical intervention as needed, whereas the LA required clinical signs of ICP prior to intervention, and the first intervention was often a VP shunt (71%). The results showed that the EA group had a smaller maximum VI, fewer complications, and higher rate of normal outcome compared with the LA group. Although this result provides more supportive evidence that earlier intervention results in a better outcome, there were limitations of the study that reduce the robustness of the conclusions. These limitations related to important differences in the two groups, as the EA neonates were older and larger at birth, had fewer signs of ICP, and lower neonatal mortality rate. Higher mortality rate in the LA group occurred even after shunt insertion, potentially related to extreme prematurity and other illnesses. There were likely other differences in populations and management between centers/countries that could have contributed to the observed differences in outcome. Finally, it is difficult to ascertain whether some subjects undergoing the EA would never have required intervention or shunt placement if left untreated, whereas the 71% of the LA group had a neurosurgical intervention as the first intervention (vs. 2% of the EA group). The results of these trials and studies demonstrate the significant challenges of conducting clinical treatment trials of PVD.

Measurement of the resistive index (RI) may be helpful in guiding management of PVD. The RI is a measure of resistance to blood flow; an elevated RI indicates low intracranial compliance with possible decrease in cerebral perfusion. Because persistent or intermittent decreases in cerebral perfusion may contribute to ischemic brain injury, the measurement of RI may help guide treatment of PVD. RI is calculated by measuring systolic and diastolic blood flow velocities by Doppler US (usually in the anterior cerebral artery) and using the formula:

$$RI = \frac{(systolic - diastolic)}{systolic}$$

where "systolic" refers to systolic blood flow velocity, and "diastolic" refers to diastolic blood flow velocity. Normal RI values are <0.7 in newborns, and baseline values >0.9 to 1.0 indicate that diastolic flow to the brain is compromised. Values of RI >1 indicate reversal of flow during diastole and potentially significant impairment of perfusion, putting the newborn at high risk for ongoing ischemic brain injury. A significant rise in RI from baseline RI values when gentle fontanelle compression is applied may indicate hemodynamic compromise and the need to remove CSF. Based on one study, a >30% increase in RI with compression compared to baseline RI, or a baseline RI >0.9, may be indications for CSF removal. Note that the interpretation of RI needs to take into account the presence of other conditions that can affect systolic and/or diastolic blood flow, such as a large PDA, significant cardiovascular compromise, use of high-frequency ventilation, or ECMO.

b. Based on the evidence described earlier, a combination of the newborn's clinical status, ventricular size (using standardized measures such as AHW and VI) and shape by serial CUS, RI by Doppler US (or measurement of ICP by manometry if Doppler US is not available), and response to CSF removal may all be used to determine the need for type and frequency of CSF removal procedures to reduce intraventricular CSF volume and reduce the risk of ischemic brain injury (see Fig. 54.1).[4] A suggested clinical tool for tracking measurements such as AHW and VI and providing suggested recommendations for monitoring and managing PHH is shown in Figures 54.3 and 54.4. Therapeutic LPs to remove CSF can be performed every 1 to 3 days, removing 10 to 15 mL of CSF per kilogram of body weight, depending on the rate of progressive ventricular dilation and the effectiveness of CSF removal. The opening pressure can be measured at the time of therapeutic LPs to help guide therapy, particularly if CUS is not available. A CUS performed before and after CSF removal may be helpful in supporting the diagnosis of PVD and determining the effect of CSF removal in decreasing ventricle size and/or improving cerebral perfusion (see Fig. 54.1).

c. If medical therapy does not successfully reduce ventricle size or PVD is rapidly progressive, surgical intervention is indicated, particularly if there are clinical signs of increased ICP. A ventriculosubgaleal shunt (VSGS), ventricular access device (reservoir), or external ventricular drain should be placed. A VSGS is preferred because (like a ventricular drain) it offers continuous CSF drainage and hence the potential to maintain normal ventricle size and cerebral perfusion as opposed to intermittent CSF removal by spinal or ventricular taps. A VSGS may be sufficient for adequate CSF drainage into the subgaleal space for days to weeks or longer, although it sometimes provides insufficient drainage or becomes blocked by particulate matter. If there is insufficient CSF drainage by the VSGS, CSF may be removed intermittently by a needle placed in the reservoir of the VSGS (or ventricular access device) every 1 to 3 days, as for serial LPs. Intraventricular CSF volume can also be reduced by tapping the subgaleal fluid collection that sometimes forms on the top of the newborn's head with a VSGS. External ventricular drains are less favored by many neurosurgeons because of the risk of infection, especially if the catheter is not tunneled subcutaneously,

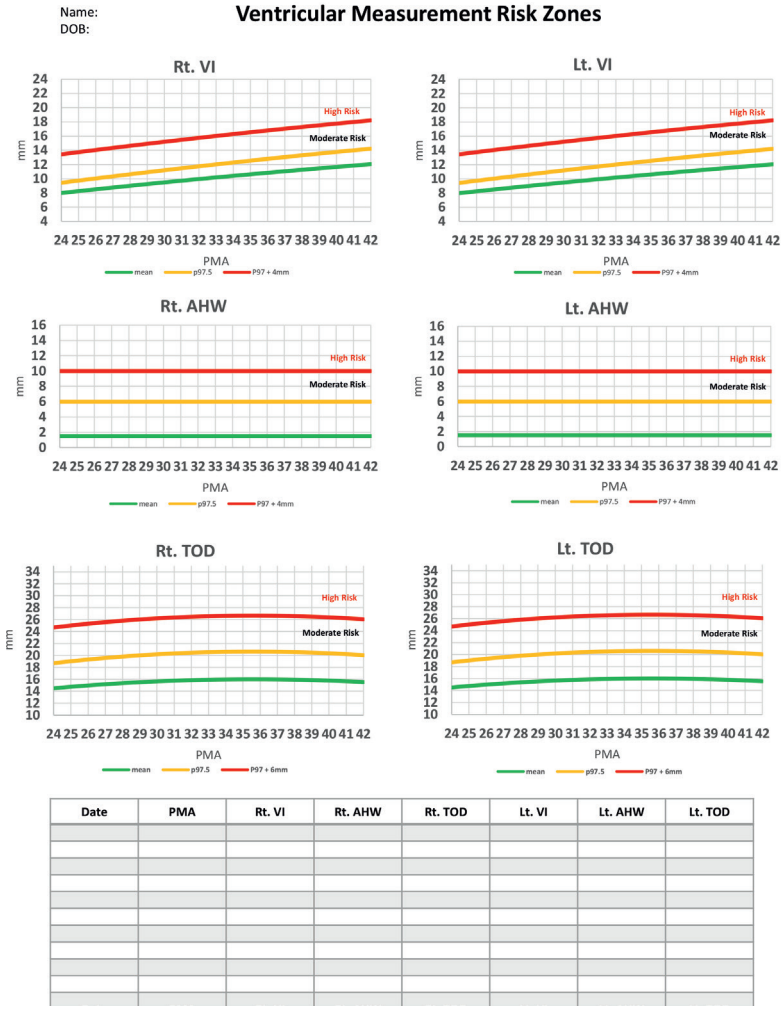

Figure 54.3. A practical clinical tool to monitor commonly used ventricular measures. Individual measures can be plotted in millimeters in the table as well as on the corresponding postmenstrual age (PMA) in the graph to identify risk zone. VI, ventricular index; AHW, anterior horn width; TOD, thalamo-occipital distance. (Reprinted from El-Dib M, Limbrick DD Jr, Inder T, et al. Management of post-hemorrhagic ventricular dilatation in the infant born preterm. *J Pediatr* 2020;226:16–27.e3. Copyright © 2020 Elsevier. With permission.)

although they also have the advantage of providing *continuous* (rather than intermittent) CSF drainage.

d. If PVD has persisted for >4 weeks despite medical/surgical interventions, or the VSGS is insufficient for CSF drainage, a permanent surgical intervention will usually be needed. A permanent VP shunt

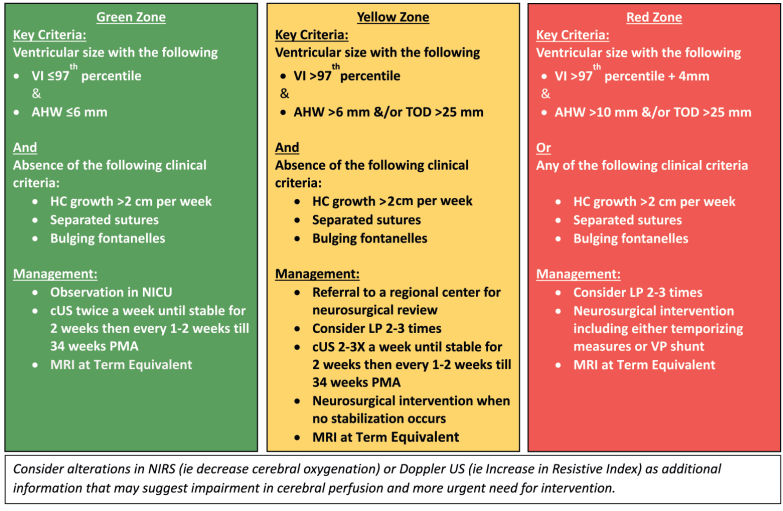

Figure 54.4. Proposed risk stratification and management of infants with posthemorrhagic ventricular dilation (PVD). VI, ventricular index; AHW, anterior horn width; HC, head circumference; NICU; neonatal intensive care unit; cUS, cranial ultrasound; PMA, postmenstrual age; MRI, magnetic resonance imaging; TOD, thalamo-occipital distance; LP, lumbar puncture; VP, ventriculoperitoneal; NIRS, near-infrared spectroscopy; US, ultrasound. (Reprinted from El-Dib M, Limbrick DD Jr, Inder T, et al. Management of post-hemorrhagic ventricular dilatation in the infant born preterm. *J Pediatr* 2020;226:16.e3–27.e3. Copyright © 2020 Elsevier. With permission.)

can usually only be placed once newborns weigh >1,500 to 2,000 g and are stable enough to undergo this surgery. If the newborn weighs <1,500 g, a VSGS, external drain, or ventricular access device will be needed (if not already placed) until the newborn is large enough to undergo VP shunt placement. Alternatively, an **endoscopic third ventriculostomy combined with choroid plexus cauterization (ETV/CPC)** procedure may be attempted instead of VP shunt in centers that have the expertise with this procedure because this procedure avoids complications associated with a permanent shunt. Success of an ETV is more likely if there is no scarring in the prepontine cistern, if the aqueduct is obstructed, if the infant is older, and if choroid plexus cauterization is performed. Depending on these factors, failure may occur in up to 60% of cases, usually within 6 months of the procedure, in which case a VP shunt will need to be placed.

e. Rarely, without neurosurgical intervention, PVD will recur weeks to months later despite apparent resolution in the neonatal period. Monitoring of head growth and fontanelle should continue after discharge home for the first year of life (see Fig. 54.1).

G. Prognosis of GMH/IVH

1. The long-term prognosis for newborns with GMH/IVH varies considerably depending on the severity of IVH, complications

of IVH or other brain lesions, birth weight/GA, and other conditions that affect neurologic outcome. Several studies show that preterm newborns with grades 1 to 2 IVH have an increased risk of CP and/or cognitive impairment compared to those without IVH. One study showed that >50% of adolescents born at <32 weeks' GA had school difficulties, with IVH being a major risk factor. In very preterm newborns, small IVH may cause loss of residual neural progenitor cells remaining in the germinal matrix. That said, these cognitive impairments likely relate at least in part to coexisting cerebral WMI (i.e., PVL; see section V), which has many of the same risk factors as GMH/IVH. Newborns with ventriculomegaly by CUS with or without GMH/IVH have been shown to be at increased risk for long-term neurologic impairments, likely because mild ventriculomegaly is a consequence of WMI that results in some cerebral atrophy. It has been difficult to define the separate contributions of small GMH/IVH and cerebral WMI, especially because these lesions frequently coexist, and the latter is often missed by CUS. Newborns with grade 3 IVH are clearly at a higher risk for cognitive and motor impairments, although they frequently have complications of IVH or other neuropathologic lesions such as PVL that likely contribute significantly to their neurologic outcome. Notably, newborns with grade 3 IVH and those with PVHI ("grade 4 IVH") are often grouped together in outcome studies. MRI is considered by many to be superior to CUS for the detection, classification, and prognosis of GMH/IVH and any associated complications or other lesions such as periventricular WMI, although serial CUS (including CUS at 35 to 42 weeks) can also be sufficient.[5,6] A trial of the benefit of term age CUS versus MRI showed increased cost of MRI with modest benefit in terms of greater prognostic accuracy and decreased parental anxiety.[7]

2. **Newborns with either or both of the two major complications of IVH, namely PVHI and PVD, are at much higher risk for neurologic impairments than those with IVH alone.** Newborns with PVD/PHH requiring significant intervention often manifest spastic diparesis and cognitive impairments due to bilateral periventricular WMI. Newborns with a localized, unilateral PVHI usually develop a spastic hemiparesis affecting the arm and leg with minimal or mild cognitive impairments. Quadriparesis and significant cognitive deficits (including mental retardation) are more likely if the PVHI is extensive or bilateral, or if there is also coexisting PVL, which is common. In addition to cognitive and motor impairments, newborns with severe PHH and/or PVHI are at risk for developing cerebral visual impairment and epilepsy.
3. **The outcome of IVH in term newborns relates to factors other than IVH alone because uncomplicated small IVH in this population has a favorable prognosis.** This is likely related in large part to the lack of any remaining neural progenitor cells in the germinal matrix at term age that could be injured or destroyed by small GMH/IVH. Newborns with a history of trauma or perinatal asphyxia, or with neuroimaging evidence of thalamic hemorrhagic infarction, hypoxic-ischemic brain injury, or other parenchymal lesions, are at high risk for significant cognitive and/or motor deficits and epilepsy.

V. WHITE MATTER INJURY/PERIVENTRICULAR LEUKOMALACIA

A. Etiology and pathogenesis. PVL is a lesion found predominantly in the preterm newborn and is the neuropathologic lesion underlying much of the cognitive, motor, and sensory impairments and disabilities in children born prematurely. The true incidence of this lesion is not known largely because detection of the mild form of this lesion is difficult using conventional neuroimaging and because the threshold for determining clinically important signal abnormality in the cerebral white matter has not been rigorously defined. WMI is a term used increasingly in place of PVL; WMI is a somewhat broader term than PVL in that it denotes the diffuse lesion of the cerebral white matter that extends beyond the periventricular regions defined in initial neuropathologic and ultrasonographic studies and is most often a noncystic lesion. Cystic PVL is uncommon, with a rate of $<1\%$ of preterm newborns born in 2000 to 2002 with birth weight $\leq 1{,}500$ g in one center. An even more encompassing term, *encephalopathy of prematurity*, was proposed by Volpe[8] to include the findings of neuronal abnormalities in gray matter structures demonstrated by neuropathology and neuroimaging studies in addition to the WMI. This term is not yet in widespread use in the literature but reflects increasing evidence that premature newborns suffer a brain injury that affects many gray matter structures in addition to the cerebral white matter, and altered brain development as well as injury. Note that WMI with a similar imaging pattern to PVL in the preterm newborn has been reported occasionally in newborns born at term, particularly those with congenital heart disease.

The **characteristic neuropathology** of PVL was first described in detail by Banker and Larroche[9] in their classic 1962 report of the histologic findings in 51 autopsy specimens. They described the classic features of PVL to include bilateral areas of focal necrosis, gliosis, and disruption of axons, with the so-called "retraction clubs and balls." The topographical distribution of the lesions was noted to be in the periventricular white matter dorsolateral to the lateral ventricles, primarily anterior to the frontal horn (at the level of the foramen of Monro) and lateral to the occipital horns. They noted that a severe "anoxic" episode occurred in 50 of 51 newborns, that the lesions were consistently observed in the location of the border zone of the vascular supply, and that 75% of the group had been born prematurely. They thus suggested two key features of the pathogenesis of PVL, namely, (i) hypoxia-ischemia affecting the watershed regions of the white matter and (ii) a particular vulnerability of the periventricular white matter of the premature brain. Further neuropathologic studies have extended these initial observations, demonstrating that in many cases, PVL consists of areas of both focal necrosis (evolves to cysts) and diffuse white matter gliosis. Neuropathology studies have demonstrated that the necrotic foci may be quite small, on the order of <1 to 5 mm, hence not detectable by most imaging techniques. The diffuse white matter lesion consists of hypertrophic astrocytes and loss of oligodendrocytes and is followed by an overall decrease in the volume of cerebral white matter myelin. Notably, volumetric MRI analysis demonstrates a significant reduction in cortical and subcortical gray matter volumes (rather than white matter volume) in newborns and children born prematurely. These MRI studies have been confirmed

by neuropathologic studies showing that there is significant neuronal loss and gliosis in the thalamus, basal ganglia, and cerebral cortex associated with WMI in newborns born prematurely. Thus, these quantitative MRI and neuropathologic data confirm the notion that PVL or WMI involves a much more diffuse destructive and developmental injury to the developing brain that involves neuronal as well as white matter abnormalities hence *encephalopathy of prematurity*.[8]

Pathogenesis of PVL. This distinctive lesion of PVL found in the immature white matter of premature newborns likely results from the interaction of multiple pathogenetic factors. **Several major factors have been identified to date: (i) hypoxia-ischemia, (ii) intrinsic vulnerability of cerebral white matter of the premature newborn, and (iii) infection/inflammation.** These three major factors are discussed briefly as follows: First, Banker and Larroche[9] originally suggested that PVL occurred in the regions of vascular border zones in the cerebral white matter and that ischemia would thus be expected to preferentially affect these zones. Subsequent authors have further defined these zones using postmortem injection of the blood vessels to demonstrate the presence of vascular border and end zones in the periventricular white matter, where PVL is found. It is hypothesized that these are watershed zones that are vulnerable to ischemic injury during times of vascular compromise. In addition, there is evidence to suggest the presence of a pressure-passive circulation in a subset of premature newborns, further predisposing these newborns to hypoxic-ischemic brain injury.[2]

Second, Banker and Larroche[9] first proposed the hypothesis that the periventricular white matter of the premature newborn may be more vulnerable to anoxia than the mature brain. A maturational vulnerability of the periventricular white matter is suggested by the finding that PVL occurs much more commonly in the premature than term newborn. Specifically, the observation that the diffuse lesion of PVL affects the oligodendrocyte (with resulting myelin loss) with relative preservation of other cellular elements suggests that the immature oligodendrocyte is the cell most vulnerable to injury. Immature oligodendrocytes are susceptible to injury and apoptotic cell death by free radical attack and by glutamate receptor–mediated excitotoxic mechanisms. Notably, apoptosis is postulated to be the mechanism of cell death by a moderate ischemic insult, as would be expected for most cases of PVL; necrosis results from severe ischemic insults. Thus, there is cellular and biochemical evidence to support the original hypothesis that the cerebral white matter of the preterm newborn displays a maturational vulnerability to hypoxic-ischemic injury.

Finally, epidemiologic and experimental studies suggest a role for infection and inflammation in the pathogenesis of PVL. Epidemiologic studies have shown an association between maternal infection, prolonged rupture of membranes, cord blood interleukin-6 levels, and an increased incidence of PVL, leading to the hypothesis that maternal infection may be an etiologic factor in the development of PVL. Experimental work has shown that certain cytokines, such as interferon-γ, have a cytotoxic effect on immature oligodendrocytes. However, cytokines may also be secreted in the setting of hypoxia-ischemia (in the absence of infection). Moreover, infection and/or cytokines may lead to ischemia-reperfusion, which may cause further injury to oligodendrocytes. Thus, there are multiple pathways

by which infection/inflammation might cause or contribute to the pathogenesis of PVL, and the interactions between the two pathogenetic pathways of hypoxia-ischemia and infection/inflammation are complex.

B. Clinical presentation and diagnosis. PVL is typically a clinically silent lesion evolving over days to weeks with few or no outward neurologic signs until weeks to months later when spasticity is first detected or at an even later age when children present with cognitive difficulties in school. With moderate to severe PVL, some evidence of spasticity in the lower extremities may be detected by the careful observer by term age or earlier. However, **PVL is usually diagnosed in the neonatal period by CUS or by MRI.** The evolution of echogenicity in the periventricular white matter over the first few weeks after birth, with or without echolucent cysts, is the classical description of PVL by CUS imaging. Ventriculomegaly due to volume loss from atrophy of the periventricular white matter is often apparent within weeks. Isolated ventriculomegaly is associated with an increased risk of CP, suggesting that ventriculomegaly without radiologically detectable white matter signal abnormality may indicate the presence of PVL with white matter volume loss.

Studies correlating CUS and autopsy data have demonstrated that the incidence of PVL is underestimated by CUS, the technique most widely used to diagnose brain abnormalities in the preterm newborn. MRI has been shown to be more sensitive than CUS for the detection of PVL, especially the noncystic form.[5] Noncystic WMI detected by MRI in the newborn period is evident as high-signal intensity in the cerebral white matter by T2-weighted MRI and low-signal intensity by T1-weighted sequences. As for CUS studies, there is no universally accepted measure of the severity or extent of signal abnormality by MRI that defines WMI. Although greater severity of WMI is correlated with a higher incidence of later neurodevelopmental deficits, there is a broad range of outcomes for mild, moderate, and severe WMI, and the threshold for defining clinically significant WMI has not been determined. For example, one study reported diffuse excessive high-signal intensity (called DEHSI) in the white matter by MRI exam at term age in 80% of newborns born at 23 to 30 weeks' GA. Although there was some correlation between this MRI finding and mild developmental delay at 18 months of age, the impact of DEHSI on neurologic outcome appears to be modest, and it is unclear if DEHSI represents injury or altered development, e.g., myelination delay. The routine use of MRI scans to detect WMI or other lesions has not been recommended for universal use by the AAN and AAP guidelines, although the clinical utility of MRI to detect brain lesions associated with prematurity has been recognized.[5,7] Although the timing of MRI has also been debated, it is probably most useful to perform an MRI scan close to term age, if an MRI scan is to be obtained during the newborn period. For an older infant or child born prematurely who presents with cognitive, motor, and/or sensory impairments, a brain MRI is the most useful imaging modality to confirm clinically suspected WMI. In older infants and children, the brain MRI may show one or more of the following findings: abnormal signal within and/or decreased volume of the cerebral white matter, a thin corpus callosum, enlarged ventricles with a square appearance to the frontal horns, and/or enlarged extra-axial CSF spaces.

There may be abnormal signal or reduced volume of the subcortical nuclei, but this may be difficult to appreciate without quantitative measures.

C. Prevention/management. There are currently no medications or treatments available for the specific treatment of PVL during the newborn period. Current efforts are directed at prevention based on knowledge of the various risk factors and pathogenetic mechanisms described earlier. Avoidance and prompt treatment of infection (including prompt delivery in the setting of chorioamnionitis) may also minimize PVL, although no studies have shown conclusively any effect of such interventions. Maintenance of normal cerebral perfusion should be attempted by careful management of systemic hemodynamics (e.g., blood pressure), intravascular volume, oxygenation and ventilation, and avoidance of sudden changes in systemic hemodynamics. It should be noted that there is controversy about the management of blood pressure in the premature newborn and that a normal blood pressure does not necessarily imply normal cerebral perfusion given the known impairments of cerebral pressure autoregulation in some premature newborns.[2] A randomized controlled trial of targeted management of cerebral tissue oxygenation saturation ($rStO_2$) in the first 72 hours after birth was conducted in 166 preterm newborns. They found that near-infrared spectroscopy (NIRS) monitoring of $rStO_2$ with specified interventions to maintain cerebral $rStO_2$ in the range of 55% to 85% reduced the time preterm newborns spent hypoxic (mainly) or hyperoxic by 58%, with a trend to lower mortality and severe brain injury (NCT01590316). Although this short-term result seemed very promising, there was no significant difference in neurodevelopmental outcome in the 115 surviving subjects tested at 2 years of age. A larger trial ($N = 1{,}600$) of this approach to managing cerebral oxygenation is currently underway (NCT03770741), which is expected to be completed in 2022.

Promising studies of neuroprotective strategies to prevent or minimize PVL have been tested in animal models and may be translated to human newborns. Clinical trials of erythropoietin (EPO) to improve neurologic outcome in preterm newborns have been conducted (NCT00413946, NCT01378273). Although term age MRI data in a subset of infants showed a beneficial effect on white matter microstructure, neither of these trials showed a beneficial effect of EPO on 2-year neurodevelopmental outcome. Additional studies and trials may still yield a positive outcome because observations from earlier studies of EPO suggest that outcome may need to be tested at school age or that different doses or durations of EPO therapy may need to be tested.

Developmental care, minimal handling, and the provision of physical and other therapies in the NICU have all been advocated to reduce the risk of brain injury and promote development, early recovery, and rehabilitation. Management of PVL after discharge from the NICU is directed at providing early intervention services to promote normal development; identifying any cognitive, social, emotional sensory, or motor impairments; and instituting appropriate therapies.

D. Prognosis. PVL is the principal cause of the cognitive, behavioral, motor, and sensory impairments found in children born at <32 weeks' GA. There is an incidence of up to 50% or more of school difficulties in children born prematurely that is largely due to PVL, with PVHI being

the other cerebral lesion that contributes significantly to neurologic disabilities. The incidence of cognitive impairments increases with lower GA, with severity of brain injury, and other risk factors known to be associated with PVL, such as severe sepsis or lung disease. Children born preterm have much higher rates of academic difficulties; a recent meta-analysis showed that these children have significantly worse scores for almost all components of reading and math skills. They are also at increased risk for social, behavioral, and emotional disorders, including autism, attention-deficit hyperactivity disorder (ADHD), anxiety, and depression, although at much lower rates than academic difficulties. The frequencies of the social, behavioral, and emotional disorders are much harder to estimate, given variability in diagnosis by testing tool, culture, and cognitive abilities. Despite these seemingly dire statistics, a substantial minority of even the most extremely preterm neonates will have a normal IQ at school age. In addition, adults born preterm typically rate their quality of life quite highly and higher than the ratings of their parents and physicians.

Children with severe PVL may develop epilepsy, although epilepsy is more commonly related to lesions with significant direct neuronal injury, such as large IVH/PVHI than PVL. Children with thalamic injury as part of PVHI or PHH may be at increased risk for developing infantile spasms and other types of generalized epilepsy.

Similar to cognition, the incidence of CP is much higher in children born extremely prematurely, occurring in up to 10% of children born at $<$27 weeks' GA but in $<$4% of children born at 32 weeks. Spastic diparesis is the most common form of CP in children born prematurely because PVL typically affects the periventricular white matter closest to the ventricles. The axons subserving the lower extremities are located closest to the ventricle, the axons of the upper extremities are situated lateral to them, and the axons of the facial musculature are located farthest from the ventricle. Thus, PVL produces abnormal tone (usually spasticity) and weakness predominantly in the lower extremities, with the upper extremities and face demonstrating milder abnormalities. Children with mild PVL may have a mild spastic diparesis that improves or resolves with age, but they remain at high risk for academic and socioemotional difficulties. When PVL is more severe and/or widespread, quadriparesis may result. Children with PVHI typically have a hemiparesis affecting the contralateral arm and leg, but if the PVHI is very large, there is often PVL affecting the opposite hemisphere, resulting in a triplegia (hemiparesis + diparesis) or asymmetric quadriparesis.

Although premature newborns can have retinopathy of prematurity affecting their vision, PVL and other cerebral lesions alone can result in strabismus, nystagmus, visual field deficits, and perceptual difficulties, which may not be recognized until school age or later. In particular, the lower visual fields may be affected by PVL because the optic radiations subserving the lower visual field pass through the white matter dorsolateral to the occipital horns frequently affected by PVL. Children with WMI may manifest visual perceptual defects or other higher order visual impairments that worsen their cognitive and school function, so these are particularly important to detect. Because visual field deficits and other types of cerebral visual impairment can be difficult to detect, routine monitoring of visual function for early detection of these problems is important.

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55 Perinatal Asphyxia and Hypoxic-Ischemic Encephalopathy

Anne R. Hansen and Janet S. Soul

KEY POINTS

- Therapeutic hypothermia is the only proven treatment for hypoxic-ischemic encephalopathy (HIE) and must be started within 6 hours of birth for maximal efficacy.
- Passive cooling is safe and effective in order to initiate hypothermia in the community setting with close temperature monitoring and management.
- Seizures occur commonly and are often subclinical (electrographic only), but abnormal movements or posture may not be seizures; hence, prolonged conventional electroencephalogram monitoring with video (cvEEG) remains the gold standard for detecting and diagnosing neonatal seizures accurately.
- Careful management of ventilation, oxygenation, perfusion, metabolic state, and fluid balance is critical to optimizing neurologic outcome.

I. PERINATAL ASPHYXIA refers to a condition during the first and second stage of labor in which impaired gas exchange leads to fetal acidosis, hypoxemia, and hypercarbia. It is identified by fetal acidosis as measured in umbilical arterial blood. Although the most widely accepted definition of fetal acidosis is a pH <7.0, the umbilical artery pH that defines asphyxia is not the major determinant of brain injury. The following terms may be used in evaluating a term newborn at risk for brain injury in the perinatal period:

A. Perinatal hypoxia, ischemia, and asphyxia are pathophysiologic terms describing respectively, decreased oxygen (O_2), blood flow, and gas exchange to the fetus or newborn. These terms should be reserved for circumstances when there are objective prenatal, perinatal, and postnatal data to support their use.

B. Perinatal/neonatal depression is a clinical, descriptive term that pertains to the condition of the infant on physical examination in the immediate postnatal period, i.e., in the first hour after birth. The clinical features of infants with this condition may include depressed mental status with decreased spontaneous activity and hypotonia, and/or disturbances in spontaneous

respiration and cardiovascular function. This term makes no association with the prenatal or later postnatal (i.e., beyond the first hour) condition, physical exam, laboratory tests, imaging studies, or electroencephalograms (EEGs). In the first hour or so after birth, neonatal encephalopathy is the preferred descriptive term for infants with persistently abnormal mental status and associated findings.

C. Neonatal encephalopathy is a clinical and not an etiologic term that describes an abnormal neurobehavioral state consisting of an altered level of consciousness (decreased consciousness or hyperalert state) and usually other signs of brainstem and/or motor dysfunction. It does **not** imply a specific etiology nor does it imply irreversible neurologic injury because it may be caused by such reversible conditions as maternal medications or hypoglycemia.

D. Hypoxic-ischemic encephalopathy (HIE) is a term that describes clinical evidence of encephalopathy as defined earlier, with objective data to support a hypoxic-ischemic (HI) mechanism as the underlying cause for the encephalopathy.

E. HI brain injury refers to neuropathology attributable to hypoxia and/or ischemia as evidenced by neuroimaging (head ultrasonography [HUS], magnetic resonance imaging [MRI], computed tomography [CT]) or pathologic (postmortem) abnormalities. Biochemical markers of brain injury such as creatine kinase brain bound (CK-BB) and neuron-specific enolase (NSE) are not used routinely in clinical practice (see section VIII.B).

The diagnosis of HIE and/or HI brain injury is not a diagnosis of exclusion, but ruling out other etiologies of neurologic dysfunction is a critical part of the diagnostic evaluation. When making a diagnosis of HIE, the following information should be documented in the medical record:

1. Prenatal history: complications of pregnancy with emphasis on risk factors associated with neonatal depression, any pertinent family history
2. Perinatal history: concerns of labor and delivery including fetal heart rate (FHR) tracing, biophysical profile, sepsis risk factors, scalp and/or cord pH (specify if arterial or venous), perinatal events such as placental abruption, Apgar scores, resuscitative effort, and immediate postnatal blood gases
3. Postnatal data
   - **a.** Admission physical exam with emphasis on neurologic exam and presence of any dysmorphic features
   - **b.** Clinical course including presence (and time of onset), or absence of seizures, oliguria, cardiorespiratory dysfunction, and treatment (e.g., need for pressor medications, ventilator support)
   - **c.** Laboratory testing, including blood gases, electrolytes, evidence of injury to end organs other than the brain (kidney, liver, heart, lung, blood, bowel), and possible evaluation for inborn errors of metabolism
   - **d.** Brain imaging studies
   - **e.** EEG and any other neurophysiologic data (e.g., evoked potentials)
   - **f.** Placental pathology

II. INCIDENCE.

The frequency of perinatal asphyxia is approximately 1.5% of live births in high-income countries with advanced obstetric/neonatal care and is inversely related to gestational age and birth weight (BW). It occurs in

0.5% of live-born newborns >36 weeks' gestation and accounts for 20% of perinatal deaths (50% if stillbirths are included). A higher incidence is noted in newborns of diabetic or toxemic mothers, those with intrauterine growth restriction, breech presentation, and newborns who are postdates.

III. ETIOLOGY.

In term newborns, asphyxia can occur in the antepartum or intrapartum period as a result of impaired gas exchange across the placenta that leads to the inadequate provision of O_2 and removal of carbon dioxide (CO_2) and hydrogen (H^+) from the fetus. There is a lack of certainty regarding the timing or severity of asphyxia in many cases. Asphyxia can also occur in the postpartum period, usually secondary to pulmonary, cardiovascular, or neurologic abnormalities.

A. Factors that increase the risk of perinatal asphyxia include the following:

1. Impairment of maternal oxygenation
2. Decreased blood flow from mother to placenta
3. Decreased blood flow from placenta to fetus
4. Impaired gas exchange across the placenta or at the fetal tissue level
5. Increased fetal O_2 requirement

B. Etiologies of hypoxia-ischemia may be multiple and include the following:

1. Maternal factors: hypertension (acute or chronic), hypotension, infection (including chorioamnionitis), hypoxia from pulmonary or cardiac disorders, diabetes, maternal vascular disease, and *in utero* exposure to cocaine
2. Placental factors: abnormal placentation, abruption, infarction, fibrosis, or hydrops
3. Uterine rupture
4. Umbilical cord accidents: prolapse, entanglement, true knot, compression
5. Abnormalities of umbilical vessels
6. Fetal factors: anemia (e.g., from fetal-maternal hemorrhage), infection, cardiomyopathy, hydrops, severe cardiac/circulatory insufficiency
7. Neonatal factors: cyanotic congenital heart disease, persistent pulmonary hypertension of the newborn (PPHN), cardiomyopathy, other forms of neonatal cardiogenic and/or septic shock, respiratory failure due to meconium aspiration syndrome, neonatal pneumonia, pneumothorax, or other etiologies

IV. PATHOPHYSIOLOGY

A. Events that occur during the normal course of labor cause most babies to be born with little O_2 reserve. These include the following:

1. Decreased blood flow to placenta due to uterine contractions, some degree of cord compression, maternal dehydration, and maternal alkalosis due to hyperventilation
2. Decreased O_2 delivery to the fetus from reduced placental blood flow
3. Increased O_2 consumption in both mother and fetus

B. Hypoxia-ischemia causes a number of physiologic and biochemical alterations:

1. With **brief asphyxia**, there is a transient increase, followed by a decrease in heart rate (HR), mild elevation in blood pressure (BP), an increase in central venous pressure (CVP), and essentially no change in cardiac output (CO). This is accompanied by a redistribution of CO with an increased proportion going to the brain, heart, and adrenal glands (diving reflex). When there is severe but brief asphyxia (e.g., placental abruption then stat cesarean section), it is thought that this diversion of blood flow to vital deep nuclear structures of the brain does not occur, hence results in the typical pattern of injury to the subcortical and brainstem nuclei.
2. With **prolonged asphyxia**, there can be a loss of pressure autoregulation and/or CO_2 vasoreactivity. This, in turn, may lead to further disturbances in cerebral perfusion, particularly when there is cardiovascular involvement with hypotension and/or decreased CO. A decrease in cerebral blood flow (CBF) results in anaerobic metabolism and eventual cellular energy failure due to increased glucose utilization in the brain and a fall in the concentration of glycogen, phosphocreatine, and adenosine triphosphate (ATP). Prolonged asphyxia typically results in diffuse injury to both cortical and subcortical structures, with greater injury to neuronal populations particularly susceptible to HI insults.

C. Cellular dysfunction occurs as a result of diminished oxidative phosphorylation and ATP production. This energy failure impairs ion pump function, causing accumulation of intracellular Na^+, Cl^-, H_2O, and Ca^{2+}; extracellular K^+; and excitatory neurotransmitters (e.g., glutamate). Impaired oxidative phosphorylation can occur during the primary HI insult(s) as well as during secondary energy failure that usually begins approximately 6 to 24 hours after the primary HI insult. Cell death can be either immediate or delayed, i.e., typically necrotic or apoptotic, respectively.

1. **Immediate neuronal death (necrosis)** can occur due to intracellular osmotic overload of Na^+ and Ca^{2+} from ion pump failure as above or excitatory neurotransmitters acting on ionotropic receptors (such as the *N*-methyl-D-aspartate [NMDA] receptor).
2. **Delayed neuronal death (apoptosis)** occurs secondary to uncontrolled activation of enzymes and second messenger systems within the cell (e.g., Ca^{2+}-dependent lipases, proteases, and caspases), perturbation of mitochondrial respiratory electron chain transport, generation of free radicals and leukotrienes, generation of nitric oxide (NO) through NO synthase, and depletion of energy stores.
3. **Reperfusion** of previously ischemic tissue may cause further injury by promoting the formation of excess reactive O_2 species (e.g., superoxide, hydrogen peroxide, hydroxyl, singlet O_2), which can overwhelm the endogenous scavenger mechanisms, thereby causing damage to cellular lipids, proteins, and nucleic acids as well as to the blood–brain barrier. This may result in an influx of neutrophils that, along with activated microglia, release injurious cytokines (e.g., interleukin 1-β and tumor necrosis factor α).

V. DIAGNOSIS

A. Perinatal assessment of risk includes awareness of preexisting maternal or fetal problems that may predispose to perinatal asphyxia (see section III) and of changing placental and fetal conditions (see Chapter 1) ascertained by ultrasonographic examination, biophysical profile, and nonstress tests.

B. Low Apgar scores and need for resuscitation in the delivery room are common but nonspecific findings. Many features of the Apgar score relate to cardiovascular integrity and **not** neurologic dysfunction resulting from asphyxia.

1. In addition to perinatal asphyxia, the differential diagnosis for a term newborn with low Apgar scores includes depression from maternal anesthesia or analgesia, trauma, infection, cardiac or pulmonary disorders, neuromuscular, and other central nervous system (CNS) disorders or malformations.
2. If the Apgar score is >6 by 5 minutes, perinatal asphyxia is not likely.

C. Umbilical cord or first postnatal blood gas determination. The pH and base deficit on the cord or first postnatal blood gas is helpful for determining which infants have asphyxia that indicates need for further evaluation for the development of HIE. Ideally, the cord gas should be sent from the umbilical artery. In the randomized clinical trials of hypothermia for neonatal HIE, severe acidosis was defined as pH $\leq$7.0 or base deficit $\geq$16 mmol/L. If umbilical cord gases are not available, a postnatal blood gas should be obtained within 1 hour of birth to assess for asphyxia, ideally including measurement of lactate.

D. Clinical presentation and differential diagnosis. HIE should be suspected in encephalopathic newborns with a history of fetal and/or neonatal distress and laboratory evidence of asphyxia. The diagnosis of HIE should not be overlooked in scenarios such as meconium aspiration, pulmonary hypertension, birth trauma, or fetal–maternal hemorrhage, where HIE may be missed because of the severity of pulmonary dysfunction, anemia, or other clinical manifestations. The differential diagnosis of neonatal encephalopathy includes many etiologies in addition to perinatal hypoxia-ischemia, such as sepsis/meningitis, *in utero* infection, perinatal stroke, inborn errors of metabolism, brain malformations, and neuromuscular and other neurogenetic disorders.

VI. NEUROLOGIC SIGNS.

The spectrum of HIE is described as mild, moderate, or severe, based on clinical examination of the newborn. EEG is useful to provide objective data to grade the severity of encephalopathy.

A. Encephalopathy. An abnormal level of consciousness is the hallmark of encephalopathy and is thus required for the definition of neonatal HIE, whether mild, moderate, or severe. Encephalopathy can consist of an apparent hyperalert or jittery state, but the newborn does not respond appropriately to stimuli, and thus consciousness is abnormal. Moderate to severe encephalopathy is characterized by more impaired responses to stimuli such as light, touch, or even noxious stimuli. The background pattern detected by EEG or amplitude-integrated electroencephalogram (aEEG) is useful for determining the severity of encephalopathy, as it provides objective data.

In clinical practice, the different severities of encephalopathy are hard to quantify by inherently subjective examinations, which vary with experience of the examiner, and can improve or worsen over hours to days. The exam features of encephalopathy following varying degrees of perinatal distress were described by Sarnat and Sarnat in 21 neonates in 1974. The table from that publication has often been used to grade encephalopathy as mild, moderate, or severe, although their paper described a progression ("stages") of exam findings over the first few days after birth. In particular, all seven neonates described initially as hyperalert (stage 1) progressed to stage 2 encephalopathy in <24 hours. Thus, a hyperalert state did not indicate a mild encephalopathy in the sense of a persistently mild encephalopathy. These definitions have been employed as inclusion criteria for clinical trials of hypothermia and have been accepted and used by many centers for defining moderate and severe encephalopathy. In contrast, neonates with mild encephalopathy were not included or included only in small numbers in these clinical trials. Also, mild encephalopathy has not been clearly defined in the literature to date. Some studies have defined mild encephalopathy as having one or two neurologic abnormalities by exam (e.g., lethargy, abnormal posture or tone). Further work is needed to define mild encephalopathy and to determine the optimal threshold for which the benefits of hypothermia warrant the cost and outweigh the risks.

B. Brainstem and cranial nerve abnormalities. Newborns with HIE may have brainstem dysfunction, which may manifest as abnormal or absent brainstem reflexes, including pupillary, corneal, oculocephalic, cough, and gag reflexes. There can be abnormal eye movements such as disconjugate gaze, gaze preference, ocular bobbing or other abnormal patterns of eye movements, or an absence of visual fixation or blink to light. Newborns may show facial weakness (usually symmetric) and have a weak or absent suck and swallow with poor feeding. They can have apnea or abnormal respiratory patterns.

C. Motor abnormalities. With greater severity of encephalopathy, there is generally greater hypotonia, weakness, and abnormal posture with lack of flexor tone, which is usually symmetric. With severe HIE, primitive reflexes such as the Moro or grasp reflex may be diminished or absent. Over days to weeks, the initial hypotonia may evolve into spasticity and hyperreflexia if there is significant HI brain injury. Note that if a newborn shows significant hypertonia within the first day or so after birth, the HI insult may have occurred earlier in the antepartum period and have already resulted in established HI brain injury.

D. Seizures occur in up to 50% of newborns with HIE and usually start within 12 to 24 hours after the HI insult. Seizures indicate that the severity of encephalopathy is moderate or severe, not mild.

1. Seizures may have any semiology and are often brief (<30 to 60 seconds in duration), so it can be easily missed. It can sometimes be difficult to differentiate seizures from jitteriness or clonus, although the latter two are usually suppressible with firm hold of the affected limb(s).
2. Because seizures are often subclinical (electrographic only) and spells of abnormal movements may not be seizure, video-EEG remains the

gold standard for diagnosing neonatal seizures, particularly in HIE. The American Clinical Neurophysiology Society guideline recommends a minimum of 24 hours of continuous video EEG monitoring (cvEEG) in any newborn with encephalopathy and/or suspected seizures.

3. Seizures and some antiseizure medications (ASMs) may involve apnea or hypoventilation, especially for newborns not receiving mechanical ventilation. It is important to adequately support respiration to avoid exacerbating hypoxemia and acidosis.

E. Increased intracranial pressure (ICP) resulting from severe diffuse cerebral edema in HIE usually reflects extensive cerebral necrosis rather than swelling of intact neurons and indicates a poor prognosis. If ICP is severely elevated, efforts to avoid exacerbating it (e.g., overhydration) can be made, but treatment to reduce ICP does not improve outcome.

VII. MULTIORGAN DYSFUNCTION.

Organ systems other than the brain usually exhibit evidence of dysfunction or damage from systemic hypoxia-ischemia. In a minority of cases (estimated <15%), the brain may be the only organ exhibiting dysfunction, but in most cases, one or more other organs are affected by systemic hypoxia-ischemia. The frequency of organ involvement in perinatal asphyxia varies among published series, depending in part on the definitions used for asphyxia and organ dysfunction.

A. The **kidney** is the most common organ to be affected in the setting of perinatal asphyxia. The proximal tubule of the kidney is especially affected by decreased perfusion, leading to acute tubular necrosis (ATN) with oliguria and a rise in serum creatinine (Cr) (see Chapter 28).

B. Cardiac dysfunction is caused by transient myocardial ischemia. The electrocardiogram (ECG) may show ST depression in the midprecordium and T-wave inversion in the left precordium. Echocardiographic findings include decreased left ventricular contractility, especially of posterior wall; elevated ventricular end-diastolic pressures; tricuspid insufficiency; and pulmonary hypertension. In severely asphyxiated newborns, dysfunction more commonly affects the right ventricle. A fixed HR may indicate severe brainstem injury.

C. Pulmonary effects include increased pulmonary vascular resistance leading to PPHN, pulmonary hemorrhage, pulmonary edema due to cardiac dysfunction, and meconium aspiration.

D. Hematologic effects include disseminated intravascular coagulation (DIC), decreased production of clotting factors due to liver dysfunction, and of platelets by the bone marrow.

E. Liver dysfunction may be manifested by isolated elevation of hepatocellular enzymes. More extensive damage may occur, leading to DIC, inadequate glycogen stores with resultant hypoglycemia, slowed metabolism or elimination of medications.

F. Gastrointestinal (GI) effects include an increased risk of bowel ischemia and necrotizing enterocolitis (see Chapter 27).

VIII. LABORATORY EVALUATION OF ASPHYXIA

A. Cardiac evaluation. An elevation of **serum creatine kinase myocardial bound** (CK-MB) fraction of >5% to 10% may indicate myocardial injury. Cardiac troponin I (cTnI), cardiac troponin T (cTnT), and cardiac regulatory proteins that control the calcium-mediated interaction of actin and myosin are markers of myocardial damage, and therefore, elevated levels of these proteins could support exposure to asphyxia; however, they are not currently used in clinical practice.

B. Neurologic markers of brain injury

1. Serum CK-BB may be increased in asphyxiated newborns within 12 hours of the insult but has not been correlated with long-term neurodevelopmental outcome. CK-BB is also expressed in placenta, lungs, GI tract, and kidneys. Other serum markers such as protein S-100, NSE, and urine markers have been measured in newborns with asphyxia and HIE.
2. In practice, serum and urine markers of brain injury are not used to evaluate for the presence of brain injury or to predict outcome.

C. Renal evaluation

1. Blood urea nitrogen (BUN) and serum Cr may be elevated in perinatal asphyxia. Typically, elevation is noted 2 to 4 days after the insult.
2. Fractional excretion of Na^+ (FENa) or renal failure index may help confirm renal insult (see Chapter 28).
3. Urine levels of β2-microglobulin have been used as an indicator of proximal tubular dysfunction, although not routinely. This low molecular weight protein is freely filtered through the glomerulus and reabsorbed almost completely in the proximal tubule.

D. Hepatic evaluation

1. Aspartate transaminase (AST)/alanine aminotransferase (ALT) may be elevated in the first few days following an asphyxial event.
2. Prothrombin time (PT)/partial thromboplastin time (PTT) and international normalized ratio (INR) may be elevated due to more severe liver dysfunction. Interpretation of lab results must take into account the effects of therapeutic hypothermia which can further contribute to coagulopathy.

IX. BRAIN IMAGING

A. Cranial sonographic examination can demonstrate edema as loss of gray-white differentiation and small ventricles when severe but is generally insensitive for the detection of HI brain injury, particularly in the first days after birth. It can be useful to rule out large intracranial hemorrhage, particularly because this may be a contraindication to therapeutic hypothermia.

B. CT may be used to detect cerebral edema, hemorrhage, and eventually HI brain injury. Because of the degree of radiation exposure, CT is only indicated if imaging is urgently needed to determine clinical treatment (e.g.,

suspected large intracranial hemorrhage), and neither ultrasound (US) nor MRI is available on an emergency basis.

C. MRI is the best imaging modality for determining the presence, severity, and distribution of irreversible HI brain injury. The injury is not fully apparent on conventional T1- and T2-weighted MRI sequences in the first days after the HI insult, unless the injury is older than suspected or very severe. Instead, conventional MRI sequences obtained at least 10 to 14 days after birth are best for the detection of brain injury, and a scan at >2 weeks of age may sometimes be needed to show the full extent of the injury, particularly if early MRI shows less injury than suspected by clinical exam or EEG findings.

1. **Diffusion-weighted imaging (DWI)** sequences can show abnormalities within hours of an HI insult that may be useful in the diagnosis of acute neonatal HIE and an early indicator of possible brain injury. However, DWI can both underestimate and overestimate the severity of HI brain injury, depending on the timing of the study. Early DWI scans will usually show restricted diffusion in brain regions affected by hypoxia-ischemia. At 7 to 10 days of age, there is pseudonormalization of diffusion, so DWI can appear normal despite the presence of HI injury. After 7 to 10 days, diffusion is usually increased in regions of HI brain injury. Hypothermia appears to delay the time to pseudonormalization of diffusion. Thus, DWI data need to be interpreted carefully within the context of the history and clinical course of the newborn with HIE.
2. **Proton magnetic resonance spectroscopy (MRS)**, also called *proton MRS* or *H-MRS*,[1] measures the relative concentrations of various metabolites in tissue. Elevated lactate, decreased *N*-acetylaspartate (NAA), and alterations of the ratios of these two metabolites in relation to choline or creatine can indicate HIE and help with determining neurologic prognosis.
3. **Susceptibility-weighted imaging** may be useful for the detection of hemorrhage, including hemorrhage within areas of ischemic injury.
4. **Magnetic resonance (MR) angiography or venography** may occasionally be useful if there is suspicion of vascular anomalies, thromboembolic disease, or sinus venous thrombosis, the latter of which can occasionally be found in association with HIE.

X. EEG. EEG is used to both detect and monitor seizure activity and also to define abnormal background patterns such as discontinuous, burst suppression, low voltage, or isoelectric patterns. When conventional 8- or 16-channel neonatal EEG is not readily available, aEEG has been used to evaluate the background pattern, particularly for rapid assessment to determine presence or severity of encephalopathy for treatment with therapeutic hypothermia. This method consists of a reduced montage with one- or two-channel EEG with parietal electrodes, and an emphasis on assessing minimum and maximum voltage, and variation in the background pattern. Although aEEG may detect some seizures, there are data showing that aEEG detects far fewer seizures compared with conventional EEG and that the quality of aEEG interpretation depends very much on the experience and expertise of the reader.

XI. PATHOLOGIC FINDINGS OF BRAIN INJURY

A. Neuropathology may reflect the type of asphyxial insult(s), although the precise pattern is not predictable.

1. Prolonged partial episodes of asphyxia tend to cause diffuse cerebral (especially cortical) necrosis, although there is often involvement of subcortical ± brainstem structures as well.
2. Acute total/profound asphyxia, when relatively brief, affects primarily the brainstem, thalamus, and basal ganglia and tends to spare the cortex in large part, except for the perirolandic cortex.
3. Partial prolonged asphyxia followed by a terminal acute asphyxial event (combination) is present in many cases.

B. Specific neuropathology may be seen after moderate or severe HIE.

1. Selective neuronal necrosis is the most common type of injury seen following perinatal asphyxia. It is due to differential vulnerability of specific cell types to hypoxia-ischemia; for example, neurons are more easily injured than glia. Specific regions at increased risk are the CA1 region of hippocampus, neurons of the thalamus and basal ganglia (particularly putamen), Purkinje cells of cerebellum, and brainstem nuclei. Preterm infants show predominantly cerebral white matter injury after HI, but severe HI insults can also result in subcortical and cortical neuronal injury.
2. A watershed pattern of ischemic injury occurs in boundary zones between cerebral arteries, particularly following significant hypotension, e.g., with prolonged, partial insults. This injury reflects poor perfusion of the vulnerable periventricular border zones in the centrum semiovale and produces predominantly white matter injury in preterm newborns. In the term newborn, prolonged hypotension result in bilateral parasagittal cortical and subcortical white matter injury.
3. Focal or multifocal cortical necrosis affecting all cellular elements can result in cystic encephalomalacia and/or ulegyria (injury to cortex in depths of sulci) due to loss of perfusion in one or more vascular beds.

XII. TREATMENT

A. Perinatal management of high-risk pregnancies

1. FHR abnormalities may provide supporting evidence of asphyxia, especially if accompanied by presence of thick meconium. However, they provide few data concerning duration or severity of an asphyxial event.
2. Measurement of fetal scalp pH is a better determinant of fetal oxygenation than partial pressure of oxygen (PO_2). With intermittent hypoxia-ischemia, PO_2 may improve transiently, whereas the pH progressively falls. Fetal scalp blood lactate has been suggested as easier and more reliable than pH but has not gained wide acceptance.
3. Close monitoring of progress of labor with awareness of other signs of *in utero* distress is important.
4. The presence of fetal distress may indicate the need to mobilize the perinatal team for a newborn who could require immediate intervention.

Alteration of delivery plans may be indicated and guidelines for intervention in cases of suspected fetal distress should be available each medical center (see Chapter 1).

B. Delivery room management. The initial management of the HI newborn in the delivery room is described in Chapter 4.

C. Postnatal management of neurologic effects of asphyxia

1. **Ventilation.** CO_2 should be maintained in the normal range. Hypercapnia can cause cerebral acidosis and cerebral vasodilation. This may result in more flow to uninjured areas and relative ischemia to damaged areas ("steal phenomenon"). Excessive hypocapnia (CO_2 <25 mm Hg) decreases cerebral perfusion so should also be avoided.
2. **Oxygenation.** O_2 levels should be maintained in the normal range, although poor peripheral perfusion may limit the accuracy of continuous noninvasive monitoring. Hypoxemia should be treated with supplemental O_2 and/or mechanical ventilation. Hyperoxia may cause decreased CBF or exacerbate free radical damage so should be avoided.
3. **Temperature.** Passive cooling by turning off warming lights is an effective way to initiate therapeutic hypothermia as soon as possible if a significant HI insult is suspected. Hyperthermia should always be avoided.
4. **Perfusion.** Cardiovascular stability and adequate mean systemic arterial BP are important in order to maintain adequate cerebral perfusion pressure.
5. **Metabolic state**
   a. Hypocalcemia is a common metabolic alteration after neonatal asphyxia. It is important to maintain calcium in the normal range because hypocalcemia can compromise cardiac contractility and may cause or exacerbate seizures (see Chapter 25).
   b. Hypoglycemia is often seen in asphyxiated newborns. Blood glucose level should be maintained in the normal range for term newborns. Hypoglycemia may increase CBF, exacerbate the energy deficit, and cause or exacerbate seizures. Hyperglycemia may lead to increased brain lactate, damage to cellular integrity, cerebral edema, or further disturbance in vascular autoregulation.
6. **Fluids** must be managed judiciously; both fluid overload and inadequate circulating volume should be avoided. Two processes predispose to fluid overload in asphyxiated newborns:
   a. ATN (see Chapter 28) can result from the "diving reflex" and result in oliguria followed by polyuria.
   b. Syndrome of inappropriate antidiuretic hormone (SIADH) secretion (see Chapter 23) is often seen 3 to 4 days after the HI event. It is manifested by hyponatremia and hypo-osmolarity in combination with low urine output and inappropriately concentrated urine (elevated urine specific gravity, osmolarity, and Na+).
   c. Fluid restriction may aid in minimizing cerebral edema, although the effect of fluid restriction on long-term outcome in newborns who are not in renal failure is not known.
7. **Seizure management.** Seizures caused by HIE generally start within 12 to 24 hours of birth, increase in frequency, and then usually resolve

within hours to days, although seizures may persist in severe cases. Seizures caused by HIE can be difficult to control and may not be possible to eliminate completely with currently available ASMs. It is important to remember that seizures in HIE are often subclinical (electrographic only) and that seizures in newborns on musculoskeletal blockade may be manifested only by abrupt changes in BP, HR, and oxygenation or have no clinical signs. Monitoring with cvEEG is thus required to detect seizures and monitor the response to ASM therapy and is superior to aEEG for this purpose.[1] There is increasing evidence that seizures exacerbate brain injury,[2] but ASMs are often incompletely effective, and it has not yet been proven that improved seizure control results in improved neurologic outcome.[2] Metabolic perturbations such as hypoglycemia, hypocalcemia, and hyponatremia that may cause or exacerbate seizure activity should be corrected.

a. Acute ASM management

i. Phenobarbital is the initial drug of choice. It is given as a loading dose of 20 mg/kg intravenously (IV). If seizures continue, additional loading doses of 5 to 10 mg/kg IV may be given as needed to control seizures. A maintenance dose of 3 to 5 mg/kg/day orally (PO) or IV divided BID should be started 24 hours after the loading dose if seizures persist. During loading doses of phenobarbital, the newborn needs to be monitored closely for respiratory depression. Therapeutic serum levels are 15 to 40 mg/dL. Because of a prolonged serum half-life, which may be increased by hepatic and renal dysfunction, serum levels need to be monitored and maintenance dosing adjusted accordingly. If seizures are controlled successfully with the phenobarbital loading doses, further maintenance doses might not be needed, again because the long half-life often results in therapeutic levels for several days after the phenobarbital load(s).

ii. Phenytoin is usually added when seizures are not controlled by phenobarbital. The loading dose is 15 to 20 mg/kg IV followed by a maintenance dose of 4 to 8 mg/kg/day divided q8h. In many centers, fosphenytoin is used in place of the parent drug (phenytoin) because of a lower risk of hypotension, and extravasation has no adverse effects. Dosage is calculated and written in terms of phenytoin equivalents to avoid medication errors. Therapeutic serum level is typically 15 to 20 mg/dL, although levels in the 20 to 25 range may be effective and consideration should be given to measurement of the free phenytoin level.

iii. Benzodiazepines such as lorazepam can be given in doses of 0.05 to 0.1 mg/kg/dose IV. Some clinicians use midazolam boluses and IV infusions to treat status epilepticus or frequent seizures, but there are few data supporting its safety and efficacy.

iv. Levetiracetam has been used recently because of its availability in IV form and relative safety and efficacy for acute seizures and epilepsy in infants and older children. A randomized, double-blind trial of levetiracetam compared with phenobarbital showed that levetiracetam appeared to be safe, at least in the short term, but was much less effective than phenobarbital ($\sim$1/2 to $<$1/3 as effective), as first-line or second-line therapy (NCT01720667).

b. Long-term ASM management. ASMs can usually be weaned when the cvEEG indicates that the newborn has been seizure-free for at least 24 hours. If a newborn is receiving more than one ASM, weaning should be in the reverse order of initiation, with phenobarbital being weaned last, unless there is strong evidence that a particular drug was more effective. There has been controversy regarding when phenobarbital should be discontinued, with some favoring discontinuation by neonatal intensive care unit (NICU) discharge and some favoring continued treatment for 1 to 6 months or more. A comparative efficacy study to address this question showed no difference in epilepsy onset or neurodevelopmental outcome at 2 years with ASM discontinuation at discharge versus several months of age (NCT02789176). Most neonatal neurology experts discontinue ASMs by NICU discharge to decrease potential for adverse neurodevelopmental effects of prolonged ASM administration and because recurrent seizures (e.g., spasms) often require different ASMs. Newborns who have a higher risk of developing epilepsy in infancy or childhood are those with a large volume of HI brain injury and those with high neonatal seizure burden.

8. **Management of other target organ injury**

a. Cardiac dysfunction should be managed with correction of hypoxemia, acidosis, hypocalcemia, and hypoglycemia and avoidance of volume depletion or overload. Diuretics may be less effective if concomitant renal impairment is present. Newborns will require monitoring of systemic mean arterial BP and urine output. Newborns with cardiovascular compromise may require inotropic drugs such as dopamine (see Chapter 40) and may need afterload reduction (e.g., milrinone) to maintain BP and perfusion.

i. Arterial BP should be maintained in the normal range to support adequate systemic and cerebral perfusion.

ii. Monitoring of CVP may be helpful to assess adequacy of preload (i.e., that the newborn is not hypovolemic due to vasodilatation or third spacing); a reasonable goal is 5 to 8 mm Hg in term newborns.

b. Renal dysfunction should be monitored by measuring urine output, with serum electrolytes, paired urine/serum osmolarity, urinalysis, and urine specific gravity.

i. In the presence of oliguria or anuria, avoid fluid overload by limiting free water administration to replacement of insensible losses (~40 mL/kg/day) plus urine output. Consider using low-dose dopamine infusion (≤2.5 μg/kg/minute) (see Chapters 23 and 28).

ii. Volume status should be evaluated before instituting strict fluid restriction. If there is no or low urine output, a 10 to 20 mL/kg fluid challenge followed by a loop diuretic such as furosemide may be helpful.

iii. To avoid fluid overload, as well as hypoglycemia, concentrated glucose infusions delivered through a central line may be needed. Glucose levels should be monitored closely and rapid glucose boluses avoided. Infusions should be weaned slowly to avoid rebound hypoglycemia.

c. GI effects. Feeding should be withheld until BP is stable, active bowel sounds are audible, and stools are negative for blood (see Chapter 27). Feeding during therapeutic hypothermia remains controversial due to

the potential for recent HI exposure of nonvital end organs such as the intestine. If enteral feedings are offered during therapeutic hypothermia, there should be a low threshold for discontinuation with any evidence for intolerance.

d. Hematologic abnormalities (see Chapters 42 to 47). Coagulation profile should be monitored with PTT and PT, fibrinogen, and platelets. Abnormalities may need to be corrected with fresh frozen plasma, cryoprecipitate, and/or platelet infusions.

e. Liver function should be monitored with measurement of transaminases (AST, ALT), clotting (PT, PTT, fibrinogen), albumin, bilirubin, and ammonia. Levels of drugs that are metabolized or eliminated by the liver must be monitored.

f. Lung (see Chapters 29, 30, and 36). Management of the pulmonary effects of asphyxia depends on the specific etiology. Persistent pulmonary hypertension, meconium aspiration syndrome, and neonatal pneumonia should be considered in newborns with HIE who have respiratory distress.

XIII. NEUROPROTECTIVE STRATEGIES.

A number of neuroprotective strategies have been proposed and/or are being tested in animal or clinical human trials.

A. Therapeutic hypothermia for 72 hours initiated within 6 hours of birth has been shown to decrease the risk of brain injury in newborns exposed to perinatal HI insult(s).[3–5] Both total body and head cooling have been shown to be safe and effective and are recommended for treating newborns with moderate to severe HIE. Total body cooling has the advantage of enabling cvEEG monitoring needed to detect frequent seizures (~50% of newborns with moderate to severe HIE). Notably, a randomized trial published in 2014 showed that neither cooling for a longer duration of 120 hours (vs. 72 hours) nor cooling to a lower temperature of 32°C (vs. 33.5°C) offered additional benefit and instead showed a trend to worse outcome, with the trial being stopped early for futility.

1. Inclusion criteria. Therapeutic hypothermia is indicated for newborns with the following criteria:

a. Postmenstrual age (PMA) ≥36 weeks, BW ≥2,000 g

b. Evidence of fetal distress or neonatal distress as evidenced by **one** of the following:

i. History of acute perinatal event (e.g., placental abruption, cord prolapse, severe FHR abnormality)

ii. pH ≤7.0 or base deficit ≥16 mmol/L in cord gas or postnatal blood gas obtained within first hour after birth

iii. 10-minute Apgar score of ≤5

iv. Assisted ventilation initiated at birth and continued for at least 10 minutes

c. Evidence of moderate to severe neonatal encephalopathy by exam and/or aEEG as follows:

i. Primary method for determining neonatal encephalopathy is physical exam.

ii. If exam shows encephalopathy, aEEG can be performed to provide further assessment of severity of encephalopathy and monitoring. A normal neurologic exam does not require confirmation by aEEG.

iii. In circumstances in which physical exam is unreliable (e.g., chemical paralysis), an aEEG or EEG should be performed to determine if there is encephalopathy.

iv. Patterns on aEEG that indicate moderate or severe encephalopathy include the following, with minimum of 20 minutes recording time with artifact-free tracing:

a) Severely abnormal: upper margin <10 μV

b) Moderately abnormal: upper margin >10 μV and lower margin <5 μV

c) Seizures identified by aEEG (or EEG)

d. As therapeutic hypothermia becomes more broadly used beyond the research setting, some providers have expanded criteria for screening and application of hypothermia. There are far fewer data supporting some of the more liberal screening and inclusion criteria listed in the following text. That said, some centers consider offering therapeutic hypothermia to newborns who meet the above criteria with some broadening of particular categories, such as:

i. **More liberal screening criteria.** Screening newborns with pH ≤ 7.1 or base deficit ≥ 10 mmol/L in cord gas or postnatal blood gas obtained within first hour after birth.

ii. **Mild HIE.** Likely the greatest area of controversy is whether to offer hypothermia to newborns who have a mild degree of encephalopathy. Although there are some objective criteria such as the pH, base excess, or voltage by aEEG, other criteria are necessarily subjective, such as the determination of fetal/neonatal distress or the severity of encephalopathy by clinical exam. The threshold for which hypothermia may provide benefit without adverse effects may be somewhat different from that which was studied in published clinical trials, which included few or no newborns with mild encephalopathy. Further data are clearly needed regarding the neurologic outcome of newborns with mild HIE and the risks and benefits of hypothermia for mild HIE; there are ongoing prospective studies and trials which may provide these data in the coming years (NCT01747863, NCT04176471, NCT03409770).

iii. **Late initiation of hypothermia.** There are data showing that hypothermia is associated with improved outcome if started at <3 to 4 hours after birth, consistent with animal data, but it is unclear if there is a benefit to hypothermia initiated >6 hours after birth. This question was tested in a trial (funded by National Institute of Child Health and Human Development) that showed a small probability of additional benefit of cooling starting at 6 to 24 hours after birth (NCT00614744). Many centers do consider cooling infants beginning at 6 to 12 hours if other criteria are met.

iv. **Late preterm newborns with PMA 34 to 36 weeks.** It is currently unclear what is the lowest gestational age for which hypothermia remains both effective and safe, but some centers consider cooling newborns at 34 to 36 weeks if other criteria are met, the newborns are of normal weight, and a cranial

US can be performed early to rule out intraventricular hemorrhage, which occurs more commonly in preterm than term newborns.

v. **Newborns with postnatal cardiorespiratory arrest** instead of perinatal asphyxia as the cause of the HI insult, e.g., postnatal collapse or sudden infant death syndrome–type (SIDS-type) presentation.

vi. **Underlying medical conditions.** There is controversy about providing hypothermia to newborns with underlying surgical or genetic conditions. This question is unlikely to be addressed in large clinical trials, so it requires careful clinical consideration of potential risks and benefits.

2. **Exclusion criteria**

a. Newborns may be excluded from this protocol according to the judgment of the attending physicians. Newborns with the following conditions would likely be excluded from cooling:

i. Severe congenital anomalies or genetic syndrome with expected short life expectancy and/or contraindication to hypothermia (e.g., some cases of trisomy 13 or 18, severe brain malformation, and complex congenital heart disease)

ii. Symptomatic systemic congenital viral infection (e.g., hepatosplenomegaly, microcephaly)

iii. Symptomatic systemic congenital bacterial infection (e.g., meningitis, DIC)

iv. Significant bleeding diathesis

v. Major intracranial hemorrhage

b. If an exclusion criterion is identified during therapy, the newborn should be warmed according to rewarming procedure described in the following text (see section XIII.A.3.a.iii below):

3. **Care** of newborns during 72 hours of therapeutic hypothermia and rewarming

a. Temperature

i. Cooling should be started before 6 hours of age; therefore, early recognition is essential. The target core temperature goal during cooling is 33.5°C (33° to 34°C) with acceptable range: 32.5° to 34.5°C.

ii. Core temperature should be monitored continuously and documented every 15 minutes until 1 hour after goal temperature of 33.5°C is achieved and then hourly. Core temperature is often measured with an esophageal temperature probe.

iii. At the end of 72 hours of induced hypothermia, the newborn is **rewarmed** at a rate of 0.5°C every 2 hours until the newborn reaches 36.5°C. This should take approximately 10 to 12 hours.

iv. If a newborn is discovered to meet an exclusion criterion or undergoes a major adverse event while undergoing hypothermia treatment, rewarm according to the same procedure.

v. During rewarming procedure, core temperature should be monitored continuously and documented every hour.

b. Respiratory status

i. Arterial blood gases and serum lactate should be monitored at baseline and then at 4, 8, 12, 24, 48, and 72 hours of treatment and as clinically indicated.

ii. Because there are only minor differences between blood gases at 33.5°C compared to 37°C, there is no need to record the infant's core temperature on the blood gas requisitions.

c. Cardiovascular/access

i. Vital signs should be monitored and documented per routine.

ii. Arterial access and central venous access should be obtained prior to initiation of therapeutic hypothermia protocol if possible. Obtaining central access in the hypothermic state can be extremely challenging.

d. Fluid, electrolyte balance, and renal/GI

i. Nothing by mouth (NPO) when passive cooling starts, typically until rewarmed to normal temperature. Glucose, serum electrolytes with calcium, BUN/Cr, and AST/ALT should be monitored at baseline, and then at 24, 48, and 72 hours of treatment, and as clinically indicated. There are some centers providing low-volume "trophic" or "gut priming" feeds of about 10 mL/kg/day, if there are no direct contraindications such as hypotension.

ii. Parenteral nutrition should generally be provided, following standard initiation and advancement guidelines, and with standard goals including protein of 3 to 3.5 g/kg/day and lipids of 3 g/kg/day. Of note, fluid restriction may limit ability to achieve goal nutrition.

iii. To avoid cerebral edema in this at-risk population, goal Na level at high end of normal range. Because many of these newborns have decreased urine output of multifactorial etiology, anticipating need for relative fluid restriction will assist in avoiding serum Na below 140.

e. Hematology. PT/PTT, INR, fibrinogen, and platelet count should be measured daily during cooling and as clinically indicated. Coagulopathy should be treated per routine, with the exception of the platelet count which should be kept >100,000 to compensate for decreased platelet function. A hematology consult may be beneficial.

f. Infectious disease

i. Antibiotics should be started after complete blood count (CBC) and blood culture drawn per routine.

ii. If concerns regarding renal function, change from gentamicin to cefotaxime.

g. Neurologic status

i. Neurology consult should be requested as soon as possible, wherever available. The 2014 American Academy of Pediatrics (AAP) guideline specifically recommends that neurology consultation, cvEEG monitoring, neuroimaging including MRI, and longitudinal neurodevelopmental follow-up be available for centers offering hypothermia.[6]

ii. An aEEG or, preferably, full cvEEG monitoring should be initiated on admission and continued through at least the first 24 hours, the 12-hour rewarming period, and potentially throughout the entire

hypothermia protocol, particularly if there are frequent seizures. The scalp should be carefully monitored for skin breakdown given the high-risk combination of ischemia, hypothermia, and decreased mobility of the newborn. Newborns with mild encephalopathy and normal or mildly abnormal EEG background in the first 24 hours have a low risk of developing seizures, so could be monitored with aEEG after the first 24 hours.

iii. Cranial US should be obtained as soon as possible after therapeutic hypothermia is initiated to assess for intracranial hemorrhage.

iv. One or more brain MRI scans should be obtained to assess the severity and location of any HI injury. MRI scans in newborns can often be obtained without use of additional sedative medications. Brain MRI scans should be deferred if the newborn has significant cardiorespiratory instability, ongoing seizures, or any other condition in which transport and MRI are considered unsafe by the medical team. MRI scans should ideally include the following:
   a) T1- and T2-weighted imaging to detect any irreversible injury or other congenital or acquired abnormalities of brain parenchyma
   b) DWI to detect evidence of acute HI injury
   c) Susceptibility-weighted imaging to detect hemorrhage
   d) Proton MRS to detect lactate or other metabolites suggestive of metabolic etiology other than HIE
   e) MR venography or arteriography may be useful if there is evidence of focal venous or arterial ischemic injury suggestive of thromboembolic disease.

v. Early brain MRI obtained within the first 1 to 5 days after birth (or after HI insult) is useful for the following:
   a) Detection of restricted diffusion as early indicator of HI injury
   b) To assess if injury is already well established (e.g., antenatal as opposed to perinatal insult)
   c) To establish any potential etiology of encephalopathy besides HI
   d) To begin to assess presence/severity of any HI injury
   Note: Early scans may underestimate HI injury, depending on timing of insult and imaging.

vi. Late brain MRI scans are useful to detect the severity and location of HI brain injury, which is best determined by conventional T1- and T2-weighted imaging sequences at 10 to 14 days of age or older. This late brain MRI scan can be obtained as an outpatient, unsedated MRI scan if the newborn has already been discharged from the NICU. Note that diffusion abnormalities detected by DWI will pseudonormalize (i.e., appear normal) at approximately 7 to 10 days following an HI insult in newborns, and following that, DWI sequences may show increased diffusion in areas of established HI injury.

h. Sedation

i. Establish sedation goal and measure with a validated sedation tool.

ii. Administer the minimum dose to achieve goal sedation and temperature. Titrate as needed over the course of the cooling and rewarming period.

iii. Generally, low-dose morphine or fentanyl is effective. Hypothermia and potential hepatic dysfunction reduce narcotic metabolism therefore careful attention must be paid to avoid excessive narcotic levels. Some centers use dexmedetomidine, although there are few data regarding its use/safety in newborns.

iv. Additional diagnoses such as meconium aspiration with pulmonary hypertension may necessitate a higher degree of sedation and pain control.

B. There are potential neuroprotective agents such as erythropoietin, melatonin, xenon, and stem cells that are undergoing evaluation in phase I/II/III trials, but there are currently no data supporting the use of any agent besides therapeutic hypothermia for neuroprotection. Agents tested in animals with few or no data in human newborns include antagonists of excitotoxic neurotransmitter receptors such as NMDA receptor blockade with ketamine or MK-801; free radical scavengers such as allopurinol, superoxide dismutase, and vitamin E; Ca^{2+}-channel blockers such as magnesium sulfate, nimodipine, nicardipine; cyclooxygenase inhibitors such as indomethacin; benzodiazepine receptor stimulation such as midazolam; and enhancers of protein synthesis such as dexamethasone.

XIV. OUTCOME IN PERINATAL ASPHYXIA

A. The overall mortality rate is approximately 20%. The frequency of neurodevelopmental sequelae in surviving newborns ranges from 30% to 50%, depending on the population, treatment with hypothermia, and eligibility criteria used for hypothermia treatment.

B. The risk of cerebral palsy (CP) in survivors of perinatal asphyxia is 5% to 10% compared to 0.2% in the general population. **Notably, most cases of CP are not related to perinatal asphyxia, and most perinatal asphyxia does not cause CP.**

C. Specific outcomes depend on the severity of the encephalopathy, treatment with hypothermia the presence or absence of seizures, EEG results, and neuroimaging findings. Note that the severity of encephalopathy does not always correlate with the severity of HI brain injury. For example, a newborn with moderate encephalopathy can have significant injury to subcortical nuclei resulting in quadriparetic CP, intellectual disability, and epilepsy, whereas a neonate with severe HIE treated with hypothermia could have no or mild neurologic impairments.

1. Severity of encephalopathy is a better predictor of outcome than asphyxia, but EEG and MRI add much more detail regarding long-term neurologic prognosis.

   a. Mild HIE: <1% mortality; 98% to 100% of newborns will have a normal neurologic outcome. The largest study to date of outcome in mild HIE of newborns (pooled data from four different prospective studies) shows a statistically significant but small decrease in cognitive composite scores by Bayley exam at 2 years of age.[7]

   b. Moderate HIE: 20% to 37% die or have abnormal neurodevelopmental outcome. Prognosis can be refined by the use of EEG and MRI

studies to detect the severity of encephalopathy, seizures, and the severity and location of HI brain injury. This group may benefit the most from therapeutic hypothermia.

c. Severe HIE: Death from effects of severe systemic asphyxia is more common with severe HIE. Elective withdrawal of medical technology may be discussed with the family when there is severe brain injury that will result in profound neurologic disability. Survivors with MRI evidence of significant HI brain injury are likely to have one or more major neurodevelopmental disability, such as CP, intellectual disability, cerebral visual impairment, or epilepsy. That said, severe HIE treated with hypothermia can sometimes result in no or minimal brain injury, with a good neurologic outcome.

2. **The presence of seizures** is associated with a significantly increased risk for later epilepsy, and intellectual and motor disability. Mortality and long-term morbidity are highest for seizures that begin within 12 hours of birth, are electrographic, and/or severe (high frequency/duration).[8] A seizure burden of >40 total minutes or >13 minutes/hour of seizure activity was found in one study to be associated with greater odds of abnormal outcome at 1 to 2 years of age.[9]
3. Persistently low-voltage activity or isoelectric background by EEG is a prognostic indicator of poor neurologic outcome. Although a transient burst suppression pattern may be associated with a good outcome, a persistent burst suppression pattern is associated with a high risk of death or neurodevelopmental disability. Of note, some maternal medications can transiently alter the neonatal EEG in the first hours after birth.
4. MRI adds a great deal of prognostic information to the clinical and EEG data because the pattern of HI brain injury demonstrated by MRI generally correlates with neurologic outcome when performed at the right age and interpreted by a physician with expertise in interpreting neonatal brain MRI scans. Significant injury to the cortex or subcortical nuclei can be associated with intellectual and/or motor disability, but the severity can vary considerably depending on the regions involved and severity of injury to each region. Notably, small discrete lesions in the subcortical nuclei or less severe watershed pattern/parasagittal injuries can be associated with a normal to mildly abnormal cognitive and motor outcome. In general, motor outcome is easier to predict from MRI findings than cognitive or sensory outcome, and it can be very difficult to predict which newborns will have later epilepsy or feeding difficulties. Thus, these studies should be interpreted with care by physicians with experience in caring for children who had neonatal HIE.

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56 Neonatal Seizures

Arnold J. Sansevere and Ann M. Bergin

KEY POINTS

- Neonatal seizures are usually due to an underlying injury or disorder. Treatable disorders should be sought.
- Hypoxic-ischemic encephalopathy (HIE) and focal ischemia/stroke are responsible for the majority of cases of neonatal seizure.
- Neonatal seizures and their treatment may compromise respiratory and cardiovascular stability.
- A high proportion of neonatal seizures are subclinical.
- Continuous electroencephalogram (cEEG) is the gold standard for detection/confirmation and quantification of neonatal seizures and assessment of treatment effect.

I. INTRODUCTION. Seizures occur more frequently in the neonatal period than at any other time of life. Estimates of the incidence of neonatal seizures vary according to case definition, method of ascertainment, and definition of the neonatal period and range from 1 to 5/1,000 live births. In neonates, the vast majority of seizures are due to underlying disorders, although primary epileptic disorders also present in this age group. The occurrence of seizure may be the first clinical indication of neurologic disorder.

Developmental immaturity influences many aspects of diagnosis, management, and prognosis of seizures in the newborn: (i) Clinical seizure patterns in the neonate reflect the "reduced connectivity" in the neonatal brain, with prominence of focal ictal characteristics and rarity of generalized patterns of clinical seizures. (ii) The balance of excitatory and inhibitory processes in the immature brain are weighted toward excitation with an excess of glutamatergic synapses over inhibitory (usually gamma-aminobutyric acid [GABA]-ergic) synapses. In fact, in some regions of the neonatal brain, GABA acts as an excitatory neurotransmitter via an alteration in chloride gradient and transportation in the immature brain. These developmental features may underlie the neonate's tendency to frequently recurrent seizures and may explain the poor efficacy of traditionally used GABA-ergic antiepileptic agents (phenobarbital, benzodiazepines). (iii) Systemic processes are also immature, leading to altered drug handling compared to older children. (iv) The immature brain may be more susceptible to developmental effects of antiseizure medications.

II. DIAGNOSIS.

An epileptic seizure is a change in neurologic function (motor, sensory, experiential, or autonomic) that is associated with an abnormal synchronous discharge of cortical neurons. This abnormal electrical discharge may be recorded by electroencephalogram (EEG). At all ages, including in the newborn, paroxysmal behaviors may occur, which raise suspicion of electrical seizure but which lack correlating patterns on scalp EEG. Management of these events is difficult at any age and controversial in the newborn. For this review, only those paroxysmal events associated with an electrographic seizure pattern are considered.

Early diagnosis of neonatal seizures is important to allow (i) identification and treatment of underlying disorders, (ii) treatment to prevent additional seizures and seizure-related systemic effects such as hypoxemia and hypertension, and (iii) treatment of seizures to possibly prevent seizure-related excitotoxic neuronal injury. Diagnosis of seizures in the neonate requires knowledge of the clinical patterns associated with electrographic seizures at this age and confirmation with EEG, ideally accompanied by video telemetry. The EEG usually demonstrates a rhythmic focal correlate associated with, but typically of longer duration than, the clinical event. A focus of origin and spread to adjacent areas can be seen (Fig. 56.1). The more severely encephalopathic the infant, the less the seizure pattern tends to evolve in waveform and topographic spread.

Nonepileptic paroxysmal events are common in the encephalopathic infant and, unlike seizures, lack an EEG seizure pattern. Nonepileptic events are often stimulus evoked and may be altered or stopped by gentle restraint and/or change in position (Table 56.1).

In addition, video EEG recordings have revealed that up to 80% of electrographic seizures in neonates lack a clinical correlate. This is particularly likely in encephalopathic newborns. This phenomenon is described as electroclinical dissociation or uncoupling. Whether subclinical electrographic seizures cause additional brain injury in the newborn is unproven to date. Recent studies have suggested that higher degrees of seizure burden and neonatal status epilepticus may impact neurologic outcome as well as mortality.

A. Common electroclinical seizure patterns

1. **Focal clonic seizures.** This pattern may occur unilaterally, sequentially in different limbs, or simultaneously but asynchronously. The movement is rhythmic and biphasic with a fast contraction phase and a slower relaxation phase. A clinical correlate may be present for only a small portion of the total duration of the electrographic seizure. Face, upper or lower limbs, eyes, or trunk may be involved.
2. **Focal tonic seizures.** Patterns include a sustained posture of a single limb, tonic horizontal eye deviation, or asymmetric tonic truncal postures. In contrast to focal tonic events, generalized tonic movements are generally not accompanied by seizure patterns on EEG.
3. **Myoclonic seizures.** These are characterized by a rapid movement usually of flexion. Of the varieties of myoclonus occurring in the newborn, generalized myoclonus, usually involving both upper limbs and less commonly the lower limbs, is most often associated with an EEG seizure pattern. Focal or multifocal myoclonic events are usually not associated with such patterns.
4. **Autonomic seizures.** Autonomic events such as apnea, often with associated tachycardia rather than bradycardia (particularly in term newborns), hypertension, and/or pupillary dilatation.

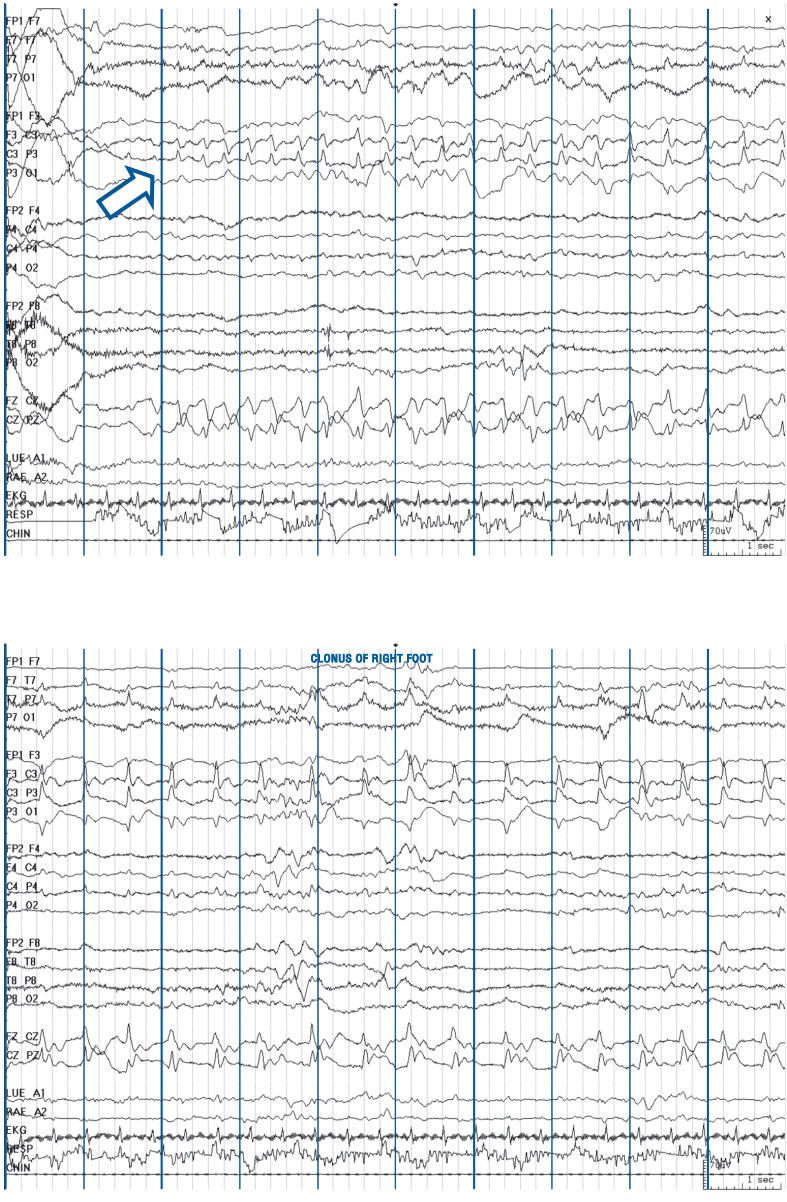

Figure 56.1. Left parasagittal neonatal seizure with focal clonic seizure. Electrographic seizure begins in the left parasagittal area (*open arrow*), and 12 seconds later, focal clonus of the right foot is noted.

Table 56.1. Differential Diagnosis of Neonatal Seizure

Paroxysmal Nonepileptic Event	History	Clinical Features	Differentiating Features
Benign neonatal sleep myoclonus Most common entity misdiagnosed as seizure in the neonate	Neonate is term, healthy, and thriving. May be present from birth to 3 months	Multifocal jerks seen in transition to and during sleep	Only present during sleep Upon wakening, the jerking ceases.
Jitteriness (tremors)	May have exposure to maternal substance abuse or use of medications, metabolic disorder, hypoglycemia, perinatal insult	Stimulus sensitive, high frequency, low amplitude, and oscillatory (not jerking movement) Activated/exacerbated by arousal	Extinguishes or decreases with flexion of the extremity and gentle restraint No associated abnormal eye movements or autonomic change
Apnea of prematurity	Neonate is preterm.	Apnea and bradycardia	Apnea associated with tachycardia suggests seizure. Assess for other associated features (i.e., automatisms, oculomotor events, motor movements, etc.).

Many newborns may have more than one seizure type. In premature infants, a wider range of clinical behaviors can be associated with electrographic seizure patterns; for instance, self-limited short periods of otherwise unexplained tachypnea, tachycardia, and other autonomic changes may represent seizures in the preterm infant, as may chewing, sucking, and cycling movements, which usually are not associated with EEG seizures in the term infant.

B. EEG diagnosis. Continuous electroencephalogram (cEEG), defined as >3 hours of monitoring, is considered the gold standard for the diagnosis of neonatal seizures. cEEG is particularly important given that up to 80% of neonatal seizures are subclinical and would go undetected without continuous monitoring due to electroclinical uncoupling/dissociation.

Including video analysis can be very helpful to correctly characterize events, preventing treatment of clinically suspicious but nonepileptic events and avoiding misinterpretation of artifactual EEG patterns, which can be seen with suctioning, ventilation events, and physical therapy/patting.

Many neonatal intensive care units (NICUs) rely on both routine EEG and amplitude-integrated electroencephalogram (aiEEG) to evaluate cerebral function in neonates.

1. **Routine neonatal EEG** recording, typically of 1 hour duration, allows assessment of background activity, including cycling state change, developmental maturity, and possibly epileptic potential (brief rhythmic discharges). Such recordings may identify patients at high risk for seizure and, especially if performed serially, are useful for prognostication. However, a typical clinical event is unlikely to be captured in such a short time. Where possible, 24-hour continuous recording is preferred.
2. **aiEEG** is a bedside technique increasingly being used by neonatologists for neuromonitoring. The background EEG activity from a limited number of electrodes (usually one to two channels, two to four electrodes) is amplified, filtered, rectified, compressed (6 cm/hour), and displayed on a semilogarithmic scale. One minute of EEG is thus represented by 1 mm of aiEEG. Electrodes are typically placed in watershed zones in the central and temporal regions. This technique allows the neonatologist to continually assess the background EEG characteristics and thereby judge the severity of encephalopathy, the improvement or deterioration over time, and response to therapies. Seizures occurring during recording of this compressed data may alter the tracing in a recognizable manner provided the seizures occur in the region of the electrodes being used for recording and are of sufficient duration. The presence of seizures may be confirmed with immediate review of raw EEG from the available one to two channels and should then be further assessed with standard EEG recording (Fig. 56.2). The sensitivity and specificity of aiEEG varies with the experience of the user.

III. ETIOLOGY. Once the presence of electrographic seizure has been identified, underlying etiologies, particularly reversible causes, must be sought. The details of the pregnancy (from conception through delivery), maternal history, and family history are most important in directing the initial evaluation. For instance, a history of traumatic delivery, with good Apgar scores in a term infant, raises the possibility of intracranial hemorrhage (ICH). The age at onset of seizure relative to the time of birth is also extremely important and may suggest likely etiologies. Hypoxic-ischemic encephalopathy (HIE), which is the single most common cause of neonatal seizures, usually causes seizures within the first 24 hours of life. Focal seizures in the setting of a well-appearing nonencephalopathic newborn raise suspicion for perinatal infarction. When seizures present after the first 48 hours of life, and particularly after a period of initial well-being, infection and biochemical disorders should be considered. Seizures occurring later (e.g., >10 days of life) are more likely to be related to disorders of calcium metabolism (now rare in the United States), cortical malformation, or neonatal epilepsy syndromes, which may be benign (e.g., benign

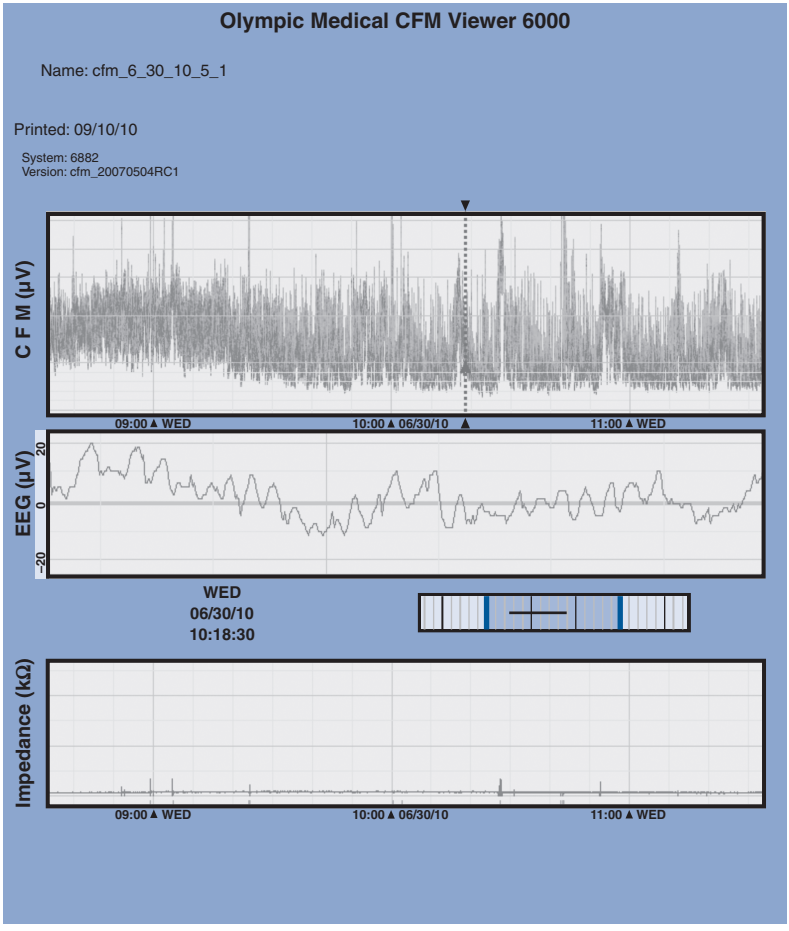

Figure 56.2. Amplitude integrated electroencephalogram (EEG). **Upper panel:** Compressed EEG data with wide band of activity, occasionally with sudden elevation of lower margin—a marker for possible seizure. **Middle panel:** Raw EEG at the timepoint indicated by the cursor in the upper panel. Single-channel EEG with rhythmicity concerning for possible seizure. Full EEG required for confirmation. **Lower panel:** Indication of electrode impedance, which is appropriately low. Patterns seen in the compressed EEG data are uninterpretable in the presence of high electrode impedance.

familial neonatal seizures) or severe (e.g., early infantile epileptic encephalopathy [EIEE]). Multiple possible etiologies (Table 56.2) may be identified in a neonate with seizures, such as HIE with hypoglycemia, hypocalcemia, and/or ICH, and each must be treated appropriately.

A. Specific etiologies

1. **HIE** (see Chapter 55). This is the most common cause of neonatal seizures, accounting for 50% to 75% of cases. In perinatal asphyxia, the seizures occur in the context of a newborn who has a history of difficulty

Table 56.2. Etiologies of Neonatal Seizures

Hypoxic-ischemic injury Perinatal asphyxia
Focal infarction Arterial Venous
Intracranial hemorrhage Intraventricular Parenchymal Subdural Subarachnoid
CNS infection (e.g., *Escherichia coli*, GBS, *Listeria monocytogenes*, HSV)
Malformations and other structural lesions Neuronal migration disorders Cerebral dysgenesis Neurocutaneous disorders, e.g., Sturge-Weber syndrome, tuberous sclerosis
Acute metabolic disorders Hypoglycemia Hyponatremia Hypocalcemia Hypomagnesemia
Inborn errors of metabolism Aminoacidopathies Organic acidurias Peroxisomal diseases Mitochondrial disorders Disorder of glucose transport (GLUT-1 deficiency) Pyridoxine-dependent seizures Folinic acid responsive seizures
Epilepsy syndromes Benign familial syndromes Severe neonatal epileptic encephalopathies (EIEE, Ohtahara syndrome, EME)

CNS, central nervous system; GBS, group B *Streptococcus*; HSV, herpes simplex virus; GLUT-1, glucose transporter 1; EIEE, early infantile epileptic encephalopathy; EME, early myoclonic epilepsy.

during labor and delivery with alterations of the fetal heart rate, decreased umbilical artery pH, and Apgar score <5 at 5 minutes. There is typically hypotonia and early alteration of mental status, sometimes with coma, in addition to the seizures, which are usually seen within the first 12 to 24 hours. Although the insult is global, the seizures are usually focal and may be multifocal. They are typically of short duration (<1 minute) but may be very frequent and refractory, especially in the first 24 hours. Treatment is urgent and complicated in many infants by the effects of hypoxic injury to other organ systems (hepatic, pulmonary, renal, and cardiovascular). Additionally, the antiseizure medications may contribute to hypotension and hypoventilation. This subpopulation is at high risk for subclinical electrographic seizures—electroclinical dissociation (incidence in this group is 22% to 65%). Where possible, prolonged EEG is invaluable in identifying ongoing subclinical seizures.

In recent years, therapeutic hypothermia has become the standard of care for neonates with suspected hypoxic injury. Therapeutic hypothermia may decrease the rate of both death and disability in neonates with hypoxic injury. It may also decrease the overall seizure burden in patients with moderate hypoxic injury. A rebound increase in seizure frequency has been documented during rewarming in some infants. Although rare, the occurrence of a first neonatal seizure during rewarming has also been described.

Perinatal stroke is the second most common cause of seizures in the newborn period accounting for up to 20% of neonatal seizures. In **focal ischemic lesions**, such as middle cerebral artery stroke, the infant usually appears well and presents with focal clonic seizures. Such arterial strokes may have occurred prior to or in early labor. Asymmetries of the motor examination are often lacking in these infants. If they do not present with neonatal seizures, diagnosis may be delayed until later in their first year when asymmetry of limb function becomes apparent. Focal electrographic seizures as well as focal attenuation of EEG background activity and focal sharp waves support the clinical suspicion for infarction.

2. **ICH.** ICH are responsible for 10% to 15% of neonatal seizures. In the term infant, primary **subarachnoid hemorrhage** (not due to extension of a deeper cerebral or intraventricular hemorrhage) is probably more common than is realized. Most are not of clinical significance and produce no symptoms. Deliveries with or without instrumentation and/or trauma may be associated with more substantial subarachnoid hemorrhages, which may present with seizures, usually on the second day of life. These infants appear clinically well between seizures and have a very good outcome. **Subdural hemorrhages** are related to large infant size, breech delivery, and instrumentation. They are due to tears in the falx, tentorium, or superficial cerebral veins. They are often associated with underlying cerebral contusions, which may be responsible for the seizures in some cases. Presenting seizures are usually focal and occur in the first few days of life. If large, subdural hematomas may require surgical treatment, making diagnosis important. In the term infant presenting with hemorrhage, sinovenous thrombosis should also be considered. In the **preterm infant, germinal matrix, intraventricular, and parenchymal**

hemorrhages are the prototypic neurologic complications of premature hypoxic injury. Seizures can occur with extension of the germinal matrix hemorrhage into the adjacent hypoxic parenchyma typically after the first 3 days of life. Generalized tonic events are usually not associated with electrographic seizure patterns, reflecting instead alterations in intracranial pressure. EEG recording may confirm seizure patterns with autonomic phenomena or cycling motor movements in these premature infants and also has identified subclinical electrographic seizures in association with these hemorrhages. Seizures occurring in the setting of premature hemorrhagic lesions are not usually associated with a good outcome.

3. **Central nervous system (CNS) infection.** CNS infections account for about 5% of neonatal seizures. **Congenital intrauterine infections** such as with cytomegalovirus (CMV), toxoplasma, rubella, and herpes viruses may present early (first 2 days) with seizures in severe cases. The clinical scenario may include microcephaly; poor intrauterine growth; prematurity; and other skin, ophthalmic, and systemic findings. Meningoencephalitis, cerebral calcification, and dysgenesis (in cases of early intrauterine infection) contribute to the pathogenesis of seizures in these cases. **Postnatal sepsis**, for example, with group B *Streptococcus* or *Escherichia coli*, is often complicated by meningitis and may be associated with seizures. In this setting, the newborn has often been well for a few days, only to deteriorate later with seizures occurring after the first 48 to 72 hours.

4. **Acute metabolic disorders.** These rapidly remediable conditions are the focus of the initial investigations in neonatal seizures and include hypoglycemia, hypocalcemia, hypomagnesemia, and hyponatremia. They account for approximately 5% of neonatal seizures.

   a. Hypoglycemia. Even when it occurs in association with other potential causes of seizure, such as HIE, hypoglycemia should be treated (see Table 56.2). The definition of hypoglycemia is controversial, but reasonable thresholds for treatment are <40 mg/dL (<2.2 mmol/L) in the first 24 hours and <50 mg/dL (<2.8 mmol/L) after 24 hours. Most hypoglycemic infants are asymptomatic, but at any point, symptoms of neuroglycopenia should prompt immediate treatment. These are jitteriness/tremor, hypotonia, alteration of consciousness, poor feeding, apnea, and seizures. Causes of neonatal hypoglycemia include the following:

   i. Decreased glucose supply, especially in the premature and small for gestational age infant
   ii. Increased utilization, such as in hyperinsulinemic states, most commonly seen in the infant of the diabetic mother but also due to the overgrowth syndrome, Beckwith-Wiedemann syndrome, erythroblastosis, and the rare primary hyperinsulinemic hypoglycemia
   iii. Disorders in which pathways of gluconeogenesis are deficient or suppressed (e.g., glycogen storage disorders, aminoacidopathies such as maple syrup urine disease, and fatty acid oxidation defects)

   b. Hypocalcemia. Whole blood ionized calcium (iCa) is the best measure of calcium status in ill infants. Hypocalcemia is considered present when iCa in term or premature infants >1,500 g birth weight is <4.4 mg/dL (<1.1 mmol/L) and in premature infants <1,500 g at birth, <4.0 mg/dL (<1 mmol/L). **Early-onset** hypocalcemia occurs

in the first 3 days of life and is associated with prematurity, infants of diabetic mothers, intrauterine growth restriction, and perinatal asphyxia. Most are asymptomatic. Symptoms of hypocalcemia include jitteriness, stimulus-induced muscle jerks, seizures, and, rarely, laryngospasm. **Late-onset** (>10 days of life) hypocalcemia can occur because of hypoparathyroidism, the feeding of high-phosphate formula, DiGeorge syndrome (chromosome 22q11.2 deletion), some mitochondrial cytopathies, and hypomagnesemia. Symptomatic or persistent cases should be treated (see Table 56.2).

c. Hypomagnesemia. The most common cause is transient neonatal hypomagnesemia. It causes parathyroid hormone resistance and so causes hypocalcemia. Hypomagnesemia must be corrected before the hypocalcemia can be corrected (see Table 56.2). Levels <1.4 mg/dL (<0.6 mmol/L) are considered low.

5. **Malformations/structural lesions.** Five percent of neonatal seizures are caused by cerebral dysgenesis. **Cerebral dysgenesis** can cause seizures from the first day of life. This is most likely with the more severe disorders such as hemimegalencephaly, lissencephaly, and polymicrogyria. Seizures are often refractory to medications. Some disorders may be amenable to surgical treatments, such as hemimegalencephaly and focal polymicrogyria. In general, these infants are not encephalopathic interictally. Clues to neurocutaneous diseases may be apparent on the newborn examination—for instance, the hemangioma in the distribution of cranial nerve V1 in Sturge-Weber syndrome, which can occasionally cause seizures in the newborn period. Hypopigmented "ash-leaf" macules of tuberous sclerosis may be seen, although neonatal seizures are rare in this disorder. Neuroimaging is primary in making these diagnoses.

6. **Inborn errors of metabolism.** Although individually very rare, inborn errors of metabolism as a group cause at least 1% of cases of seizures in the newborn. Typically caused by an enzyme defect in the metabolic pathways of carbohydrates, proteins, or fat, many cause disease due to accumulation of toxic products unable to proceed along the appropriate metabolic pathways. In these disorders, infants initially appear well, due to the benefits of placental clearance of toxins until birth, and only become encephalopathic and have seizures after 2 to 3 days. Parental report of "hiccough" *in utero* may correlate with postnatal seizures and/or myoclonus. Biochemical markers for these disorders include hypoglycemia, metabolic acidosis, hyperammonemia, as well as specific patterns of alteration in amino acid or organic acid profiles. Other disorders cause disease due to a mutation-related defect in a vital function, for example, in glucose transporter 1 (GLUT-1) deficiency, which impairs glucose transport across the blood–brain barrier, with resulting developmental delay and seizures. This disorder illustrates the importance of identifying these disorders because it and some others are treatable, providing an opportunity to prevent brain injury. Diagnosis also allows reproductive counseling for later pregnancies. Among metabolic disorders, **glycine encephalopathy (nonketotic hyperglycinemia)** commonly causes myoclonic events, with or without EEG correlate, encephalopathy with depressed sensorium, respiratory compromise, and hypotonia. The EEG background often reveals a very abnormal

"burst-suppression" pattern. Glycine is elevated in the cerebrospinal fluid (CSF) and usually, but not always, in plasma. The defect is in the glycine cleavage system, and because glycine is a co-agonist with the excitatory glutamate, it results in enhanced cortical excitability. In spite of efforts to block glutamate neurotransmission pharmacologically with dextromethorphan, most of these infants do very poorly. **Pyridoxine dependency**, although rare, is an important cause of neonatal seizures as treatment is available. The most common form is due to a defect in the ALDH7A1/antiquitin gene, which results in deficiency of alpha amino-adipic semialdehyde (α-AASA) dehydrogenase and accumulation of α-AASA in blood, urine, and CSF, thus providing a biologic marker for the disorder. This enzyme is involved in lysine breakdown in the brain and is believed to impact the metabolism of the neurotransmitters glutamate and GABA. Seizures present early, sometimes *in utero*, and infants are irritable. A test dose of pyridoxine 100 mg IV, with EEG and cardiorespiratory monitoring, resulting in immediate seizure cessation and resolution of EEG abnormalities within hours, is diagnostic. Because some infants do not respond to the initial IV dose, a 3-day trial of oral pyridoxine (30 mg/kg/day) is recommended for nonresponders. If successful, supplementation is lifelong as seizures recur on withdrawal of the pyridoxine. The poorly understood disorder, **folinic acid–responsive seizures**, has recently been shown to be genetically and biochemically identical to pyridoxine dependency. Previously, this disorder, initially identified by novel peaks in CSF chromatography, was treated by supplementation with folinic acid (3 to 5 mg/kg/day). This was effective in stopping seizures in some of these cases but did not prevent severe developmental sequelae. Similarly, many patients with pyridoxine dependency, although seizure free, had long-term developmental deficits. For this reason, and based on their allelic nature, it has been suggested that patients diagnosed with either of these disorders be treated with both supplements.

7. **Epilepsy syndromes.** These syndromes are rare, together accounting for about 1% of cases of seizures in the newborn period. **Benign familial neonatal convulsions** occur in otherwise well infants on day 2 or 3 of life. Seizures may be focal clonic or tonic (usually asymmetrical). Family history should be sought because it is often unreported. Seizures resolve after a variable period, usually within 6 months. This disorder is associated with abnormality of voltage-gated potassium channels, usually KCNQ2 and less frequently KCNQ3. Developmental outcome is normal, but 5% to 15% may have later nonfebrile convulsions. **Benign infantile neonatal seizures** ("fifth day fits") present suddenly on days 4 to 6 of life, often with frequent seizures leading to status epilepticus. Seizures are initially focal clonic often with apnea. Tonic seizures are not expected in this disorder. Seizures usually cease within 2 weeks. The etiology is unknown. More severe epilepsy syndromes are also seen, presenting in this period. These include the following:

   a. EIEE with burst suppression (EIEE + BS). Previously, this group was divided into (i) **early myoclonic epilepsy** (EME) or (ii) EIEE (Ohtahara syndrome) based mainly on the predominant presenting seizure type, myoclonic +/− focal seizures in EME and tonic/spasms in EIEE/Ohtahara syndrome, and also because etiology was thought more

likely metabolic in EME and structural in Ohtahara syndrome. However, they are increasingly considered to exist on a spectrum, although the pathophysiologic basis for the clinical differences are as yet unknown. It is now clearer that the epileptic syndrome (clinical and electrographic features) does not predict etiology. Seizures tend to be very refractory to antiseizure medications, and outcome for normal development is poor. There is a high early mortality in the first 1 to 2 years of life. Structural abnormalities are a common etiology. In those without a malformation, a pathogenic alteration in epilepsy genes can be identified in up to 60% (e.g., KCNQ2, STXBP1, SCN2A, ARX, and others), and this proportion is likely to increase with advances in molecular understanding of the epilepsies. Establishing a genetic etiology is helpful for family counselling, reproductive considerations, and increasingly to guide choice of seizure medications/approaches. With respect to seizure types, early myoclonus is often fragmentary, can be subtle, and usually affects the face and limbs. Tonic seizures develop later in surviving infants. Especially in those with tonic seizures, the epilepsy may evolve to other syndromes over time, e.g., West syndrome/infantile spasms and/or Lennox-Gastaut syndrome. The EEG is characterized by a burst-suppression pattern, which may only be seen in sleep, and, if present throughout the sleep–wake cycle, is exacerbated by sleep. Occasionally, a child with HIE has an unusually severe and unremitting seizure and EEG course for the degree of injury. In this setting, genetic testing may be revealing. The proportion of these cases for which a genetic diagnosis is found continues to increase.

b. Epilepsy of infancy with migrating focal seizures (EIMFS/Coppola syndrome) may present from the 1st to the 10th month of life. Focal motor seizures occur and escalate aggressively, shifting clinically and electrographically from side to side and proving highly refractory to antiseizure medications. Developmental status is acutely affected and prognosis for normal outcome is poor, although cases with less than devastating outcome have now been described. Early mortality is high in severe cases in this situation also. A recent study describes the underlying genetic etiologies, most commonly due to pathogenic changes in the KCNT1 gene, followed by SCN2A gene with 31 other genes implicated in other cases.

8. Other high-risk subpopulations

a. Extracorporeal membrane oxygenation (ECMO). Critically ill neonates requiring ECMO have been identified by recent guidelines as a population at high risk for seizure due to the high risk of cerebral injury during the transition to ECMO. These patients typically remain chemically paralyzed and sedated, further masking clinical signs of seizure. Several single-center studies have identified electrographic seizures ranging from 16% to 40% in neonates and children on ECMO. Seizures and high seizure burden have been associated with mortality and poor neurodevelopmental outcome. Additionally, electrographic seizures have an association with cerebral injury, and the EEG background can aid in prognosis.

b. Congenital heart disease. Neonates who undergo surgery for congenital heart disease are known to be at risk for seizures specifically in the postoperative period. Electrographic seizures have been documented to occur in 5% to 26% of this population. Studies suggest that the average time to first seizure is 20 to 22 hours into the postoperative period.

IV. INVESTIGATIONS. The approach to investigations should be individualized with an emphasis on early identification of correctable disorders. Testing is guided by a detailed history of the pregnancy, labor and delivery, and subsequent course. It should proceed in parallel with stabilization of vital functions, including supported respiration if necessary, EEG confirmation of seizures if available, and with antiseizure treatment of ongoing seizures. General metabolic screening and assessment for evidence of sepsis (which may include lumbar puncture and/or screening for inborn errors of metabolism) should all be considered and the approach modified by the individual case history. Neuroimaging should be considered. Cranial ultrasound examination can be accomplished at the bedside and may identify ICH, especially in the premature. However, its ability to identify convexity hemorrhages and cortical abnormalities is very limited. Head computed tomography (CT) and especially brain magnetic resonance imaging (MRI) are more helpful to confirm these disorders, with MRI preferable to avoid radiation exposure and generally provide superior views. However, they may not be available and if available usually require transportation, with the risk of destabilization of ill infants and must often be deferred until after the infant is stabilized and treatment has been initiated.

V. TREATMENT. Seizures themselves and treatment with antiseizure medication may impair respiratory drive and the ability to maintain adequate circulation. Therefore, supportive management to ensure maintenance of adequate ventilation and perfusion is imperative (see Table 56.3 for treatment of common acute metabolic derangements; see Chapters 23 and 60).

The decision to treat neonatal seizures with antiseizure medications depends on the risk of acute seizure-related respiratory or cardiac decompensation in a critically ill newborn as well as the potential for long-term seizure-related neurologic injury balanced against the potential adverse effects of antiseizure medications. Some newborns may not need treatment with antiseizure medication, for instance, those with seizures due to reversible and appropriately treated metabolic derangements or those with rare, short-lived events. However, in considering a decision not to treat, it is important to recognize that a significant proportion of newborns, with electroclinical seizures, have additional subclinical events. In the setting of severe neonatal encephalopathy, these

Table 56.3. Initial Management of Acute Metabolic Disorders

Hypoglycemia	Dextrose 10%, 2–3 mL/kg IV
Hypocalcemia	Calcium gluconate, 5% (50 mg/mL) 100–200 mg/kg IV; 10% (100 mg/mL) 50–100 mg/kg IV if inadequate time for dilution
Hypomagnesemia	Magnesium sulphate, 12.5% (125 mg/mL) 50–100 mg/kg IV

IV, intravenous.

events may be prolonged and refractory to treatment, and efforts to eliminate them may be limited by systemic vulnerability to the circulatory effects of antiseizure medications. It is also important to recognize that most neonatal seizures are acute symptomatic seizures and that their natural history is to escalate, peak, and then decline in frequency over a period of days, a timeframe that is sometimes prolonged by use of hypothermia. In refractory cases, third- and fourth-line agents may therefore appear more effective due to the coincidence of the naturally declining number of seizures at the time of their introduction.

Adverse effects of antiseizure medications, aside from respiratory and cardiovascular suppression, are also of concern in the developing brain. In studies of normal immature animals, many antiseizure medications, including phenobarbital, phenytoin, diazepam, clonazepam, valproic acid, and vigabatrin, increased the rate of apoptotic neuronal cell death, as do *N*-methyl-D-aspartate (NMDA) receptor antagonists. How this relates to the risk–benefit balance in human neonates with seizures is not known, and further study is required. The AMPA antagonist, topiramate, as well as levetiracetam do not appear to have this effect.

A number of factors alter the pharmacokinetics of the antiseizure medications in neonates. Physiologic immaturity delays drug elimination, and asphyxial injury to the liver and kidney may further delay metabolism. Maturation of the various pathways involved in drug metabolism occurs at variable rates over the first weeks of life, and recovery from perinatal injury improves hepatic and renal function. Overall, there is a dramatic increase in the ability to eliminate the commonly used antiseizure medications so that changes in dosing are required to maintain therapeutic drug levels over the first weeks of life.

When antiseizure treatment is indicated, phenobarbital is the drug most commonly used as first-line therapy. Other first-line options include benzodiazepines (diazepam, lorazepam) and phenytoin or, if available, its prodrug fosphenytoin. Painter et al. compared treatment with phenobarbital and phenytoin and found no difference in efficacy between the two drugs, with fewer than 50% of infants achieving control with either drug. Typical initial doses of the first-line drugs are provided in Table 56.3, and additional discussion of the individual drugs is given in the following text.

A. Phenobarbital. Phenobarbital affects $GABA_A$ receptors to enhance GABA-related inhibition. It may also inhibit excitatory amino acid transmission and block voltage-activated calcium currents. It is a weak acid, with low-lipid solubility. Phenobarbital is subject to protein binding, and it is the unbound (free), unionized fraction that is active. Alterations in acid–base balance in the newborn may affect efficacy of the drug for this reason. Phenobarbital is metabolized in the liver and excreted by the kidney. Its half-life is long, from 100 to 300 hours, or longer in premature infants but declines to 100 hours or less over the first weeks of life. An initial IV loading dose of 20 mg/kg may be followed by increments of 5 to 10 mg/kg IV to a total of 40 mg/kg, with higher doses associated with improved efficacy. If required, the maintenance dose should be started at 5 mg/kg/day divided twice daily. Careful monitoring of cardiac and respiratory function is required in vulnerable infants.

B. Phenytoin/fosphenytoin. Phenytoin acts by blockade of voltage-dependent sodium channels, probably by binding to inactivated channels and stabilizing the inactive state. This decreases the tendency of neurons to high

frequency, repetitive firing, and therefore their excitability. Phenytoin is a weak acid and is poorly soluble in water. High lipid solubility results in rapid entry to the brain, but it is quickly redistributed and levels decline, requiring continued administration to restore brain levels. It is protein bound, although to a lesser degree in newborns than in older children and adults. Phenytoin is metabolized in the liver and eliminated in the kidney. Its half-life varies with concentration, increasing with higher concentrations due to decreased clearance as levels increase. An IV loading dose of 20 mg/kg of phenytoin administered at no >1 mg/kg/minute (to avoid cardiac arrhythmia and hypotension) is followed by a maintenance dose of 2 to 3 mg/kg/day IV divided between two and four doses. Fosphenytoin is a prodrug of phenytoin. Its advantages are its higher water solubility and lower pH, which, in addition to the lack of toxic vehicles required for its formulation, reduce local irritation of skin and blood vessels at the site of infusion. Fosphenytoin is converted to phenytoin by plasma phosphatase enzymes in neonates as in adults. Phenytoin induction of hepatic enzymes should be taken into consideration when attempting to keep additional agents in a therapeutic range.

C. Benzodiazepines. Diazepam, lorazepam, and midazolam, like other benzodiazepines, bind to the postsynaptic $GABA_A$ receptor to enhance GABA-activated inhibitory chloride currents. At high levels, benzodiazepines may also influence voltage-gated sodium channels and calcium channels. Benzodiazepines are lipid soluble. Differential lipid solubility confers some advantage on lorazepam, which is less lipid soluble and therefore is not redistributed away from the brain as rapidly as diazepam. Benzodiazepines are metabolized in the liver, and the majority of the drug is excreted in the urine. The plasma half-life of both lorazepam and diazepam is approximately 30 hours and may be longer in premature and/or asphyxiated newborns. Onset of action is within minutes for both drugs; however, duration of action is longer for lorazepam (up to 24 hours). Diazepam may be more effective as a continuous infusion. Lorazepam is given IV at a dose of 0.05 to 0.1 mg/kg. Diazepam dose is 0.3 mg/kg IV. An infusion rate of 0.3 mg/kg/hour IV has been described. Midazolam is a short-acting benzodiazepine that has been used as a continuous IV infusion (0.1 to 0.4 mg/kg/hour) after an initial loading dose (0.15 mg/kg). Benzodiazepines are typically used as second- or third-line agents in neonatal seizures but may also be used as an initial treatment due to their earlier onset of action in anticipation of the effect of a concurrent dose of phenobarbital.

Upward of 90% of neonatal seizures will ultimately be controlled by the combined use of the earlier antiseizure medications. The natural history and evolution/resolution of underlying brain injury in the first days of neonatal life may also contribute to a reduction in seizures.

D. Levetiracetam (Keppra). The use of levetiracetam in the treatment of neonatal seizures continues to increase. Its IV formulation, benign side effect profile, and limited interactions make it an attractive treatment option. However, a recent multicenter, randomized, blinded controlled trial of comparing first-line efficacy of levetiracetam (up to 60 mg/kg) versus phenobarbital (up to 40 mg/kg) revealed better efficacy for phenobarbital (80% seizure free for 24 hours vs. 28% for levetiracetam, $P < .001$). It will

likely continue to be used in refractory cases as a later option. Reported loading doses vary from 10 to 20 mg/kg to as high as 40 to 60 mg/kg. Maintenance doses described also vary widely from 10 to 80 mg/kg/day with most providers starting at 20 mg/kg/day, whereas others suggest 40 mg/kg/day. Although twice-daily dosing is usual, three-times-daily dosing has been suggested.

E. Topiramate. Topiramate is often used adjunctively after the acute phase of neonatal seizure for continued refractory neonatal seizures. Topiramate is an antagonist for glutamate AMPA receptors which may be potentiated by hypoxia, and it is thought to have neuroprotective properties. Studies of topiramate in human neonates are lacking and an IV formulation is not available. Appropriate dosing for neonates has not been established.

Many other drugs have been used in an attempt to control refractory cases. Support for their use is based on reports of efficacy in small, uncontrolled series. Lidocaine has been used, mostly in Europe, as an IV infusion of 4 mg/kg/hour with decreasing doses over 4 to 5 days. This drug has a narrow therapeutic range and may induce seizures at higher levels.

Orally administered antiseizure medications that have been used adjunctively include carbamazepine (10 mg/kg initially followed by 15 to 20 mg/kg/day), primidone (loading dose 15 to 25 mg/kg followed by 12 to 20 mg/kg/day), and valproic acid (3 of 6 neonates developed hyperammonemia).

No guidelines exist as to the appropriate duration of antiseizure treatment for newborns with seizures, and there is wide variation in practice. There is a trend toward shorter therapy, taking into account the short-lived nature of precipitating causes, the recovery from acute HIE in many instances, and the possible detrimental effect of antiseizures on the immature brain. Newborns with persistent, difficult to control seizures; persistently abnormal EEG; and/or persistently abnormal neurologic examination should be considered for longer term treatment following discharge from hospital.

VI. PROGNOSIS.

Advances in obstetric management and in neonatal intensive care have yielded a reduction in mortality in infants with neonatal seizures from about 40% to <20%, with <10% mortality in term infants in one recent series. Morbidity rates have changed less, partly due to increased numbers of survivors among ill premature newborns who have a greater risk of neurologic sequelae. Long-term sequelae in infants with neonatal seizures, including cerebral palsy and intellectual disabilities, still occur at a high rate of up to 35%, with post–neonatal seizures (epilepsy) occurring in up to 20%. The most important factor affecting outcome for infants with neonatal seizures is the **underlying etiology**. For instance, normal development can be expected in infants with benign idiopathic neonatal seizures and in 90% of those with primary subarachnoid hemorrhage, whereas only 50% of those with HIE, and even fewer with a brain malformation will have normal outcome. **Gestational age** is also an important factor with increasing mortality and morbidity with increasing immaturity.

Useful clinical indicators for a good outcome include a normal neonatal neurologic exam, normal or mildly abnormal neonatal EEG background activity, and normal neuroimaging or abnormalities limited to extraparenchymal injury (Table 56.4).

Table 56.4. Antiseizure Medication Doses for Initial Management of Neonatal Seizures

Drug	Initial Dose	Maintenance
Phenobarbital	20 mg/kg IV Consider further 5–10 mg/kg increments to a total of 40 mg/kg.	Check drug levels—may not need further doses for many days. 5 mg/kg/day divided bid
Phenytoin	20 mg/kg IV Fosphenytoin: 20 mg PE/kg IV (see text, section V.B)	5 mg/kg/day divided bid to tid
Benzodiazepines	Lorazepam: 0.05–0.1 mg/kg IV Diazepam: 0.3 mg/kg IV Midazolam: 0.15 mg/kg bolus	
Levetiracetam	40–60 mg/kg bolus (see text, section V.D)	40–80 mg/kg divided bid or tid

IV, intravenous; PE, phenytoin equivalent.

Suggested Readings

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57 Neural Tube Defects

Anne R. Hansen and Benjamin C. Warf

KEY POINTS

- Preoperatively, minimize bacterial colonization and tissue damage by keeping the newborn in prone position with sterile saline–moistened gauze sponge placed over the defect covered by plastic wrap.
- Administer intravenous antibiotics (ampicillin and gentamicin) to diminish the risk of meningitis, a particularly devastating complication.
- Ensure that no latex equipment is used to avoid the development of severe allergy to latex rubber due to repeated exposure in medical devices.
- Postoperatively, closely follow anterior fontanel tension, head circumference, serial cranial ultrasounds, as well as onset of feeding difficulties or stridor due to likelihood of progressive hydrocephalus following closure of the back.

I. DEFINITIONS AND PATHOLOGY. The central nervous system (CNS) starts as a neural tube and folds into the brain and spinal cord by a complex mechanism during early embryologic development. Failure of normal closure results in neural tube defects, one of the most serious congenital malformations in newborns. The term refers to a group of disorders that is heterogeneous with respect to embryologic timing, involvement of specific nervous system elements, clinical presentation, and prognosis.

A. Types of neural tube defects

1. **Primary neural tube defects** constitute the majority of neural tube defects and can be viewed as due to primary failure of closure of the neural tube or disruption of an already closed neural tube between 18 and 25 days' gestation. The resulting abnormality usually manifests in two anatomic lesions: an exposed (open or *aperta*) neural placode along the midline of the back caudally and, rostrally, the type 2 Chiari malformation (Chiari II), which is a global brain malformation marked by downward displacement of cerebellum, brainstem, and fourth ventricle into the upper cervical region. There may be associated brainstem dysfunction that is either intrinsic or exacerbated by external pressure on these crowded structures. Hydrocephalus, typically secondary to dysfunctional cerebrospinal fluid (CSF) outflow from the fourth ventricle, develops in the majority. There can be neuronal migrational anomalies of the brain ranging from mild to severe.

a. Myelomeningocele is the most common primary neural tube defect. It involves a dorsal herniation of the defective spinal cord segment (neural placode), through a defect in the dura, bone (the spina bifida defect), and soft tissues of the posterior thoracic, sacral, or lumbar regions—the latter being most common. Arachnoid (meningo) is typically included in the CSF-filled sac (cele), which contains visible spinal cord tissue (myelo), and the skin is discontinuous over the sac. Hydrocephalus occurs in around two-thirds of these children; Chiari II malformation occurs in approximately 90%, although the link between hydrocephalus and the malformation has been significantly reevaluated in recent years, with therapeutic implications discussed in the following text. Various associated anomalies of the CNS are noted, most importantly, cerebral cortical dysplasia in up to 92% of cases.

b. Encephalocele. This defect is often grouped with neural tube defects but is likely a mesenchymal defect rather than a failure of neural tube closure. This is an outpouching of dura, with or without brain, through a cranial defect. In North America and Europe, it occurs in the occipital region in 80% of cases and less commonly in the frontal, parietal, or temporal regions. The defect can vary in size from a few millimeters to several centimeters, and the fluid-filled, skin-covered, sac can range from small to very large.

c. Anencephaly. This is the most severe form of neural tube defect. The scalp, cranial vault, and dura are defective, exposing neural tube derivatives that should have been brain. The defect usually extends through the foramen magnum and involves the brainstem. It is not compatible with long-term survival. Rachischisis is an even more severe form in which the spine is also involved due to nonfusion of the majority of the primary neural tube.

2. **Secondary neural tube defects.** After primary neurulation, which forms the majority of the CNS, a process occurs called secondary neurulation. Briefly, the caudal cell mass (tail bud), formed of pluripotent cells, gives rise to a small secondary neural tube that fuses with the end of the primary neural tube. The majority of this structure regresses by apoptosis (a process called retrogressive differentiation), leaving behind the filum terminale and the distal tip of the conus medullaris. Abnormalities of this process may lead to several types of skin-covered spina bifida lesions (spina bifida occulta) that cause "tethering" of the spinal cord, which can result in harmful abnormal traction on the caudal cord that worsens with normal axial growth of the child. This heterogeneous group of anomalies are rarely associated with hydrocephalus or a Chiari malformation. Because the hindbrain abnormality of the Chiari II malformation is evident on prenatal scans, this radiographic finding is useful in distinguishing open (aperta) from closed (occulta) spina bifida lesions.

   a. Meningocele is a dorsal herniation of the thecal sac through a spina bifida and fascial defect. These are skin covered and do not contain neural elements aside from a commonly associated band of nonfunctional neurovascular or fibrous tissue connecting the dorsal spinal cord to the inside of the sac that causes tethering of the spinal cord.

b. Lipomyelomeningocele is, generally speaking, a complex lesion involving a lipomatous mass intrinsic to the conus of the spinal cord that extends dorsally through defects in the dura, bone (spina bifida defect), and fascia into a skin-covered subcutaneous lipoma.

c. Filum lipoma is the simplest secondary neurulation anomaly. An abnormality of retrogressive differentiation is thought to lead to a malformed filum terminale that typically contains fat and abnormal fibrous tissue and is thicker and tighter than normal. This can cause symptomatic spinal cord tethering as the child grows.

d. Diastematomyelia (or split cord malformation) is not a neural tube defect but rather an earlier embryologic mishap during gastrulation. **Myelocystocele** is a very rare spinal cord anomaly that is typically associated with caudal regression and cloacal exstrophy.

B. Etiologies. The exact cause of failed neural tube closure (primary neural tube defects) remains unknown, and proposed etiologies for both primary and secondary neural tube defects are heterogeneous. Factors implicated include folic acid deficiency; maternal ingestion of the anticonvulsants carbamazepine and valproic acid; and folic acid antagonists such as aminopterin and certain antimalarial drugs, maternal diabetes, and disruptive influences such as prenatal irradiation and maternal hyperthermia. A genetic component is supported by the fact that there is concordance for neural tube defect in monozygotic twins and an increased incidence with consanguinity and with a positive family history. Neural tube defects can occur with trisomies 13 and 18, triploidy, and Meckel syndrome (autosomal recessive syndrome of encephalocele, polydactyly, polycystic kidneys, cleft lip and palate) as well as other chromosome disorders. Although specific genes (particularly the MTHFR gene and those in the folate-homocysteine pathway as well as in genes involved in planar cell polarity) have been implicated as risk factors, the genetics are likely complex and multifactorial (see Chapter 10).

C. Epidemiology and recurrence risk. The incidence of neural tube defects varies significantly with geography and ethnicity. In the United States, the overall frequency of neural tube defects is approximately 0.6 to 1 in 2,000 live births.[1] This underestimates the true incidence because of the effects of terminating prenatally diagnosed pregnancies. A well-established increased incidence is known among individuals living in parts of Ireland and Wales and carries over to descendants of these individuals who live elsewhere in the world. This may be true also for other ethnic groups, including Sikh Indians and certain groups in Egypt. More than 95% of all neural tube defects occur to couples with no known family history. Primary neural tube defects carry an increased empiric recurrence risk of 2% to 3% for couples with one affected pregnancy, with a higher risk if more than one sibling is affected. Similarly, affected individuals have a 3% to 5% risk of having an offspring with a primary neural tube defect. Recurrence risk is strongly affected by the level of the lesion in the index case, with risks as high as 7.8% for lesions above T11. In 5% of cases, neural tube defects may be associated with uncommon disorders; some, such as Meckel syndrome, are inherited in an autosomal recessive manner, resulting in a 25% recurrence risk. Secondary neural tube defects are generally sporadic and carry no known increased recurrence risk. In counseling families for recurrence, however, it is critical to obtain a careful family history and history of drug exposure.

D. Prevention. Randomized controlled clinical studies of prenatal multivitamin administration both for secondary prevention in mothers with prior affected offspring and for primary prevention in those without a prior history have shown a 50% to 70% reduced incidence of neural tube defects in women who take multivitamins for at least 3 months prior to conception and during the first month of pregnancy.[2] The Centers for Disease Control and Prevention recommends that women of childbearing age who are capable of becoming pregnant consume 0.4 mg of folic acid per day to reduce their risks of having a fetus affected with myelomeningocele or other neural tube defects. Higher doses are recommended for women with prior affected offspring. In addition, folate supplementation of enriched cereal-grain products has been mandated by the U.S. Food and Drug Administration (FDA); however, the level of folate intake from this source is not high enough to forgo additional supplementation in the large majority of women. It is estimated that about 30% of neural tube defects are not folate sensitive.

II. DIAGNOSIS

A. Prenatal diagnosis. The combination of maternal serum α-fetoprotein (AFP) determinations, prenatal ultrasonography, rapid-acquisition fetal magnetic resonance imaging (MRI) scans, and AFP and acetylcholinesterase determinations in amniotic fluid where indicated, greatly improves the ability to make a prenatal diagnosis and to distinguish from abdominal wall defects. Maternal serum AFP measurements of 2.5 multiples of the median (MoM) in the second trimester (16 to 18 weeks) have a sensitivity of 80% to 90% for myelomeningocele. The exact timing of this measurement is critical as AFP levels change throughout pregnancy. Karyotype may also be performed at the time of amniocentesis to detect associated chromosomal abnormalities. Ultrasonographic diagnosis through direct visualization of the spinal defect or through indirect signs related to Chiari II malformation has a sensitivity of >90%. The Chiari malformation is seen as a flattened cerebellum curving around the brainstem, called a "banana sign," and a transient frontal bone anomaly called a "lemon sign." Ultrasound can also demonstrate the level of termination of the normal cord and placode. Prenatal MRI may define the defect more accurately. Determining the prognosis based on prenatal ultrasonography remains difficult, except in obvious cases of encephalocele or anencephaly (see Chapter 1). The level of motor dysfunction can be approximated by the spinal level of the myelomeningocele. Some patients with rare higher thoracic or cervical lesions, however, have remarkable preservation of function; often, continuation of the spinal cord below the lesion is evident by MRI in these cases. The embryopathology of these lesions is likely different.

B. Postnatal diagnosis. Except for some secondary neural tube defects, most neural tube defects, especially meningomyelocele, are immediately obvious at birth. Occasionally, some saccular masses, usually in the low sacrum, including sacrococcygeal teratomas, can be mistaken for a neural tube defect. Rarely, anterior sacral meningoceles can occur that are not evident at birth.

III. EVALUATION

A. History. Obtain a detailed family history. Ask about the occurrence of neural tube defects and other congenital anomalies or malformation syndromes. Note should be made of any of the risk factors described in the preceding text, including maternal medication use in the first trimester or maternal diabetes.

B. Physical examination. It is important to perform a thorough physical examination, including a neurologic examination. The following portions of the examination are likely to reveal abnormalities.

1. **Back.** Inspect the defect and note if it is leaking CSF. Use a sterile nonlatex rubber glove when touching a leaking sac (in most circumstances, only the neurosurgeon needs to touch the back). Note the location, shape, and size of the defect and the thin "parchment-like" overlying skin, although it has little relation to the size of the sac. Often, the sac is deflated and has a wrinkled appearance. It is important to note the curvature of the spine and the presence of a bony gibbus underlying the defect. For suspected closed lesions, document hemangioma, hairy patch, deep dimple, or sinus tract, if present; ultrasonography of the lower spine can show the level of the conus and presence of normal root movement in cases where this is in question.
2. **Head.** Record the head circumference and plot daily until stable postoperatively. At birth, some infants will have macrocephaly because of hydrocephalus, and still, more will develop hydrocephalus after closure of the defect on the back. Ultrasonography is useful to assess ventricular size. Assess the intracranial pressure (ICP) with the baby's head elevated about 30 degrees by palpating the anterior fontanel. A normal fontanel is level with the surrounding skull or slightly sunken. In hydrocephalus, the fontanels may be quite large and distended with widening of the calvarial sutures.
3. **Eyes.** Abnormalities in conjugate movement of the eyes are common and include esotropias, esophorias, and abducens paresis. The classic finding in infant hydrocephalus is the sunset sign, in which the eyes are deviated downward.
4. **Neurologic examination.** Observe the child's spontaneous activity and response to sensory stimuli in all extremities. Predicting ambulation and muscle strength based on the "level" of the neurologic deficit can be misleading, and very often, the anal reflex, or "wink," will be present at birth and absent postoperatively, owing to spinal shock and edema.
5. **Lower extremities.** Look for deformities (e.g., clubfeet) as well as muscle weakness and limited range of motion. Examine the thigh positions and skinfolds and perform the Ortolani and Barlow maneuvers for evidence of congenital dysplasia of the hips. With open lesions, this exam should be deferred until after the repair of the meningomyelocele. Dislocation of the hips can also be diagnosed by ultrasonography (see Chapter 58).

Repeated neurologic examinations at periodic intervals are more helpful in predicting functional outcome than a single newborn examination. Similarly, sensory examination of the newborn can be misleading because of the potential absence of a motor response to pinprick. Examination of the deep tendon reflexes can be helpful (Table 57.1).

6. **Bladder and kidneys.** Palpate the abdomen for evidence of bladder distension or kidney enlargement. Observe the pattern of urination and check the infant's response to the Credé maneuver to evaluate residual urine in the bladder.

C. General newborn assessment. Evaluate all newborns with neural tube defects for the presence of congenital heart disease (especially ventricular septal defect), renal malformation, and structural defects of the airway, gastrointestinal tract, ribs, and hips. Although uncommon in primary neural tube defects, these can be encountered and should be considered before beginning surgical treatment or before discharge from the hospital. Other findings of associated chromosomal anomalies may be noted. In addition, plan an ophthalmologic examination and hearing evaluation during the hospitalization or following discharge.

IV. CONSULTATION.

The care of an infant with a neural tube defect requires the coordinated efforts of a number of medical and surgical specialists as well as specialists in nursing, physical therapy, and social service. Some centers have a neural tube defect team to help coordinate the following specialists.

A. Specialty consultations

1. **Neurosurgery.** The initial care of the child with an open neural tube defect is predominantly neurosurgical. The neurosurgeon is responsible for assessment and surgical closure of the defect and for evaluation and treatment of elevated ICP.
2. **Neonatology/pediatrics.** A thorough evaluation before surgical procedures is important, particularly to detect other abnormalities, such as congenital cardiac anomalies that might influence surgical and anesthetic risk.
3. **Genetics.** A clinical geneticist should conduct a complete dysmorphology evaluation during the first hospitalization. Follow-up during outpatient visits should include genetic counseling.
4. **Urology.** Consult a urologist on the day of birth because of the risk of obstructive uropathy.
5. **Orthopedics.** The pediatric orthopedic surgeon is responsible for the initial assessment of musculoskeletal abnormalities and long-term management of ambulation, seating, and spine stability. Clubfeet, frequently encountered in these newborns, should be assessed and may be addressed during the initial hospitalization.
6. **Physical therapy.** Involve physical therapists in planning for outpatient physical therapy programs.

Table 57.1. Correlation between Segmental Innervation; Motor, Sensory, and Sphincter Function; Reflexes; and Ambulation Potential

Lesion	Segmental Innervation	Cutaneous Sensation	Motor Function	Working Muscles	Sphincter Function	Reflex	Potential for Ambulation
Cervical/ thoracic	Variable	Variable	None	None	—	—	Poor, even in full braces
Thoracolumbar	T12	Lower abdomen	None	None	—	—	—
	L1	Groin	Weak hip flexion	Iliopsoas	—	—	Full braces, long-term ambulation unlikely
	L2	Anterior upper thigh	Strong hip flexion	Iliopsoas and sartorius	—	—	—
Lumbar	L3	Anterior distal thigh and knee	Knee extension	Quadriceps	—	Knee jerk	—
	L4	Medial leg	Knee flexion and hip abduction	Medial hamstrings	—	Knee jerk	May ambulate with braces and crutches

(continued)

Table 57.1. Correlation between Segmental Innervation; Motor, Sensory, and Sphincter Function; Reflexes; and Ambulation Potential *(Continued)*

Lesion	Segmental Innervation	Cutaneous Sensation	Motor Function	Working Muscles	Sphincter Function	Reflex	Potential for Ambulation
Lumbosacral	L5	Lateral leg and medial knee	Foot dorsiflexion and eversion	Anterior tibial and peroneals	—	Ankle jerk	—
	S1	Sole of foot flexion	Foot plantar	Gastrocnemius, soleus, and posterior tibial	—	Ankle jerk	Ambulate with or without short leg braces
Sacral	S2	Posterior leg and thigh	Toe flexion	Flexor hallucis	Bladder and rectum	Anal wink	—
	S3	Middle of buttock	—	—	Bladder and rectum	Anal wink	Ambulate without braces
	S4	Medial buttock	—	—	Bladder and rectum	Anal wink	—

Source: Reprinted from Noetzel MJ. Myelomeningocele: current concepts of management. *Clin Perinatol* 1989;16:311–329. Copyright © 1989 Elsevier. With permission.

7. **Social service.** Arrange for a social worker familiar with the special needs of children with neural tube defects to meet the parents as early as possible. Children with meningomyelocele may require a great deal of parents' time and resources, thereby placing considerable strain on both parents and siblings.

V. MANAGEMENT

A. Fetal surgery. *In utero* repair was first performed in 1994. Observational studies have found that *in utero* repair is associated with lower rates of hydrocephalus and consistent reversal of hindbrain herniation. Long-term effects remain uncertain. A multicenter randomized controlled trial comparing *in utero* surgical correction with standard management found that performing prenatal surgery on fetuses with myelomeningocele may lead to better outcomes than if the surgery is performed postnatally.[3] After 12 months, the 91 infants who had prenatal surgery were 30% less likely to die or need additional surgical procedures than the 92 infants who were treated postnatally. Follow-up at 2½ years of age revealed that those treated prenatally demonstrated improved physical development and motor function, such as unassisted walking, compared to those treated after birth. However, prenatal surgery was associated with increased risk of complications during pregnancy including premature delivery and tearing of the uterine wall from the surgical scar. When the diagnosis of myelomeningocele is made prenatally, *in utero* repair is an option that parents may consider.

B. Perinatal. Cesarean section prior to the onset of labor has been the preferred mode of delivery because it decreases the likelihood of rupturing the meningeal sac,[4] but this practice is being questioned.[5,6]

C. Preoperative management

1. **Neurology**

   a. Care of placode: At birth, the very thin sac is often leaking. Keep the newborn in the prone position with a sterile saline–moistened gauze sponge placed over the defect covered by plastic wrap. This reduces bacterial contamination and tissue damage related to dehydration.

   b. Chiari II: A cranial ultrasound should generally be obtained soon after birth. Chiari II malformations may result from *in utero* CSF leak and deflation of the fourth ventricle anlage. This leads to inadequate posterior fossa development. Brainstem and portions of the cerebellum may herniate through the foramen magnum into the upper cervical spinal canal. Obstructed flow of CSF results in hydrocephalus the majority of the time. *In utero* repair can sometimes prevent or reverse that process.

   c. Seizures: There is a 20% to 25% incidence of seizures in this population due to brain anomalies that typically accompany the Chiari II malformation, such as neuronal migration anomalies.

2. **Infectious disease.** Administer intravenous antibiotics (ampicillin and gentamicin) to diminish the risk of meningitis, particularly due to group B streptococci. Newborns with an open spinal defect can receive a massive inoculation of bacteria directly into the nervous system at the time of vaginal delivery or even *in utero* if the placental membranes rupture early. Meningitis is a particularly devastating complication.

3. **Fluids/nutrition.** Because insensible losses are minimized by covering the lesion with plastic wrap, standard maintenance fluids are generally appropriate.
4. **Urologic/renal**
   a. Clean intermittent catheterization (CIC) is indicated to check postvoid residuals until urologic and renal function are assessed.
   b. If voiding pattern is abnormal, it is important to determine if the etiology is abnormal bladder emptying, renal function, or both. A serum creatinine level is useful in making this distinction.
5. **Latex allergy.** Because of the potential for development of a severe allergy to latex rubber due to repeated exposure in medical devices, no latex products should be used.

D. Surgical treatment. Open defects must be closed urgently due to the risk of infection. Infants whose defect is covered with skin and whose nervous system is therefore not at risk for bacterial contamination may undergo elective repair, typically within the first 6 months of life. The initial neurosurgical treatment of an open myelomeningocele consists of closing the defect to prevent infection. The back should be closed within the first 24 to 48 hours of life if safely possible to minimize the risk of infection. Techniques are available to rapidly close even very large cutaneous defects without skin grafting. The surgical approach varies with the precise anatomy. In brief, the translucent tissue and skin too thin to use are trimmed away around the circumference of the defect, then the placode is rolled into a more normal shape and gently held in this configuration with fine, pial sutures. The edges of the dural defect are identified, reflected medially, and closed over the placode, then the fascia and skin are closed with the goal of attaining a well-vascularized, watertight closure. Plastic surgery may be helpful in gaining soft tissue coverage in larger defects.

1. If **hydrocephalus** is severe from birth, it can be treated at the same time as the back closure. More typically, hydrocephalus progresses following closure of the back, so anterior fontanel tension and head circumference should be carefully monitored along with serial cranial ultrasound. Due to common and troublesome complications with lifelong shunt dependence, increasingly, practitioners are trying to delay or avoid permanent shunting and to consider endoscopic third ventriculocisternostomy with choroid plexus cauterization (ETV-CPC) instead.[7] This combination of procedures may eliminate the need for shunts in about 75% of the infants with myelomeningocele requiring hydrocephalus treatment.[8–10] In some centers, this has become the primary initial treatment for the majority of these patients.

   Regardless of the planned strategy for dealing with hydrocephalus, close monitoring and timely treatment are important.

E. Postoperative management

1. **Neurology**
   a. The infant must remain prone or side-lying until the wound heals. Head circumference needs to be measured daily, particularly in the infant who has not had shunt placement.

b. MRI of the brain and spine should generally be obtained postoperatively, even if there is no clinical evidence of hydrocephalus. It is particularly valuable in assessment of the posterior fossa and syringomyelia. **Computed tomography (CT) scans** should be avoided unless no other options are available because of the relatively high radiation exposure.

c. Sensory impairment can be associated with myelomeningocele. Strabismus is commonly associated with Chiari malformation. Hearing and vision screens may be performed prior to discharge.

d. Seizures should be monitored because there is up to a 25% incidence in this population, in part due to brain anomalies such as neuronal migration abnormalities associated with Chiari II malformations.

e. Stridor suggests vocal cord weakness that can lead to airway obstruction. This may signal the need to treat hydrocephalus or remedy treatment failure such as a shunt malfunction. If the hydrocephalus is adequately treated, surgical decompression of the posterior fossa may be indicated.

2. **Nutrition.** Feeding difficulties are commonly associated with the Chiari II malformation. Growth and nutritional status must be watched closely as well as the infant's ability to suck and swallow. As with stridor, acute deterioration in feeding skills may signal the need to assess the status of hydrocephalus and, less commonly, consideration of posterior fossa decompression.

   a. Monitor daily weight and input/output.

   b. Observe for spitting, gagging, choking, nasal regurgitation, and episodes of oxygen desaturation.

3. **Urologic/renal**

   a. Obtain urine culture, urinalysis, and serum creatinine as a baseline, if not already measured preoperatively.

   b. Ultrasound of the urinary tract will detect associated renal anomalies as well as possible hydronephrosis from vesicoureteral reflux.

   c. Postvoid residuals and urodynamic studies should be performed early in the hospitalization or shortly after discharge to document the status of the bladder as well as urinary sphincter function and innervation. This study will serve as a basis for comparison later in life.

   d. Consider a voiding cystourethrogram to assess for vesicoureteral reflux if there is an abnormality seen on ultrasonographic or urodynamic study or in the setting of a rising serum creatinine level.

   e. CIC is recommended for those infants who have large postvoid residuals, evidence of significant hydronephrosis, and/or increased bladder pressure on urodynamics studies. CIC is started in the hospital and continued at discharge. Those infants who do not manifest these problems can safely be allowed to spontaneously void.

4. **Orthopedics**

   a. Obtain plain films of lower extremities if there is concern regarding clubfeet or other anomalies raised by physical exam.

   b. Obtain chest x-ray (CXR). Rib deformities are common; cardiac malformations may also be identified.

   c. Obtain plain films of spine. Abnormalities in vertebral bodies, absent or defective posterior arches, and evidence of kyphosis are common.

d. Evidence of dysplasia of hips is common, and some children with neural tube defects are born with dislocated hips. Ultrasonographic examination of the hips can be very helpful to the orthopedic surgeon (see Chapter 58).

5. **Family and social worker**

a. Family care providers will need to play an active role in home management. It is critical for them to understand the child's condition and the implications for home care. The involvement of multiple specialists heightens the importance of the identification of a primary care provider (pediatrician or family practitioner) to coordinate the flow of information.

b. The family stress of caring for a child with myelomeningocele cannot be underestimated. A social worker should be available for the family from the time of diagnosis. An excellent information and support resource is the Spina Bifida Association of America (https://www.spinabifidaassociation.org).

VI. PROGNOSIS

A. Survival. Nearly all children with neural tube defects, even those severely affected, can survive for many years, with a 78% survival rate to age 17 years for those with myelomeningocele. Survival rates appear to have increased since folic acid fortification of the U.S. grain supply was started, possibly because of a general decrease in severity or location of lesions. Survival rates are significantly influenced by selection bias of prenatal diagnosis and termination of severely affected fetuses and by decisions to intervene versus to withhold aggressive medical and surgical care in the early neonatal period. Most deaths occur in the most severely affected children and are likely related to brainstem dysfunction.

B. Long-term outcome. There are a wide variety of medical and developmental issues associated with myelomeningocele. Children with myelomeningocele require a comprehensive multidisciplinary team of providers including neurosurgery; orthopedic surgery; urology; physiatry; gastroenterology; endocrinology; pulmonary medicine; and physical, occupational, and speech language pathology.

1. **Neurosurgical issues.** In one cohort study of myelomeningocele patients, 88% underwent ventriculoperitoneal (VP) shunt of whom 15% suffered shunt-related infections; 18% underwent Chiari II decompression, and 16% tethered cord release.[11] Early symptomatic cord tethering appears to be much more common in children closed *in utero*. The majority are affected in some way by the Chiari II malformation in the form of hydrocephalus, syringomyelia, or brainstem dysfunction. In addition to hydrocephalus, sleep apnea and dysphagia are very common in these patients.

a. Increased ICP can result from evolving hydrocephalus in the untreated child, shunt malfunction or infection in the shunted child, or failure of ETV-CPC to adequately address the problem. The vast majority of ETV-CPC treatment failures occur within 6 months of surgery, whereas the risk of shunt failure continues throughout life. Beyond infancy,

elevated ICP requires urgent assessment because symptoms may progress rapidly and can be fatal. In the myelomeningocele population, this sometimes presents primarily as symptoms related to brainstem dysfunction or evolving syringomyelia rather than the classic symptoms of elevated ICP. Common symptoms and signs may include the following:

i. Headache, irritability, bulging fontanel, sixth nerve palsy, paralysis of upward gaze
ii. New onset of respiratory complications, particularly stridor from vocal cord paralysis, central and/or obstructive apnea
iii. Worsening oromotor function, abnormal gag, and vomiting (often confused with gastroesophageal reflux)
iv. Change in cognitive function

These symptoms may indicate untreated hydrocephalus or treatment failure. After ensuring adequate treatment for hydrocephalus, surgical decompression of the Chiari malformation should be considered. If the symptoms persist, especially in association with cyanosis, the prognosis is poor, with risk of respiratory failure and death. Tracheostomy is occasionally necessary. Posterior fossa decompression and cervical laminectomy are surgical options but are often not successful.

b. Shunt infection should be suspected if symptoms of ICP are accompanied by fever and increased peripheral white blood cell count.

i. A shunt tap is necessary to rule out a shunt infection.
ii. A shunt series and brain imaging (e.g., rapid-sequence MRI) may be necessary in conjunction with neurosurgical evaluation.
   a) **Seizures** remain a risk, and families should be familiar with signs and symptoms to monitor as well as an initial treatment approach.
   b) **Acquired symptomatic tethering of the spinal cord**[11] can result in the onset of new neurologic symptoms (e.g., worsening bladder dysfunction or new motor weakness), new orthopedic deformities (e.g., scoliosis or progressive foot deformities), or pain. Surgery to release the spinal cord from its attachment in scar at the site of the original myelomeningocele closure may be indicated.

2. **Motor outcome.** This depends more on the level of paralysis and surgical intervention than it does on congenital hydrocephalus. In a 12-year study of adult myelomeningocele patients, one-third experienced deterioration in their ambulatory capacity over the study period. All those with lesions at the L5 neurologic levels were community ambulators, except one who was a household walker. At the L4 level, there was a slight decrease in functional ambulators. For the L3-level patients, less than one-third were still community or household ambulators at the end of the 12 years of observations.[12] Most children with neural tube defects will have a delay in motor progress, but appropriate bracing, physical therapy interventions, and monitoring and treatment of kyphosis and scoliosis can mitigate this. Factors such as obesity, frequent hospitalizations, tethering of the spinal cord, and decubitus ulcers may also contribute to reduced mobility.

3. **Intellectual outcome.** Approximately 75% of children with myelomeningocele have IQ scores >80. Many children with myelomeningocele require some sort of special education. Learning disabilities arise from challenges in language processing, visual/perceptual, and fine motor deficits. A formal neurodevelopmental assessment should be obtained if any questions arise about a child's social and cognitive abilities. An increased risk of cognitive delay is associated with high thoracic-level lesions, severe hydrocephalus at birth, development of a CNS infection early in life, intracranial hypertension, and seizures.
4. **Hearing and vision** status must be formally reassessed to rule out any contribution to learning difficulties. Hearing loss has historically been a problem associated with antibiotic use in the setting of urinary tract infections but has been dramatically reduced with the advent of CIC.
5. **Urologic/renal issues**
   a. Approximately 85% of children require CIC for bladder dysfunction; 80% achieve social bladder continence.
   b. Urinary tract infections are common. Prophylactic antibiotics may be indicated, especially if vesicoureteral reflux is present. Amoxicillin is commonly used in newborns and young infants. Other antibiotics, such as Bactrim and nitrofurantoin, are used in older children.
6. **Growth and nutrition.** Failure to thrive is a common problem in infants and young children.
   a. Some children require gastrostomy tube placement secondary to aspiration risk or inability to take in adequate calories orally. A videofluoroscopic swallowing study can be helpful to assess risk of aspiration with oral feeds.
   b. Arm span may be a more accurate reflection of growth than height because growth below the waistline is usually disproportionately slow or distorted by lower extremity or spinal deformities.
   c. Skinfold thickness is a valuable measure of nutrition.
   d. Bowel incontinence and constipation are prominent problems. An aggressive, consistent bowel program is often required and may include laxatives, suppositories, enemas, or even antegrade colonic enemas.
7. **Orthopedic complications**
   a. Worsening scoliosis or kyphosis may cause restrictive lung disease.
   b. Osteopenia, particularly in the nonambulatory patient, increases the risk for pathologic fractures.
   c. Contractures of hips, knees, and ankles, and hip dislocation are common. Treatments include physical therapy, orthotics, neuromuscular blockades, and surgeries.
   d. Decubitus ulcers may develop, especially involving pressure points such as the sacrum and ischial tuberosity and the feet, secondary to limited movement and diminished peripheral sensation. Secondary infection is an additional problem. Regular assessment of appropriate fit, padding, and positioning of wheelchairs and other seating systems minimizes ulcer risk.
8. **Endocrinopathies.** Children can develop precocious puberty as well as growth hormone deficiency, presenting as poor growth despite adequate nutrition.

9. **Rehabilitation** therapies including physical, occupational, and speech/language services are critical to optimize the health and development of a child with myelomeningocele.
   a. Initially, services should be established through state early intervention (EI) programs, which are mandated under the Individuals with Disabilities Education Act (IDEA). EI referral should be made early during an infant's initial hospitalization because there can be a waiting list.
   b. After age 3 years, services are provided through the public school system.
10. **Latex allergy.** Despite trying to avoid latex exposure, latex hypersensitization is seen in approximately one-third of children with neural tube defects and may be associated with life-threatening anaphylaxis. Risk is minimized by the following:
    a. Ongoing avoidance of latex containing products
    b. Avoidance of foods that may cross-react with latex, such as avocado, banana, and water chestnuts
11. **The primary care physician** plays a critical role in coordinating the care of a child with myelodysplasia. The role includes general pediatric care as well as surveillance for complications, communication with multiple subspecialists, and advocacy in school programs and the community.

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58 Orthopedic Problems

Craig M. Birch

KEY POINTS

- **Foot deformity**—Club feet, fixed deformity of the feet, or vertical talus at birth should be treated with casting within the first several weeks.
- **Hips**—Hip instability or contracture in the newborn should be recognized clinically and diagnostic ultrasound performed to document the structural abnormality.
- **Neonatal compartment syndrome**—Rare but serious finding typically presents with upper extremity swelling and skin ulceration or bulbous lesion requiring emergency treatment

I. INTRODUCTION.

This chapter discusses the common musculoskeletal abnormalities that may be detected in the neonatal period. For these abnormalities, early recognition clinically within the neonatal period is important. Consultation with an orthopedic surgeon is frequently required to provide definitive treatment after the initial evaluation.

II. CONGENITAL MUSCULAR TORTICOLLIS

A. Congenital muscular torticollis (CMT) is a disorder characterized by limited motion of the neck, asymmetry of the face and skull, and a tilted position of the head. It is usually caused by shortening of the **sternocleidomastoid (SCM) muscle**, which is thought to be secondary to either an *in utero* or perinatal vascular insult to the muscle or to muscle adaptation from an abnormal *in utero* position of the head and neck.

1. **The etiology** of the shortened SCM muscle is unclear; in many infants, it is due to an abnormal *in utero* position, and in some, it may be due to stretching of the muscle at delivery. The result of the latter is a contracture of the muscle associated with fibrosis. One hypothesis is that the SCM abnormality is secondary to a compartment syndrome occurring at the time of delivery.
2. **Clinical course.** The limitation of motion is generally minimal at birth but increases over the first few weeks. At 10 to 20 days, a pseudomass, or swelling, is frequently found in the SCM muscle. This mass gradually subsides, and the muscle fibers are partially replaced by fibrous tissue. The fibrous tissue does not function with elongation and contraction like muscle fiber therefore limiting head motion. Due to the limited rotation of the head, the infant rests on the ipsilateral side of the face in

the prone position and on the contralateral occiput when supine. The relatively fixed, asymmetric pressure from resting on one side of the face and the opposite occipital bone contributes to the facial and skull asymmetry. The ipsilateral zygoma is depressed and the contralateral occiput flattened leading to a consistent plagiocephaly in these infants.

3. **Treatment.** Most infants will respond favorably to stretching and positioning the head in the direction opposite to that produced by the tight muscle. Improved position can be maintained with padding or soft supports until the child develops further and is able to move actively to free the head. The most critical aspect of management is regular passive stretching by rotating the head to the ipsilateral side and tilting it toward the contralateral side. This helps to stretch the fibrous tissue of the muscle which is limiting the muscular function. The torticollis in most infants resolves by the age of 1 year. Helmets are sometimes used to treat persistent plagiocephaly, or head asymmetry, after a few months of age. Patients who have persistent asymmetry of the face and head and limited motion after 1 year should be considered for referral to the orthopedic surgeon for further evaluation and possible surgical release of the SCM muscle.

B. Differential diagnosis. Torticollis may be secondary to several other pathologies which require evaluation and a different treatment. Head tilt without any SCM asymmetry or restricted motion may be secondary to ophthalmologic anomalies. In this situation, the head tilt compensates for a dysconjugate gaze and is subconsciously voluntary without any scarring or limited passive motion. Torticollis with an associated limited motion of the neck may be due to a congenital abnormality of the cervical region of the spine. Some infants with this disorder will also have a tight SCM muscle. These infants are likely to have significant limitation of motion at the time of birth, generally not seen in CMT. Radiologic evaluation of the cervical region is necessary to make this diagnosis. Infection in the retropharyngeal area may present with torticollis. The neck pseudomass seen in torticollis in the SCM muscle may be differentiated from other cervical lesions by ultrasound.

III. POLYDACTYLY

A. Duplication of a digit may range from a small cutaneous bulb to an almost perfectly formed and functional digit. Treatment of this problem is generally surgical. Syndromes associated with polydactyly include Laurence-Moon-Biedl syndrome, chondroectodermal dysplasia, Ellis-van Creveld syndrome, and trisomy 13. Polydactyly is generally inherited in an autosomal dominant manner with variable penetrance as an isolated problem, not syndromic.

B. Treatment

1. The small functionless skin bulb without bone or cartilage at the ulnar border of the hand or lateral border of the foot can be ligated with either a suture or a vascular clip and allowed to develop necrosis for 24 hours. The part distal to the suture should be removed. The residual stump

should have an antiseptic applied twice a day to prevent infection until healed. It is important to distinguish this from treatment for radial-sided (thumb) accessory digits and medial border of the foot accessory digits. These should not be ligated but rather require orthopedic evaluation for other underlying deformities.

2. When duplicated digits contain bone or muscle attached by more than a small bridge of skin, treatment is delayed until the patient is evaluated by an orthopedist or hand surgeon. In general, polydactyly is managed surgically in the first year of life after 6 months of age. X-rays can be delayed until necessary for definitive management.

IV. ORTHOPEDIC BIRTH INJURIES (see Chapter 6)

A. Clavicle fracture

1. **The clavicle** is the site of the most common fracture associated with delivery.
2. **Diagnosis** is usually made soon after birth, when the infant does not actively move the arm on the affected side or cries when that arm is moved passively. There may be tenderness, swelling, or crepitus at the site. Occasionally, the bone is angulated and subtle asymmetry can be noted on physical exam. Diagnosis can be confirmed by radiographic examination. A "painless" fracture discovered by radiography of the chest may be a congenital pseudarthrosis (nonunion). All pseudarthroses occur on the right side unless associated with dextrocardia.
3. **The clinical course** of perinatal clavicle fractures is short and consistent. Essentially, all these fractures heal without difficulty and without long-term effects. **Treatment** consists of providing comfort for the infant. If the arm and shoulder are left unprotected, motion occurs at the fracture site when the baby is handled, causing pain. Standard treatment is to pin or tape the infant's sleeve of the affected side to the opposite shoulder of the onesie. It can also be helpful to put a sign on or near the baby to remind personnel to decrease motion of the clavicle. No reduction is necessary. If the fracture appears exceedingly painful, a gentle swath or wrap to decrease motion of the arm can be useful.

B. Humerus fracture

1. **The humerus** is the second most common fracture associated with delivery.
2. **Diagnosis** is made in a similar fashion as for the clavicle fracture. The affected extremity will be moved less than the contralateral or may be painful with passive motion or positioning of the baby. Radiographs are required for diagnosis of the injury. Humerus fractures typically appear angulated on the radiographs due to the various muscular attachments on the bone. Clinically, the deformity is less obvious due to the soft tissue envelope of the upper extremity.
3. **The clinical course** is similar to clavicle fractures as well. Healing occurs rapidly in the neonatal period. **Treatment** is the same as the clavicle fracture. Pinning of the onesie is used and no reduction is required.

Bulkier methods of immobilization such as casting are not effective in this age group because of the rapid healing and small size of the extremity. Bone remodeling occurs quickly in infants and no long-term deficits are observed.

C. Brachial plexus birth injury (BPBI)

1. **BPBI** is a very rare occurrence, but recognition is important as treatment differs from bony injury. The brachial plexus is the network of nerve roots responsible for function of the upper extremity, and traumatic delivery can cause a stretching type injury or avulsion type injury.
2. **Diagnosis** of BPBI requires a detailed neurologic exam which can be challenging in the neonatal period. Clinically, the findings of decreased active upper extremity movement can resemble a fracture of the clavicle or humerus; however, radiographs show no bony injury. Perinatal fractures heal rapidly and increased active movement of the extremity is expected to occur between 10 and 21 days. If resumption of motion is not noted in this time frame, orthopedic evaluation is necessary.
3. **The clinical course** of BPBI varies depending on the severity of injury.
4. **Treatment** is initially observation for resumption of neurologic function. Orthopedic referral is essential for this disorder. The most positive prognostic factor for nonoperative treatment is return of motor function before 3 months. If there is no return of function within 3 to 6 months, then surgery is recommended.

V. CONGENITAL AND INFANTILE SCOLIOSIS

A. Congenital scoliosis is a lateral curvature of the spine secondary to a failure either of formation of a vertebra or of segmentation of a vertebra. Terminology can be challenging because congenital scoliosis is distinct from infantile scoliosis. In congenital scoliosis, there is always a bony malformation present which causes the curvature. Congenital scoliosis can be diagnosed at any age. **Infantile scoliosis** is a curvature without a vertebral anomaly and refers to a typically segmented spine with a curvature diagnosed within the first 2 years of life. Scoliosis in the newborn may be difficult to detect; by bending the trunk laterally in the prone position, however, a difference in motion can usually be observed. Some infantile scoliosis can improve spontaneously, although the condition may be progressive in infants who have a spinal curvature of >20 degrees. If the scoliosis is progressive, treatment is indicated and magnetic resonance imaging (MRI) of the spine looking for spinal cord pathology should be done; however, no further studies are indicated. With congenital scoliosis, because there is a bony malformation which occurs during embryologic development, other systems that develop during the same time frame must be examined. In addition to a full spine MRI, cardiac echo and renal ultrasound are indicated. Rarely, severe congenital scoliosis may result in *thoracic insufficiency syndrome* and be associated with pulmonary compromise. For this reason, recognition and referral to orthopedic surgery is important.

B. Clinical course. Congenital scoliosis will increase in many patients; however, it depends on the type of individual malformation, which can

vary widely. Bracing of congenital curves is usually not helpful because the area of the atypical bony structure cannot be corrected. Body casts for correction of the overall spinal alignment and deformity may be beneficial but still cannot correct the focal deformity. The most important aspect is overall spinal balance and allowing growth at the chest and lungs. Surgical correction with chest expansion or limited fusion may be indicated before the curve becomes too severe.

VI. DEVELOPMENTAL DISLOCATION OF THE HIP

A. Examination and screening

1. Most (but not all) hips that are dislocated at birth can be diagnosed by a careful physical examination (see Chapter 8).
2. The American Academy of Pediatrics Committee on Quality Improvement, Subcommittee on Developmental Dysplasia of the Hip issued a clinical practice guideline on the early detection of developmental dislocation of the hip (DDH) (Fig. 58.1).
3. Ultrasonographic examination of the hip is useful for diagnosis in high-risk cases. Ultrasonography is delayed as a screening technique until 4 to 6 weeks of age to avoid a high incidence of false-positive examinations.
4. X-ray examination will not lead to a diagnosis in the newborn because the femoral head is not ossified but may reveal an abnormal acetabular fossa seen with hip dysplasia. Due to its limited utility in newborns, radiographs are typically only used after 6 months of age.
5. The practice of triple diapers in infants with physical signs suggestive of DDH is not recommended and lacks data on effectiveness.
6. Swaddling of the lower extremities may increase the incidence of DDH. Isolated swaddling of the upper extremities with the legs free has not been associated with an increase and remains safe practice. With this information, almost all commercially available carriers and wearable supports or apparel do not restrict hip motion and are safe for newborn hips.

B. There are three types of congenital dislocations.

1. The **classic DDH** is diagnosed by the presence of either Ortolani or Barlow sign. The hip is unstable and dislocates with adduction and extension of the hip but readily reduces when the femur is abducted in flexion. No asymmetry of the pelvis is seen. This type of dislocation is more common in females and is most frequently unilateral, but it may be bilateral. Hips that are unstable at birth often become stable after a few days. The infant with hips that are unstable after 5 days of life should be treated with some type of support that keeps the hips flexed and abducted. The **Pavlik harness** has been used effectively to treat this group of patients, with reported success rates of 80% or higher. Ultrasonography is used to monitor the hip during treatment, typically at 4-week intervals.
2. The **teratologic type of dislocation** occurs very early in pregnancy. The **femoral head does not reduce with flexion and abduction**; that is, Ortolani sign is not present. In this situation, there is a fixed

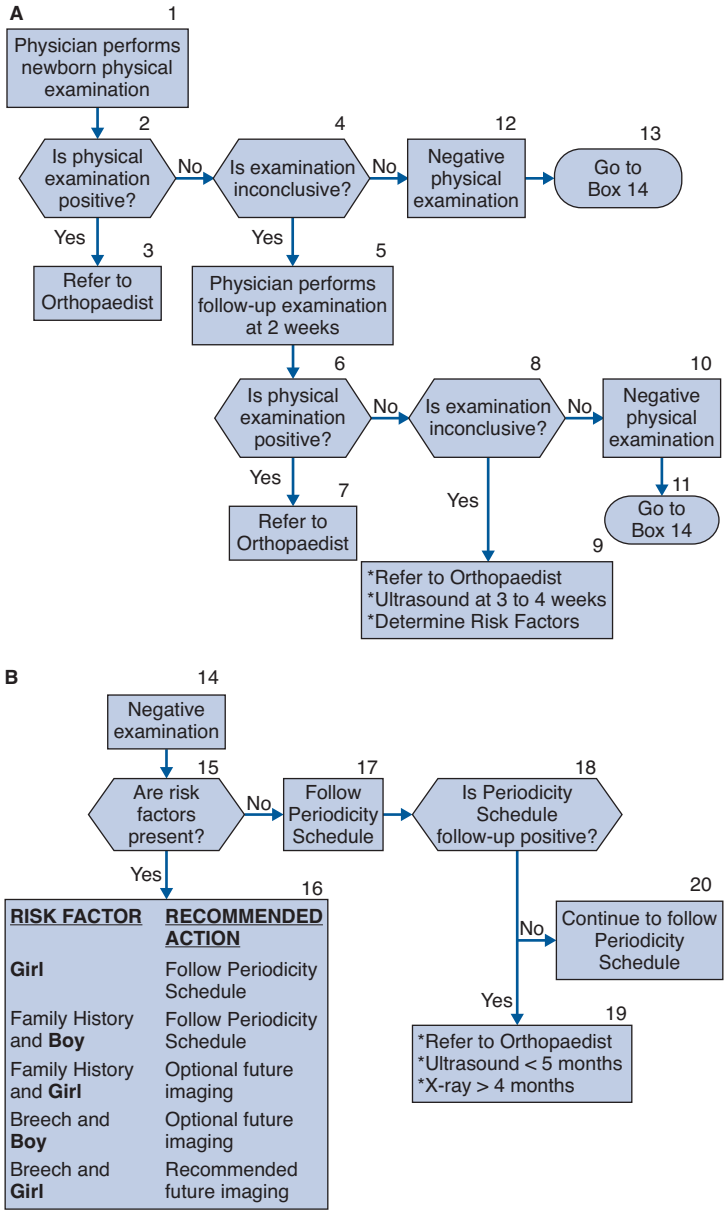

Figure 58.1. Screening for developmental hip dysplasia—clinical algorithm. (Reproduced with permission from American Academy of Pediatrics, Committee on Quality Improvement, Subcommittee on Developmental Dysplasia of the Hip. Clinical practice guideline: early detection of developmental dysplasia of the hip. *Pediatrics* 2000;105[4, pt 1]:896–905. Copyright © 2000 by the American Academy of Pediatrics.)

dislocation which is not reducible. If the dislocation is unilateral, there may be asymmetry of the gluteal folds and asymmetric motion, most notably, limited abduction. In bilateral dislocation, the perineum is wide, and the thighs give the appearance of being shorter than normal. This may be subtle and can be easily overlooked therefore requiring an extremely careful physical examination. Limited abduction at birth is a characteristic of this type of dislocation. Treatment of the teratologic hip dislocation is by open reduction. Exercise to decrease contracture is indicated but use of the Pavlik harness or abduction orthosis is not beneficial.

3. The **third type of dislocation** occurs late, is unilateral, and is associated with a **congenital abduction contracture** of the contralateral hip. The abduction contracture causes a pelvic obliquity. The pelvis is lower on the side of the contracture, which is unfavorable for the contralateral hip, and the acetabulum may not develop well. After the age of 6 weeks, infants with this type of dislocation develop an apparent short leg and have asymmetric gluteal folds. Some infants will develop a dysplastic acetabulum, which may eventually allow the hip to subluxate, or slowly migrate out of the socket without a complete dislocation. Treatment of the dysplasia is with the Pavlik harness or abduction orthosis. After the age of 8 months, abduction orthosis or Pavlik harness is less successful, and other methods of treatment such as spica casting or surgical intervention may be necessary.

VII. GENU RECURVATUM

or hyperextension of the knee, is not a serious abnormality and is easily recognized and treated. It must be differentiated, however, from subluxation or dislocation of the knee, which also may present with hyperextension of the knee. Although the latter two abnormalities are still not an emergency, it does require more extensive treatment.

A. Congenital genu recurvatum is secondary to *in utero* position with hyperextension of the knee. This can be treated successfully by repeated splinting or serial casting, with progressive flexion of the knee until it reaches 90 degrees of flexion. Minor degrees of recurvatum can be treated with passive stretching exercises. It may be associated with DDH, so screening ultrasound of the hips is recommended at 4 to 6 weeks of age.

B. All infants with **hyperextension of the knee** should have a thorough physical exam and may require radiographic examination to differentiate genu recurvatum **from true dislocation of the knee**. In congenital genu recurvatum, the tibial and femoral epiphyses are in proper alignment except for the hyperextension. In the knee with a true dislocation, the tibia is completely anterior or anterolateral to the femur. Congenital fibrosis of the quadriceps may limit the success of serial casting or splinting. If there is a fixed dislocation of the knee, an open reduction may be required as further attempted stretching or casting may result in epiphyseal plate damage.

C. Treatment. Hyperextended or subluxated knees are treated with manipulation and splinting after delivery with progressive knee flexion and reduction. Fixed dislocation of the knee may require open reduction but does not need to be performed within the neonatal period.

VIII. DEFORMITIES OF THE FEET

A. Metatarsus adductus (MTA) is a condition in which the metatarsals rest in an adducted position, but the appearance does not always reveal the severity of the condition. Whether treatment is necessary is determined by the difference in the degree of structural change in the metatarsals and tarsometatarsal joint.

1. Most infants with MTA have **positional deformities** that are thought to be caused by *in utero* position. The positional type of MTA is flexible, and the metatarsals can be passively corrected into abduction with little difficulty. **This condition does not need treatment.**
2. The **structural MTA** has a relatively fixed adduction deformity of the forefoot, and the metatarsals cannot be abducted passively. The etiology has not been definitively identified but is probably related to *in utero* position. This is seen more commonly in the firstborn infant and in pregnancies with oligohydramnios. Most infants with the structural types of MTA have a valgus deformity of the hindfoot. **The structural deformity needs to be treated with manipulation and immobilization in a shoe or cast** until correction occurs. Although there is no urgency to treat this condition, it is more easily corrected earlier than later and should be done before the child is of walking age but exercise only in the neonatal period.

B. Calcaneovalgus deformities result from an *in utero* position of the foot that holds the ankle dorsiflexed and abducted. At birth, the top of the foot lies up against the anterior surface of the tibia. Structural changes in the bones are not present with calcaneovalgus deformity, it is solely a positional finding. The sequela to this deformity appears to be a valgus or pronated foot that is more prominent than the typical pronated foot seen in toddlers. Whether this disorder is treated or not is variable, and no study supports either course. **Treatment consists of either exercise or, less frequently, application of a short leg cast** that will keep the foot plantarflexed and inverted. If the foot cannot be plantarflexed to a neutral position, casts are indicated. Casts are changed appropriately for growth and maintained until plantar flexion and inversion are equal to those of the opposite foot. Generally, the foot is held in plaster for approximately 6 to 8 weeks. Feet that remain in the calcaneovalgus position for several months may be more likely to have significant residual *pes valgus*. If the calcaneovalgus deformity is fixed or rigid rather than flexible, it commonly represents a **congenital vertical talus**. In these situations, there is a subluxation or dislocation of the midfoot where the tarsal bones are dorsally displaced relative to the hindfoot. A congenital vertical talus always requires serial casting and orthopedic referral is necessary. Casting attempts to bring the midfoot and forefoot plantarly and then may require surgical intervention with pinning to maintain alignment until sufficient stability is achieved.

C. Congenital clubfoot is a deformity with a multifactorial etiology. It occurs with frequency of about 1 to 2/1,000 live births. A first-degree relative of a patient with this deformity has 20 times the risk of having a clubfoot than does the normal population. The risk in subsequent siblings is 3% to 5%.

The more frequent occurrence in the firstborn and the association with oligohydramnios suggest an influence of *in utero* pressure as well. Sometimes, clubfoot is part of a syndrome. Infants with neurologic dysfunction of the feet (spina bifida) often have clubfoot.

1. **Clubfoot deformity is composed of a combination of four components.** The foot is in equinus, cavus, and varus position, with a forefoot adduction; therefore, the clubfoot is a talipes equinocavovarus with metatarsal adduction. Each of these deformities is sufficiently rigid to prevent passive correction to a neutral position by the examiner. The degree of rigidity is variable in each patient and is classified with the Dimeglio score.
2. Treatment should be started early within a few weeks of birth. An effective method of treatment consists of manipulation and application of plaster or fiberglass casts that are changed weekly to gradually correct the sequential deformities. The Ponseti method is the treatment of choice for idiopathic clubfoot in which the midfoot is sequentially corrected with casts, followed by a heel cord tenotomy to correct equinus after 6 to 8 weeks of cast correction. After tenotomy, the foot is immobilized in a corrected position for 3 weeks; braced full time for 3 months and a night bracing program is used until age 4 years.

IX. COMPARTMENT SYNDROME OF THE NEWBORN

A. Compartment syndrome of the newborn is a rare condition in which a neonate presents with upper limb swelling and skin lesion evolving into compression ischemia in the hand and arm. Although very rare, it is potentially devastating condition if diagnosis is delayed, making it one of the few neonatal orthopedic emergencies. At presentation, all patients have distal limb edema with a bulbous or ulcerative skin lesion varying in size from 1 cm to the entire arm. It may be associated with distal gangrene of fingertips or hand and associated with ecchymosis and swelling of the extremity.

1. **Etiology.** The exact cause of this syndrome is unknown. It is suspected that mechanical compression of the upper extremity, combined with fetal position, plays a major role in evolution of neonatal compartment syndrome. Intrauterine abnormalities or birth trauma may be related to this abnormality.
2. **Treatment.** If recognized early, surgical treatment with emergency fasciotomy or revascularization of the limb has been beneficial. Prolonged ischemia results in scarring (known as Volkmann ischemic contracture of muscle), nerve injury, permanent disability, and potential loss of a portion of the extremity.

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59 Osteopenia (Metabolic Bone Disease) of Prematurity

Sarah N. Taylor

KEY POINTS

- Osteopenia remains a common problem for very preterm infants. The most common cause is inadequate dietary minerals.
- Other factors which may contribute to osteopenia include use of diuretics, steroids, limited physical movement, and vitamin D deficiency.
- Prevention of osteopenia is best performed by attention to calcium and phosphorus delivery in parenteral nutrition, use of human milk fortifiers and preterm infant formulas, and minimizing use of steroids and diuretics.

I. GENERAL PRINCIPLES

A. Definition

1. Osteopenia is defined as postnatal bone mineralization that is inadequate to fully mineralize bones. Osteopenia occurs commonly in very low birth weight (VLBW) infants. Prior to the use of high-mineral–containing diets for premature infants, which is the current practice, significant radiographic changes were seen in about half of infants with birth weight <1,000 g.
2. The current incidence is unknown and likely closely associated with the severity of overall illness and degree of prematurity. It may still be seen in as many as half of all infants <600 g birth weight.

B. Etiology

1. **Deficiency of calcium and phosphorus is the principal cause.** Demands for rapid growth in the third trimester are met by intrauterine mineral accretion rates of approximately 120 mg of calcium and 60 mg of phosphorus/kg/day. Poor mineral intake and absorption after birth result in undermineralized new and remodeled bone.
   a. Parenteral amino acids provision. With provision of amino acids, cellular catabolism is active, and therefore, parenteral phosphorus is needed to avoid hypophosphatemia and depletion of bone phosphorus stores.
   b. Diets low in mineral content. These diets predispose preterm newborns to metabolic bone disease.

c. Unfortified human milk. In this circumstance, urinary calcium increases, suggesting a phosphorus deficiency that is greater than the calcium deficiency.
d. Excessive fluid restriction. This may lead to low mineral intake.
e. Long-term use of parenteral nutrition.
f. Formulas not designed for use in preterm infants (e.g., full-term, elemental, soy-based, lactose-free). Soy-based formulas should be avoided after hospital discharge as well.
g. Diuretic therapy. Diuretics, specifically furosemide, causes renal calcium wasting but are not likely the principal contributor to osteopenia for most preterm infants. When providing supplemental sodium, the thiazide-induced calcium reuptake may be impaired.
h. Long-term steroid use

2. **Vitamin D deficiency.** In mothers not supplemented with high amounts of vitamin D (e.g., >4,000 IU/day), human milk has a total vitamin D content of 25 to 50 IU/L, which is insufficient for maintaining 25-hydroxyvitamin D (25(OH)D) levels in preterm infants at >20 ng/mL. However, when vitamin D intake is adequate, even VLBW newborns can synthesize 1,25-dihydroxyvitamin D.
a. Maternal vitamin D deficiency can cause congenital rickets (uncommon) or hypocalcemia (more common).
b. Inadequate vitamin D intake or absorption produces nutritional rickets, but this is not the primary cause of osteopenia or rickets in preterm infants.
c. Vitamin D malabsorption and inadequate conversion of vitamin D to 25(OH)D can worsen osteopenia in infants with intestinal resection and cholestatic liver disease.
d. Chronic renal failure (renal osteodystrophy)
e. Chronic use of phenytoin or phenobarbital increases 25(OH)D metabolism.
f. The 25(OH) status to avoid osteopenia and to optimize bone mineralization is not established.

3. **Limited physical movement**
a. In randomized, controlled trials of preterm infant exercise programs increase physical movement is associated with higher bone mineralization.

II. DIAGNOSIS

A. Clinical presentation

1. Osteopenia (characterized by bones that are undermineralized or "washed out") develops during the first postnatal weeks. Signs of rickets (epiphyseal dysplasia and skeletal deformities) usually become evident after 6 weeks' postnatal age. The risk of bone disease is greatest for the sickest, most premature infants.

B. History

1. A history of VLBW, especially <26 weeks or 800 g birth weight, and use of fluid restriction, prolonged parenteral nutrition, or long-term steroids are very common.
2. Rapid increase in alkaline phosphatase value is common.

3. A history of a fracture noticed by caregivers or incidentally on x-rays taken for other purposes may be seen.

C. Physical examination

1. **Clinical signs** include respiratory insufficiency or failure to wean from a ventilator; hypotonia; pain on handling due to pathologic fractures; decreased linear growth with sustained head growth; frontal bossing; enlarged anterior fontanel and widened cranial sutures; craniotabes (posterior flattening of the skull); "rachitic rosary" (swelling of costochondral junctions); Harrison grooves (indentation of the ribs at the diaphragmatic insertions); and enlargement of wrists, knees, and ankles.

D. Laboratory studies

1. **Laboratory evaluation.** The earliest indications of osteopenia are often a decreased serum phosphorus concentration, typically <4 to 5.6 mg/dL (1.3 to 1.8 mmol/L), and an increased alkaline phosphatase activity. Alkaline phosphatase values >800 IU/L are worrisome, especially if combined with serum phosphorus values <5.6 mg/dL (1.8 mmol/L). However, it is often difficult to distinguish the normal rise in alkaline phosphatase activity associated with rapid bone mineralization from the pathologic increase related to early osteopenia. In this circumstance, decreased bone mineralization observed on a radiograph assists with the diagnosis.
   a. For infants born <800 g, requiring total parenteral nutrition (TPN) for ≥2 weeks, receiving diuretic therapy, receiving systemic steroids, and/or with difficulty tolerating fortified enteral nutrition at ≥120 kcal/kg/day; serum calcium and phosphorus should be assessed biweekly starting at 2 postnatal weeks, and alkaline phosphatase should be assessed at 4 to 6 postnatal weeks (Fig. 59.1). If serum levels are consistently within normal range with fortified enteral nutrition without diuretic or steroid therapy, no further routine monitoring is needed.
   b. Serum calcium level (low, normal, or slightly elevated) is not a good indicator of the presence or severity of metabolic bone disease. However, it should be monitored when assessing serum phosphorus and serum alkaline phosphatase status.
   c. Serum alkaline phosphatase level (an indicator of osteoclast activity) is often but not invariantly correlated with disease severity (>1,000 IU/L in severe rickets).
   d. Normal neonatal range of alkaline phosphatase is much higher than in adults. Values of 400 to 600 IU/L are common in VLBW infants with no evidence of osteopenia.
   e. Intestinal and hepatobiliary disease also elevates alkaline phosphatase level. Determining bone isoenzymes may be helpful but is not usually clinically necessary.
   f. Solitary elevated alkaline phosphatase level rarely occurs in the absence of bone or liver disease (transient hyperphosphatasemia of infancy). This elevation can be >2,000 IU/L and persist for several months. It is not associated with any pathology, and the etiology is unknown.
   g. Serum 25(OH)D levels do not need to be routinely assessed in preterm infants. The 25(OH)D concentration required to optimize preterm infant bone mineralization is not known. Based on studies in older infants, a 25(OH)D level <20 ng/mL is defined as vitamin D deficiency.

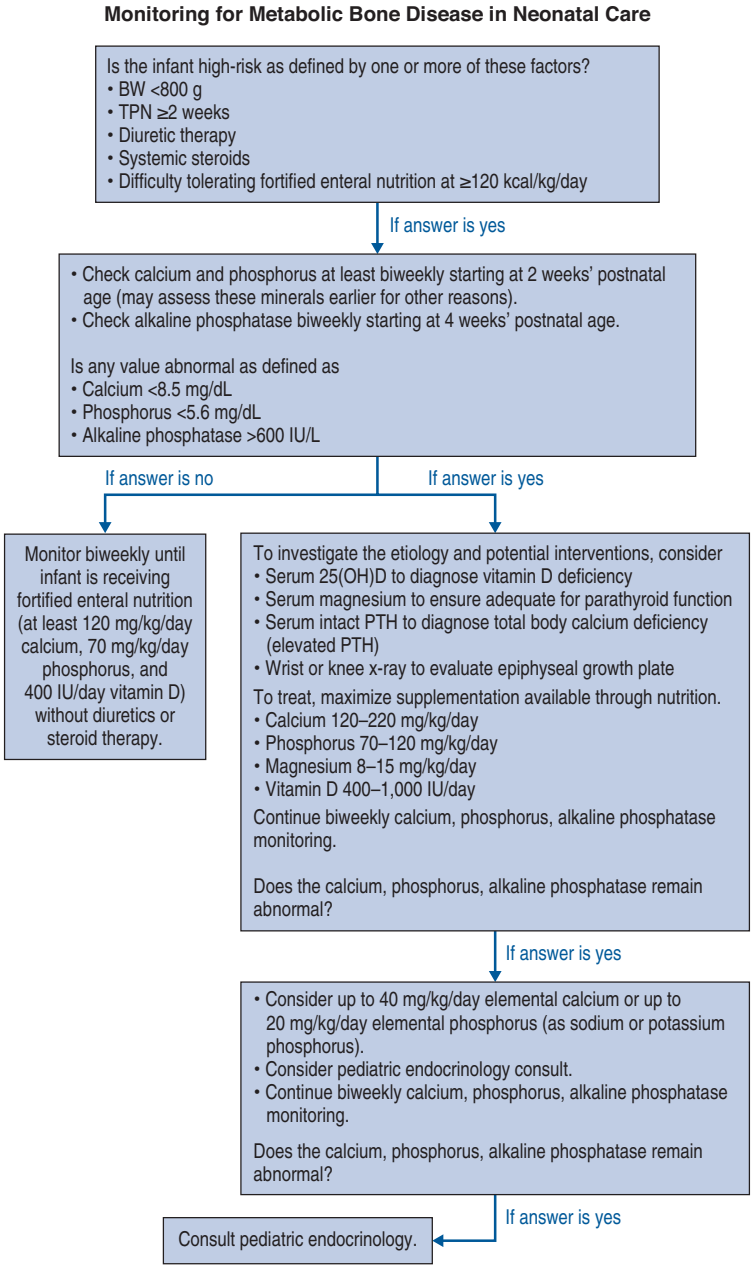

Figure 59.1. Monitoring for metabolic bone disease in neonatal care. BW, birth weight; TPN, total parenteral nutrition; 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone.

h. An elevated serum parathyroid hormone (PTH) level may be indicative of osteopenia but is not commonly used as a first-line screening tool. When osteopenia is present, serum PTH evaluation may assist in identifying the cause because PTH elevation occurs when an infant is calcium or vitamin D deficient.

E. Imaging

1. **Radiographic signs** include widening of epiphyseal growth plates; cupping, fraying, and rarefaction of the metaphysis; subperiosteal new bone formation; osteopenia, particularly of the skull, spine, scapula, and ribs; and occasionally, osteoporosis or pathologic fractures.
   a. A loss of up to 40% of bone mineralization can occur without radiographic changes. Chest films may show osteopenia and sometimes rachitic changes.
   b. Wrist or knee films can be useful. Generally, if marked abnormalities are present, films should be obtained again 4 to 6 weeks later after a clinical intervention.
   c. Dual-energy x-ray absorptiometry or quantitative computed tomography (CT) scan are reliable measures of bone mineralization but are not readily available clinical tools.
   d. Bone ultrasound, which measures bone strength, requires further research to determine its utility in preterm infant bone assessment.

III. TREATMENT

A. Management

1. In VLBW infants, early enteral feeding significantly enhances the establishment of full-volume enteral intake, leading to increased calcium and phosphorus accumulation and decreased osteopenia.
2. Mineral-fortified human milk is the appropriate diets for preterm infants weighing <1,800 to 2,000 g. When human milk is not available, preterm formula is the appropriate diet for these infants. Feeding these regimens at 120 kcal/kg/day, when estimating human milk as 20 kcal/oz, can prevent and treat metabolic bone disease of prematurity.
3. Bone formation is dependent on a combination of adequate calcium and phosphorus availability; supplementation of either only calcium or only phosphorus alone does not provide the correct balance to prevent osteopenia.
4. Elemental mineral supplementation of human milk is less desirable than the use of prepackaged, multicomponent fortifiers containing calcium and phosphorus because of concern over medication error and potential hyperosmolarity. In special circumstances, including babies with radiologic evidence of rickets not responding to fortified human milk or premature formula, smaller amounts of calcium (usually up to 40 mg of elemental calcium/kg/day) and/or sodium or potassium phosphate (usually up to 20 mg of elemental phosphorus) may be provided. This is usually needed in babies whose birth weights were <800 g or who had a prolonged hospital course including long-term TPN, fluid restrictions,

or bronchopulmonary dysplasia. Due to concerns about tolerance, it is usual to add the intravenous forms of phosphorus (sodium or potassium phosphate) orally to the diet. This may also be done when the serum phosphorus is persistently <4.0 mg/dL, although evidence supporting this practice is lacking.

5. The long-term use of specialized formulas in VLBW infants, including soy and elemental formulas, should be discouraged because they may increase the risk of osteopenia.
6. Ensure adequate vitamin D stores by an intake of at least 400 IU/day once the infant is tolerating enteral feeds. This may require giving supplemental vitamin D to both breastfed and formula-fed infants throughout hospitalization and following hospital discharge. Vitamin D intake should remain <1,000 IU/day unless vitamin D deficiency is observed even with this level of supplementation.
7. Avoid nonessential handling and vigorous chest physiotherapy in preterm infants with severely undermineralized bones.
8. Daily passive physical activity (range of motion, 5 to 10 minutes) may enhance both growth and bone mineralization.
9. Infants at risk for osteopenia should have serum calcium, phosphorus, and alkaline phosphate levels monitored periodically until values are established as normal on fully fortified enteral nutrition without diuretic or steroid therapy. Measurement of vitamin D metabolite levels and PTH levels are rarely useful in this setting. Alkaline phosphatase measure is most useful at 4 to 6 weeks' postnatal age.
   a. Use of premature infant formula can usually be discontinued when the infant reaches 36 weeks' gestational age (GA) and 2,200 g and is tolerating enteral feeds well. It may be continued longer for infants who are fluid restricted or have a markedly elevated alkaline phosphatase activity or radiologic evidence of osteopenia. If continuing fortification or preterm formula when >2,200 g, serum calcium and phosphorus should be monitored to avoid excess supplementation.
   b. Multicomponent human milk fortification may be switched to powdered formula supplementation of human milk when the infant reaches 36 weeks' GA and 2,200 g. Formula supplementation of human milk adds minimal calcium, phosphorus, and vitamin D. Therefore, for infants with osteopenia or high-risk of osteopenia, consider continuing multicomponent human milk fortifier for at least a portion of feeds. Continuing the addition of multicomponent human milk fortification of 50% of human milk feeds for 12 weeks posthospital discharge was shown to improve bone mineral content at 12 months corrected age in one study.
   c. For human milk–fed infants with osteopenia, if multicomponent human milk fortification is not available posthospital discharge, consider the addition of a few formula feeds to provide calcium and phosphorus until bone mineralization and laboratory values are improved.
   d. Postdischarge enriched formula is not associated with improved bone mineralization or bone strength in preterm infants without osteopenia. However, preterm infants discharged prior to term corrected age may

benefit from enriched formula for 12 weeks. Infants diagnosed with osteopenia should receive enriched formula at least until normalization of x-ray and lab values.

e. Consult endocrinology if laboratory values do not improve with adequate calcium, phosphorus, and vitamin D supplementation or at hospital discharge if infant needs further monitoring.

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60 Inborn Errors of Metabolism

Monica H. Wojcik

KEY POINTS

- Inborn errors of metabolism (IEMs) represent a group of disorders in which early recognition and prompt intervention can be lifesaving. However, many neonates with IEMs are initially well appearing with nonspecific signs and symptoms.
  - A blood gas, serum electrolytes, glucose, lactate, ammonia, liver function tests, and urinalysis with urine ketones are reasonable lab tests to start with when an IEM is suspected due to other clinical features (abnormal respiratory pattern, hypotonia, seizures, family history) because the results return rapidly and can guide management.
  - If possible, obtain the results of the newborn screen and take a family history.
- Acute management for many conditions entails:
  - Stopping enteral feeds temporarily
  - Providing higher than usual caloric intake to halt catabolism (typically with intravenous [IV] dextrose)
  - Reintroduce enteral feeds with an appropriate formula usually within 24 to 48 hours to avoid nutritional deficiencies that would lead to catabolism. If this is not possible, consider parenteral nutrition (ideally under the supervision of a specialist in metabolic disorders).

I. INTRODUCTION. Inborn errors of metabolism (IEMs) classically involve impaired function of a specific enzyme in a metabolic pathway, leading to accumulation of upstream metabolites and depletion of those downstream. Although this enzyme function is deficient throughout the body, the affected tissue may vary depending on the disorder. Age of onset may also vary depending on the condition and severity of the enzyme defect, with milder forms not presenting until adulthood and severe disorders presenting early in the neonatal period or even *in utero*. Neonatal presentations may be difficult to detect, particularly early on, due to nonspecific signs such as poor feeding, lethargy, vomiting, abnormal respiratory pattern, seizures, or hypotonia, all of which can be seen in more

common conditions such as sepsis. Having a low threshold to send basic labs such as a blood gas, chemistry panel, lactate, and ammonia can help detect these cases as early as possible. Because IEMs are caused by genetic variants which can run in families, the family history may be helpful in raising clinical suspicion as can prenatal carrier screening. Finally, many disorders are included on state newborn screening panels, the results of which may be available by days 3 to 4 of life—although by this time, clinical decompensation may have already occurred.

II. CLINICAL PRESENTATION. Many infants with IEMs appear normal and healthy at birth but begin to have symptoms within the first few days to weeks of life. Some common clinical presentations are described in the following text:

A. Neurologic. Metabolic derangements such as hypoglycemia, hyperammonemia, and severe metabolic acidosis can result in altered mental status, which in neonates typically manifests as poor feeding, decreased level of alertness, or lethargy and can progress to apnea and/or unresponsiveness. Other neurologic signs include seizures, abnormal respiratory pattern, and hypotonia (Table 60.1).

B. Hepatic. Liver disease can be seen classically in galactosemia, which may present with liver failure and coagulopathy. Other IEMs can also present with hepatomegaly, liver failure, and/or cholestasis (Table 60.2).

C. Cardiac. Cardiomyopathy is a presenting feature of many mitochondrial disorders as well as other IEMs such as Pompe disease (Table 60.3).

D. Other manifestations. Other signs such as abnormal odor (Table 60.4), distinct facial features (Table 60.5), or nonimmune hydrops fetalis can also be suggestive of an IEM (Table 60.6).

III. EVALUATION AND MANAGEMENT. After suspicion is raised for an IEM, either due to an abnormal lab finding such as hypoglycemia or hyperammonemia, or due to a clinical presentation such as unexplained liver failure, evaluation should include a targeted history and physical examination in addition to a laboratory investigation—often with the guidance of a specialist in genetic metabolic disorders. Concurrently, nutritional support and management of laboratory derangements are critical, even while awaiting a diagnosis.

A. Prenatal evaluation and management. Special plans should be made for safe delivery of the infant suspected prenatally to be affected by an IEM. This suspicion may arise if there is a family history of an IEM, particularly a recessive condition (25% recurrence risk) or an X-linked condition (such as ornithine transcarbamylase [OTC] deficiency, 50% recurrence risk in males). Other concerning family history would be a history of unexplained infant or early childhood death, particularly in a country that does not have expanded newborn screening. As many parents are now obtaining expanded genetic carrier screening, this may also identify couples at risk for having an affected baby. If this is the case, the family should be counseled appropriately and prenatal diagnosis (via chorionic villous sampling or amniocentesis) can be pursued. If the fetus is known to be affected or prenatal testing of the pregnancy is not possible, delivery should occur in a facility with access to appropriate laboratory testing and the capability to manage neonates

Table 60.1. Inborn Errors of Metabolism Associated with Neurologic Manifestations in Neonates

Deterioration in consciousness
■ Metabolic acidosis
□ Organic acidemias
□ Maple syrup urine disease (MSUD)
□ Disorders of pyruvate metabolism
□ Fatty acid oxidation defects
□ Fructose-1,6-bisphosphatase deficiency
□ Glycogen storage disease type I
□ Mitochondrial diseases
□ Disorders of ketone body metabolism
■ Hyperammonemia
□ Urea cycle disorders
□ Organic acidemias
□ Disorders of pyruvate metabolism
■ Hypoglycemia
□ Fatty acid oxidation defects
□ Fructose-1,6-bisphosphatase deficiency
□ Glycogen storage disease type I
□ Organic acidemias
□ Mitochondrial diseases
□ Disorders of ketone body metabolism
Seizures
■ Biotinidase deficiency
■ Pyridoxine-dependent epilepsy
■ Pyridoxal phosphate–responsive epilepsy
■ Glycine encephalopathy
■ Mitochondrial diseases
■ Zellweger syndrome

(continued)

Table 60.1. *(Continued)*
■ Sulfite oxidase/molybdenum cofactor deficiency
■ Purine and pyrimidine metabolism disorders
■ Disorders of creatine biosynthesis and transport
■ Neurotransmitter defects
■ Congenital disorders of glycosylation

Table 60.2. Inborn Errors of Metabolism Associated with Neonatal Hepatic Manifestations
Hepatomegaly with hypoglycemia
■ Fructose-1,6-bisphosphatase deficiency
■ Glycogen storage disease type I
Cholestatic jaundice
■ Citrin deficiency
■ Zellweger syndrome
■ α1-antitrypsin deficiency
■ Niemann-Pick disease type C
■ Inborn errors of bile acid metabolism
■ Congenital disorders of glycosylation
Liver failure
■ Galactosemia
■ Tyrosinemia type I
■ Hereditary fructose intolerance
■ Mitochondrial diseases
■ Fatty acid oxidation defects

Table 60.3. Inborn Errors of Metabolism Associated with Neonatal Cardiomyopathy

Disorders of fatty acid oxidation
■ Very long chain acyl-coenzyme A dehydrogenase (VLCAD) deficiency
■ Long-chain hydroxyacyl-coenzyme A dehydrogenase (LCHAD) deficiency
■ Trifunctional protein deficiency
■ Carnitine transport defect
■ Carnitine–acylcarnitine translocase (CAT) deficiency
■ Carnitine palmitoyltransferase II (CPT II) deficiency
Glycogen storage disease type II (Pompe disease)
Tricarboxylic acid cycle defects: α-ketoglutarate dehydrogenase deficiency
Mitochondrial diseases
Congenital disorders of glycosylation

Table 60.4. Inborn Errors of Metabolism Associated with Abnormal Urine Odor in Newborns

Inborn Error of Metabolism	Odor
Glutaric acidemia type II	Sweaty feet
Isovaleric acidemia	Sweaty feet
Maple syrup urine disease	Maple syrup
Cystinuria	Sulfur
Tyrosinemia type I	Sulfur
Hypermethioninemia	Boiled cabbage
Multiple carboxylase deficiency	Cat urine
Phenylketonuria	Mousy
Trimethylaminuria	Old fish
Dimethylglycine dehydrogenase deficiency	Old fish

Table 60.5. Inborn Errors of Metabolism Associated with Distinctive Facial Features

Disorder	Unique Features
Zellweger syndrome	Large fontanelle, prominent forehead, flat nasal bridge, epicanthal folds, hypoplastic supraorbital ridges
Pyruvate dehydrogenase deficiency	Epicanthal folds, flat nasal bridge, small nose with anteverted flared alae nasi, long philtrum
Glutaric aciduria type II	Macrocephaly, high forehead, flat nasal bridge, short nose, ear anomalies, hypospadias, rocker bottom feet
Cholesterol biosynthetic defects (Smith-Lemli-Opitz syndrome)	Epicanthal folds, flat nasal bridge, toe 2/3 syndactyly, genital abnormalities, cataracts
Congenital disorders of glycosylation	Inverted nipples, lipodystrophy (very wide variety of findings among many disorders)
Miller syndrome (dihydroorotate dehydrogenase deficiency)	Micrognathia, cleft lip/palate, malar hypoplasia, eyelid coloboma, downslanted palpebral fissures, and absence of fifth digits

Table 60.6. Inborn Errors of Metabolism Associated with Hydrops Fetalis

Lysosomal disorders
■ Mucopolysaccharidosis types I, IVA, and VII
■ Sphingolipidosis: GM1 gangliosidosis, Gaucher disease, Farber disease, Niemann-Pick disease type A, multiple sulfatase deficiency
■ Lipid storage disorders: Wolman disease, Niemann-Pick disease type C
■ Oligosaccharidosis: galactosialidosis, sialic acid storage disease, mucolipidoses I (sialidosis), mucolipidoses II (I cell disease)
Zellweger syndrome
Glycogen storage disease type IV
Congenital disorders of glycosylation
Mitochondrial diseases

with IEMs. Disorders at high risk for metabolic decompensation, such as a male infant with possible OTC deficiency, may necessitate immediate treatment while diagnostic studies are pursued.

B. Initial evaluation. Certain laboratory studies should be obtained immediately once IEMs are suspected (Table 60.7) because these may help to narrow the differential diagnosis and direct management including further, more specialized diagnostic testing.

1. **Blood gas, electrolytes, glucose.** Many IEMs result in an anion gap metabolic acidosis due to the presence of abnormal metabolites such as propionic acid or methylmalonic acid. Hyperammonemia, as is seen in urea cycle defects, may present as a respiratory alkalosis due to the abnormal breathing pattern but progresses to metabolic acidosis in the later stages. Hypoglycemia is also seen in many IEMs, classically fatty acid oxidation disorders (FAODs).
2. **Plasma ammonia** should be sent in any infant suspected of having an IEM because treatment to lower ammonia levels is critical to prevent brain damage (see V.A.4.b). In order to be accurate, the sample should be drawn from a free-flowing blood vessel without tourniquet, immediately placed on ice, and run as soon as possible to avoid false elevations.

Table 60.7. Initial Laboratory Studies for a Newborn Suspected of Having an Inborn Error of Metabolism

Complete blood count with differential
Serum glucose and electrolytes
Blood gases
Liver function tests and coagulation profile
Plasma ammonia
Plasma lactate
Plasma amino acids
Plasma carnitine and acylcarnitine profile
Urine reducing substances, pH, ketones
Urine organic acids
Additional Laboratory Studies Considered in Neonatal Seizures
Cerebrospinal fluid (CSF) amino acids
CSF neurotransmitters
Sulfocysteine in urine
Very long chain fatty acids

3. **Plasma lactate** can help to identify the cause of a metabolic acidosis. Primary lactic acidosis is seen in disorders of gluconeogenesis, pyruvate metabolism, and mitochondrial diseases, whereas many other IEMs may cause a secondary lactic acidosis. As many other conditions in critically ill infants can result in lactic acidosis due to poor tissue perfusion, persistently elevated plasma lactate >3 mmol/L in a neonate without other evidence of end-organ injury or failure should raise suspicion for an IEM. As with plasma ammonia, the sample should be drawn from a free-flowing sample without use of a tourniquet to avoid false elevations.
4. **Liver function tests.** Liver dysfunction may be seen in many IEMs.
5. **Complete blood cell count.** Certain IEMs are associated with neutropenia (organic acidemias, mitochondrial disorders, glycogen storage disease Ib) or thrombocytopenia (organic acidemias).
6. **Urinalysis, urine ketones, urine reducing substances.** A urine pH >5 in the presence of a metabolic acidosis suggests renal tubular acidosis (which can be seen in certain IEMs that cause renal Fanconi syndrome). Positive urine reducing substances may indicate galactosemia. The presence of urine ketones in a neonate is unusual and is cause for concern.
7. **Plasma amino acid analysis, homocysteine, urine organic acid analysis, plasma carnitine and acylcarnitine profile, and urine acylglycines.** These can result in abnormal patterns characteristic of a particular IEM. Of note, secondary carnitine deficiency can be seen in many metabolic diseases and high or low carnitine can also be seen in infants on total parenteral nutrition (TPN) depending on the carnitine content.
8. **Very long chain fatty acids (VLCFAs).** An abnormal pattern may suggest peroxisomal disorders such as Zellweger syndrome.

C. Management of acute metabolic decompensation. As infants with IEMs may not properly metabolism protein, fat, or carbohydrate depending on the disorder, acute management involves removing exogenous sources of these substrates (stopping enteral feeds) and reversing the catabolic processes that can produce these substrates endogenously (provide high calories, usually via intravenous [IV] dextrose). Thus, in the acute setting, many IEMs are managed by the following basic principles:

1. **Decrease production of the toxic metabolites** by stopping enteral feeds for 24 to 48 hours. High dextrose fluids (i.e., D_{10} at 1.5 times the usual maintenance rate, although higher dextrose concentrations may be needed particularly if total fluids must be restricted) are started to halt catabolism and promote anabolism via endogenous insulin release. High caloric provision is important. If the suspected disorder is not a FAOD, lipids can be another source of calories.
   a. An insulin infusion can be used to stop catabolism and promote anabolism, particularly in the setting of hyperglycemia seen in response to the high dextrose IV fluids.
   b. If possible, reintroduce enteral feeds within 24 to 48 hours using a formula specialized for the disorder in question. Otherwise, certain important nutrients may be deficient in the diet that can lead to catabolism and further production of toxic intermediates. TPN can also be considered if enteral feeding is not possible, under the guidance of a metabolic specialist.

2. **Elimination of toxic metabolites** by hydration and other targeted therapies:
   a. Carnitine supplementation (100 to 300 mg/kg/day) may help to excrete toxic metabolites produced by organic acidemias.
   b. Other cofactors may be provided depending on the disorder because some enzymes may be vitamin responsive—such as thiamine for maple syrup urine disease (MSUD).
   c. Ammonia can be lowered by the use of IV scavengers such as sodium benzoate and sodium phenylbutyrate and through enteral scavengers. Arginine or citrulline supplementation may also be provided for certain urea cycle defects.
   d. Hemodialysis is indicated for ammonia >500 or >300 μmol/L with symptoms; it can also be used to remove toxic leucine in the case of MSUD.
3. **Correction of metabolic acidosis.** If the infant is acidotic (pH <7.22) or the bicarbonate level is <14 mEq/L, sodium bicarbonate can be given at dose of 1 to 2 mEq/kg as a bolus followed by a continuous infusion.
4. **Correction of hypoglycemia** (see Chapter 24)
5. **Treatment of precipitating factors** such as infection or other sources of metabolic stress

D. Monitoring response to treatment. Blood gases, electrolytes, glucose, and ammonia levels may need to be followed closely over time. Plasma amino acids are another important lab to monitor (particularly for MSUD), although not all facilities are able to access timely results.

E. Recovery and transition to long-term management

1. Once enteral feeds are restarted, a specialized diet is often required. Breastfeeding may be challenging depending on the severity of the disorder, although mothers may pump and save breast milk for possible future use.
2. If the infant is not able to feed by mouth, nasogastric tube feedings can be used. Infants with severe disorders at high risk for decompensation may require surgical placement of a gastrostomy tube prior to discharge home in order to have a reliable way to administer feeds.
3. Infants with IEMs may need specialized medications in addition to their specific diet. Other disorders have enzyme therapy available, and gene therapies are also being developed. Transplants are also used to treat certain disorders such as X-linked adrenoleukodystrophy (hematopoietic stem cell transplant) and MSUD, OTC deficiency, and propionic acidemia (PA) (liver transplant).

IV. IEMs WITH METABOLIC ACIDOSIS.

An IEM is often suspected in an infant with an anion gap metabolic acidosis, particularly if it does not appear to be secondary to poor perfusion or tissue ischemia due to sepsis or hypoxic injury. The organic acidemias, MSUD, FAODs, disorders of pyruvate metabolism, glycogen storage diseases, and mitochondrial disorders (see Table 60.1) can all present with an anion gap metabolic acidosis related to elevated lactate or another toxic metabolite. These disorders are described

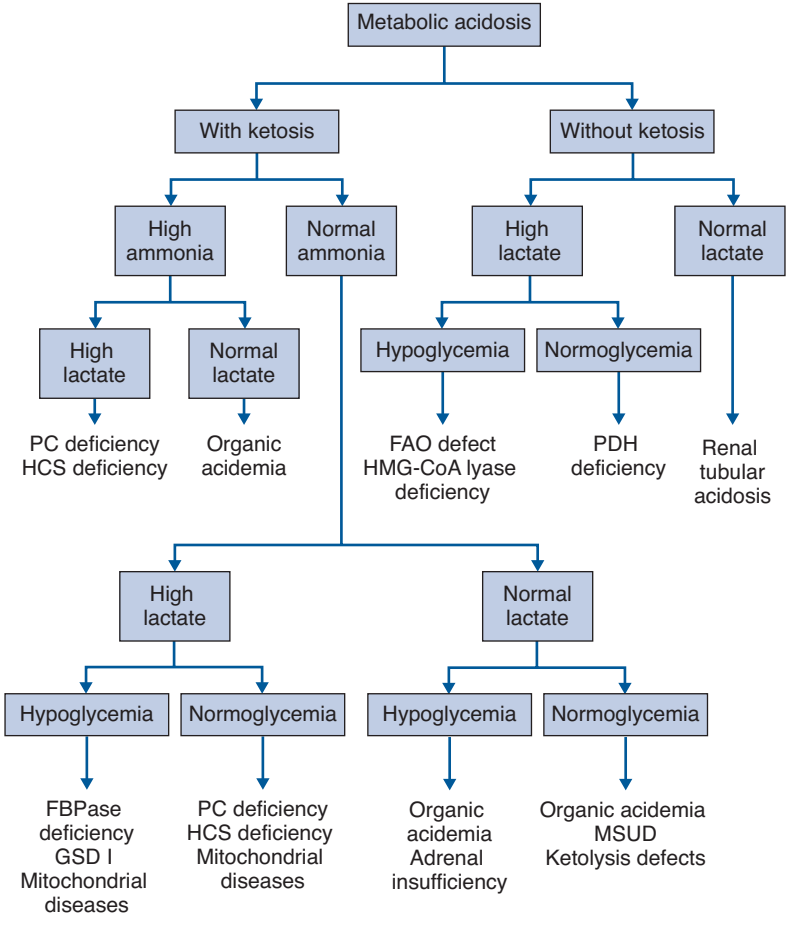

Figure 60.1. Approach to neonatal metabolic acidosis. Note that although a significant elevation in lactate is more associated with mitochondrial diseases and pyruvate metabolism disorders, milder lactate elevations can be seen in organic acidemias and maple syrup urine disease (MSUD). PC, pyruvate carboxylase; HCS, holocarboxylase synthetase; FAO, fatty acid oxidation; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; PDH, pyruvate dehydrogenase; FBPase, fructose-1,6-bisphosphatase deficiency; GSD I, glycogen storage disease type I.

and their distinguishing features (particularly ketosis) are presented in the following text (Fig. 60.1).

A. MSUD

1. An autosomal recessive disorder due to deficiency of branched-chain α-ketoacid dehydrogenase (Fig. 60.2)
2. **Manifestations.** The severe form of MSUD presents during the first week of life with poor feeding, vomiting, irritability, ketosis, lethargy,

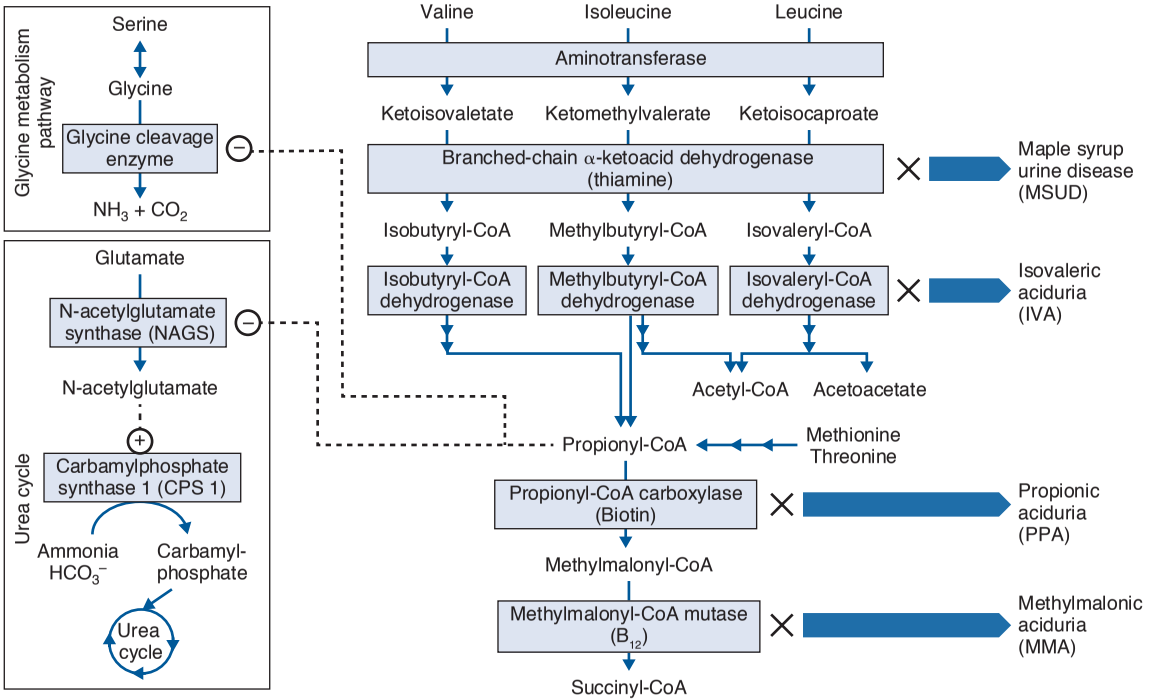

Figure 60.2. Branched-chain amino acid metabolism and enzyme defects associated with inborn errors of metabolism. Note that propionic acid inhibits glycine cleavage enzyme and N-acetylglutamate synthetase resulting in elevated glycine and hyperammonemia in propionic and methylmalonic acidemias. ⊖, negative effect/inhibition; ⊕, positive effect/acceleration.

seizures, hypertonicity, opisthotonus, coma, and maple syrup odor of urine and cerumen (see Table 60.4).

3. **Diagnosis.** MSUD can be diagnosed biochemically by the identification of increased plasma levels of branched-chain amino acids (leucine, isoleucine, alloisoleucine, and valine with perturbation of the normal 1:2:3 ratio of isoleucine:leucine:valine) and the presence of branched-chain keto- and hydroxyacids in urine organic acid analysis. Most newborn screening programs include MSUD. A biochemical diagnosis can be confirmed via gene testing or enzyme assay.
4. **Management.** Leucine, an amino acid, is the primary neurotoxic metabolite. Management of the acute presentation involves removing protein from the diet and reversing catabolism with glucose infusion (+/− insulin infusion). Isoleucine and valine supplementation (20 to 120 mg/kg/day) and adequate caloric intake plus the reintroduction of branched-chain amino acid-free formula are also needed to prevent endogenous protein breakdown. Hemodialysis may be used for severely elevated leucine. A thiamine (10 mg/kg/day) trial for 4 weeks can be considered. Long-term management requires a branched-chain amino acid–restricted diet and isoleucine/valine supplementation.

B. Organic acidemias

1. Organic acidemias are autosomal recessive disorders that are characterized by the excretion of organic acids in urine. The most commonly encountered organic acidemias in the neonatal period, PA, methylmalonic acidemia (MMA), and isovaleric acidemia (IVA), result from enzymatic defects in the metabolism of certain branched-chain amino acids (see Fig. 60.2).
2. **Manifestations.** Organic acidemias can present in the neonatal period with lethargy, poor feeding, vomiting, truncal hypotonia with limb hypertonia, myoclonic jerks, hypothermia, cerebral edema, coma, multiorgan failure, and unusual odor (see Table 60.4).
3. **Diagnosis.** Laboratory tests usually reveal a high anion gap metabolic acidosis and occasionally hyperammonemia, hyperglycinemia, hypoglycemia, neutropenia, thrombocytopenia, pancytopenia, and elevated transaminases. A specific biochemical diagnosis can be made via urine organic acid analysis and serum acylcarnitine profile (Table 60.8). Molecular genetic tests and enzyme assays are available for confirmation. Newborn screening programs that have expanded metabolic screening can detect IVA, PA, and MMA.
4. **Management.** Management of acute decompensation includes holding protein intake, suppressing catabolism with glucose (and insulin) infusions, correcting acidosis with sodium bicarbonate infusion, and administering carnitine (100 to 300 mg/kg/day IV) to enhance the excretion of organic acids in urine. Carbamyl glutamate (Carbaglu) may also be used to manage hyperammonemia in these conditions. Hemodialysis may be considered if these measures fail. Chronic treatment includes oral carnitine and dietary management. A diet low in amino acids producing propionic acid (isoleucine, valine, methionine, and threonine) is used for PA and MMA, and a leucine-restricted diet

Table 60.8. Biochemical Diagnosis of Organic Acidemias

Organic Acidemias	Enzymes	Urine Organic Acid Analysis	Plasma Acylcarnitine Profile
Propionic acidemia (PPA)	Propionyl-CoA carboxylase	Elevated 3-hydroxypropionic acid, methylcitric acid, and propionyl glycine	Elevated propionylcarnitine (C3)
Methylmalonic acidemia (MMA)	Methylmalonyl-CoA mutase	Elevated methylmalonic, and methylcitric acids	Elevated propionylcarnitine (C3)
Isovaleric acidemia (IVA)	Isovaleryl-CoA dehydrogenase	Elevated 3-hydroxyisovaleric acid and isovalerylglycine	Elevated pentanoyl carnitine (C5)

CoA, coenzyme A.

is used for IVA. Vitamin B_{12} (adenosylcobalamin) is a cofactor for methylmalonyl-coenzyme A (CoA) mutase, and hydroxocobalamin injection (1 mg daily) can be given as a trial in MMA. Glycine (150 to 250 mg/kg/day) enhances the excretion of isovaleric acid in urine and should be used in IVA. Organ transplant may also be considered for these conditions.

C. Defects of pyruvate metabolism can present with severe neonatal metabolic acidosis with elevated lactate and include pyruvate dehydrogenase (PDH), pyruvate carboxylase (PC), and holocarboxylase synthetase (HCS) deficiencies (Fig. 60.3).

1. PDH deficiency

a. PDH deficiency is usually inherited in an X-linked manner with the most severe illness in male infants.

b. Manifestations. Neonates with PDH deficiency typically present with severe lactic acidosis, hypotonia, feeding difficulties, apnea, seizures, lethargy, coma, brain changes (cerebral atrophy, hydrocephaly, corpus callosum agenesis, cystic lesions, gliosis, and hypomyelination), and distinctive facial features (see Table 60.5).

c. Diagnosis. Very high lactate in various body fluids is suggestive of the diagnosis. The diagnosis is confirmed by molecular genetic testing with enzyme studies if needed.

d. Management. The prognosis is very poor, and treatment is generally not effective. Acidosis correction with bicarbonate and hydration with glucose infusion are needed during the acute presentation. However, excess administration of glucose may worsen the acidosis, and a ketogenic diet (where ~80% of caloric intake is from fat) may reduce the lactic acidosis. Thiamin, a cofactor for PDH, can be used (10 mg/kg/day).

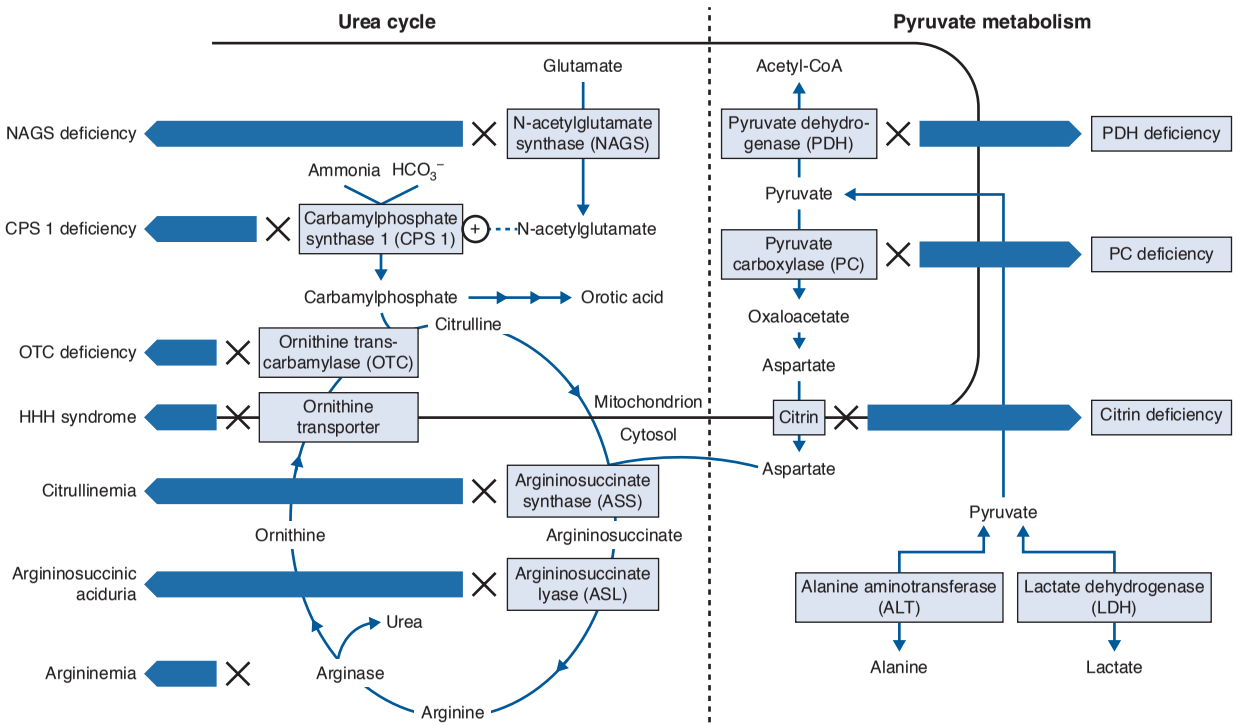

Figure 60.3. Metabolic pathways for urea cycle and pyruvate with the related inborn errors of metabolism. CoA, coenzyme A; HHH, hyperornithinemia-hyperammonemia-homocitrullinuria.

2. **PC deficiency**

a. PC deficiency is an autosomal recessive disorder.

b. Manifestations. Neonates with severe form of PC deficiency present with severe neonatal lactic acidosis, lethargy, coma, seizures, and hypotonia.

c. Diagnosis. Lactic acidosis, ketosis, hyperammonemia, hypercitrullinemia, and low aspartate are suggestive of the diagnosis. The diagnosis is confirmed by molecular genetic testing and/or enzyme studies.

d. Management. The prognosis is poor, and treatment is generally not effective. Correction of acidosis with bicarbonate and hydration with glucose infusion are needed during the acute presentation. Biotin is a cofactor for PC and can be given at a dose of 5 to 20 mg/day.

3. **HCS deficiency**

a. HCS deficiency (multiple carboxylase deficiency) is an autosomal recessive disorder due to deficiency of HCS enzyme that catalyzes the binding of biotin with the inactive apocarboxylases, leading to carboxylase activation. Deficiency of this enzyme causes malfunction of all carboxylases including propionyl-CoA, acetyl-CoA, 3-methylcrotonyl-CoA, and PCs.

b. Manifestations. Affected infants become symptomatic in the first few weeks of life with respiratory distress, hypotonia, seizures, vomiting, and failure to thrive. Skin manifestations include generalized erythematous rash with exfoliation and alopecia totalis. These infants may also have an immunodeficiency manifested by a decrease in the number of T cells.

c. Diagnosis. The biochemical profile for HCS deficiency includes lactic acidosis, ketosis, hyperammonemia, and urine organic acids showing methylcrotonylglycine and 3-hydroxyisovaleric, 3-hydroxypropionic, and methylcitric acids. Enzyme studies and molecular genetic studies are available. Many individuals are identified by newborn screening through elevation of hydroxypentanoylcarnitine (C5-OH) and/or propionylcarnitine (C3).

d. Management. Almost all affected infants respond to treatment with very large dose of biotin (10 to 40 mg/day), although in some affected infants, the response may be only partial.

V. IEMs WITH HYPERAMMONEMIA.

Hyperammonemia is a critical metabolic derangement to recognize in a sick neonate because irreversible brain damage can occur within hours. Hyperammonemia can be caused by IEMs or acquired disorders (Table 60.9) and is the principal presentation for most urea cycle disorders (UCDs). The presence of respiratory alkalosis or metabolic acidosis can help in distinguishing UCDs from organic acidemias, respectively (Fig. 60.4). Transient hyperammonemia of the newborn (THN) can be seen in premature neonates with respiratory distress; plasma glutamine is typically normal in THN in contrast to UCDs where glutamine is elevated (this can be seen on a plasma amino acid sample).

A. UCDs

1. UCDs are among the most common IEMs. Most UCDs are inherited as autosomal recessive conditions, with the exception of the X-linked disorder OTC deficiency. UCDs result from defects in urea cycle enzymes leading to the accumulation of ammonia and urea cycle intermediates (see Fig. 60.3).

Table 60.9. Differential Diagnosis of Hyperammonemia

Inborn Errors of Metabolism
■ Urea cycle enzyme defects
□ N-Acetylglutamate synthase (NAGS) deficiency
□ Carbamoyl phosphate synthase 1 (CPS 1) deficiency
□ Ornithine transcarbamylase (OTC) deficiency
□ Argininosuccinate synthase (ASS) deficiency (citrullinemia)
□ Argininosuccinate lyase (ASL) deficiency (argininosuccinic aciduria)
□ Arginase deficiency
■ Transport defects of urea cycle intermediates
□ Mitochondrial ornithine transporter (HHH syndrome)
□ Aspartate–glutamate shuttle (citrin) deficiency
□ Lysinuric protein intolerance
■ Organic acidemias
□ Propionic acidemia
□ Methylmalonic acidemia
□ Isovaleric acidemia
■ Pyruvate carboxylase deficiency
■ Fatty acid oxidation disorders
□ Very long chain acyl-coenzyme A dehydrogenase (VLCAD) deficiency
□ Carnitine transport defect
■ Tyrosinemia type I
■ Galactosemia
■ Ornithine aminotransferase deficiency
■ Hyperinsulinism-hyperammonemia syndrome
■ Mitochondrial respiratory chain defects

(continued)

Table 60.9. Differential Diagnosis of Hyperammonemia *(Continued)*

Acquired Disorders
■ Transient hyperammonemia of the newborn
■ Disorders of the liver and biliary tract
□ Herpes simplex virus infection
□ Biliary atresia
□ Liver failure
□ Vascular bypass of the liver (portosystemic shunt)
■ Severe systemic neonatal illness
□ Neonates sepsis
□ Infection with urease-positive bacteria (with urinary tract stasis)
□ Reye syndrome
■ Medications (valproic acid, cyclophosphamide, 5-pentanoic acid, asparaginase)
■ Technical
□ Inappropriate sample (e.g., capillary blood)
□ Sample not immediately analyzed

HHH, hyperornithinemia-hyperammonemia-homocitrullinuria.

2. **Manifestations.** UCDs can present at any age. Neonates with severe forms of UCDs typically present with rapidly progressive symptoms appear between 48 and 72 hours of life after a short, symptom-free interval. These symptoms include poor feeding, vomiting, lethargy, hypotonia, hypothermia, and hyperventilation. Affected neonates may also develop seizures, apnea, coma, and increased intracranial pressure unless hyperammonemia is diagnosed and treated promptly.
3. **Diagnosis.** In neonatal-onset UCDs, ammonia levels are usually >300 μmol/L and are often in the range of 500 to 1,500 μmol/L. Respiratory alkalosis secondary to hyperventilation (ammonia stimulates the respiratory center) is an important initial clue for the diagnosis of a UCD. Other laboratory abnormalities may include low blood urea nitrogen (BUN), mild/modestly elevated liver transaminases, and coagulopathy. Plasma amino acid analysis and urinary orotic acid can aid in biochemical diagnosis (see Fig. 60.4), which is typically confirmed by molecular genetic testing (enzyme assays are also available). Newborn screening programs that have expanded metabolic screening typically detect most UCDs, although proximal disorders such as OTC

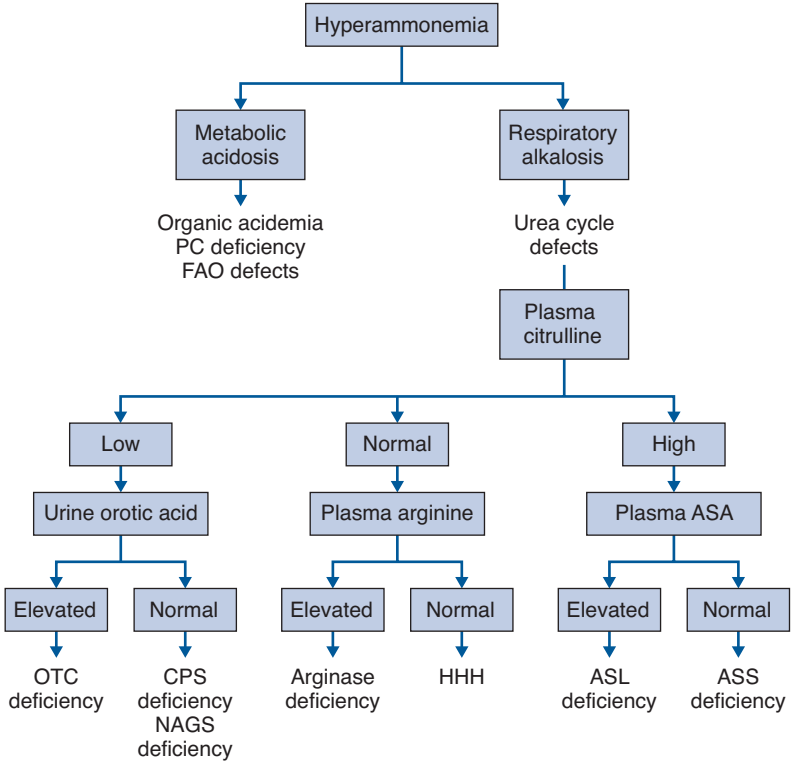

Figure 60.4. Approach to the investigation of neonatal hyperammonemia. PC, pyruvate carboxylase; FAO, fatty acid oxidation; ASA, argininosuccinic acid; OTC, ornithine transcarbamylase; CPS, carbamyl phosphate synthetase; NAGS, N-acetyl glutamate synthase; HHH, hyperornithinemia-hyperammonemia-homocitrullinuria; ASL, argininosuccinic acid lyase; ASS, argininosuccinic acid synthetase.

and carbamoyl phosphate synthase (CPS)/N-acetylglutamate synthase (NAGS) deficiencies are not detected by newborn screening.

4. **Acute management.** Goals of acute management are aimed at reducing ammonia levels to minimize neurologic injury:
   a. *Decrease production* of ammonia from protein intake and breakdown by dietary protein restriction and administering IV glucose (possible insulin infusion) and intralipid administration. Specialized formula is typically reintroduced within 24 to 48 hours to provide essential amino acids necessary to prevent endogenous protein breakdown.
   b. *Ammonia clearance* using IV ammonia–scavenging drugs (Ammonul) and/or dialysis. Ammonia scavengers may be attempted to treat ammonia levels >300 μmol/L, although dialysis should also be considered, particularly if the infant has neurologic symptoms. Ammonul (sodium

benzoate 100 mg/mL and sodium phenylacetate 100 mg/mL) is given as loading dose of 2.5 mL/kg in 25 mL/kg of 10% dextrose solution over a 60- to 120-minute period followed by the same dose over 24 hours as maintenance infusion. L-arginine hydrochloride is used with Ammonul (200 mg/kg for loading dose and maintenance dose in CPS and OTC deficiencies and 600 mg/kg in argininosuccinate synthase [ASS] and argininosuccinate lyase [ASL] deficiencies). L-arginine hydrochloride is contraindicated in arginase deficiency. A repeat loading dose of Ammonul can be given in neonates with severe illness not sooner than 24 hours of the first loading dose. Iatrogenic hypernatremia may be seen due to the high sodium load from Ammonul. Oral citrulline (170 mg/kg/day) should be given for OTC and CPS deficiencies. Hemodialysis/hemofiltration is the only method for rapid removal of ammonia from blood and is preferred over peritoneal dialysis because it is much more effective at removing ammonia. Exchange transfusion is not helpful due to the associated protein load. However, while preparing for dialysis, the glucose, insulin, and ammonia scavenger therapy should be maintained.

c. Rebound hyperammonemia can be seen after dialysis or the bolus dose of Ammonul due to delayed clearance of the ammonia from tissues in the body, including the brain, even after the serum levels have cleared.

d. Reduce the risk of neurologic damage via cerebral edema by avoiding fluid overload and treating seizures that can be subclinical.

5. **Long-term management.** Maintenance therapy includes the following:

a. Protein-restricted diet. After the patient is stabilized, enteral feeding should be started in consultation with a dietitian with expertise in managing UCDs. In general, infants require 1.2 to 2.0 g protein per kilogram with half of the required protein provided from essential amino acids formula and half from regular infant formula and ammonia levels are monitored while reintroducing protein.

b. Oral ammonia scavenger medications include sodium benzoate (250 to 400 mg/kg/day), sodium phenylbutyrate (250 to 500 mg/kg/day), and glycerol phenylbutyrate (Ravicti) (4.5 to 11.2 mL/m^2/day divided TID).

c. Replacement of arginine (200 to 600 mg/kg/day for ASS and ASL deficiencies) and citrulline (100 to 200 mg/kg/day for OTC and CPS deficiencies)

d. Carbamyl glutamate (Carbaglu) is a synthetic analogue for N-acetylglutamate, which is the natural activator of CPS. Therefore, Carbaglu may be effective NAGS deficiency and can be tried in individuals with CPS deficiency.

e. In children with severe forms of UCDs, liver transplantation can be considered.

VI. IEMs WITH HYPOGLYCEMIA.

Although hypoglycemia is a frequent finding in neonates, an IEM may be suspected if hypoglycemia is severe and persistent without any other etiology (see Chapter 24). The presence or absence of ketosis can help in guiding the diagnostic evaluation (Fig. 60.5).

A. Defects of fatty acid oxidation. FAODs can present in the neonatal period with hypoketotic hypoglycemia, and the biochemical diagnosis is based on

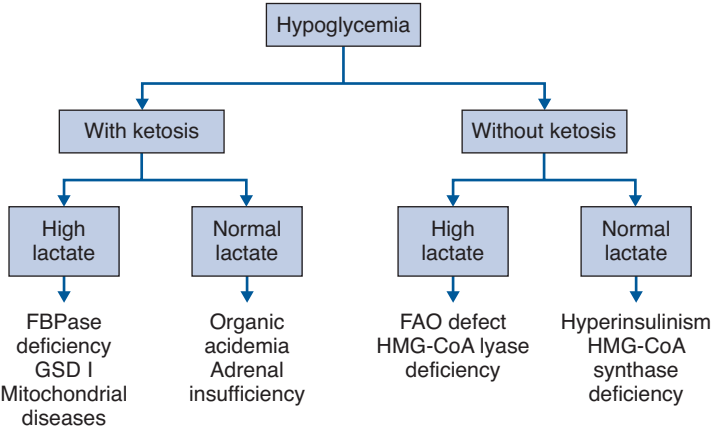

Figure 60.5. Approach to persistent hypoglycemia in the newborn with suspected inborn errors of metabolism. FBPase, fructose-1,6-bisphosphatase; GSD I, glycogen storage disease type I; FAO, fatty acid oxidation; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A.

the abnormalities found in acylcarnitine profile (Table 60.10), enzyme studies, and molecular genetic testing. Expanded newborn screening programs detect most FAODs.

1. **Long-chain FAODs.** Very long chain acyl-coenzyme A dehydrogenase (VLCAD), long-chain hydroxyacyl-coenzyme A dehydrogenase (LCHAD), trifunctional protein (TFP), carnitine-acylcarnitine translocase (CACT) deficiency and carnitine palmitoyltransferase II (CPTII) deficiencies.
   a. Manifestations. Infants with the severe forms typically present in the first months of life with cardiomyopathy, arrhythmias, hypotonia, hepatomegaly, rhabdomyolysis, and hypoglycemia.
   b. Management. Hypoglycemia should be avoided by frequent feeding and treated with glucose infusion. Diet restrictions with a low-fat formula and supplemental medium-chain triglycerides (MCTs) should be initiated early. These therapies will ideally reverse cardiac dysfunction. Triheptanoin (Dojolvi) is a newly approved medication to treat long-chain FAODs that provides an odd carbon medium-chain fat, which allows for increased citric acid cycle intermediates (anaplerotic therapy).
2. **Medium-chain FAODs.** Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency
   a. Manifestations. Infants with MCAD deficiency usually present between ages 3 and 24 months with hypoketotic hypoglycemia, vomiting, hepatomegaly elevated hepatic transaminases, lethargy, and seizures. Sudden and unexplained death can be the first manifestation of MCAD deficiency.
   b. Management. Hypoglycemia should be treated with glucose infusion and avoided by frequent feeding. Uncooked cornstarch also can be used to prevent hypoglycemia.

Table 60.10. Acylcarnitine Profile in Fatty Acid Oxidation Defects

Fatty Acid Oxidation Defect	Acylcarnitine Profile
Very long chain acyl-CoA dehydrogenase (VLCAD) deficiency	Elevated: C16 (hexadecanoylcarnitine) C14 (tetradecanoylcarnitine) C14:1 (tetradecenoylcarnitine) C12 (dodecanoylcarnitine)
Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency	Elevated: C6 (hexanoylcarnitine) C8 (octanoylcarnitine) C10 (decanoylcarnitine) C10:1 (decenoylcarnitine)
Short-chain acyl-CoA dehydrogenase (SCAD) deficiency	Elevated: C4 (butyrylcarnitine)
Long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency	Elevated: C14OH (hydroxytetradecenoylcarnitine) C16OH (hydroxyhexadecanoylcarnitine) C18OH (hydroxystearoylcarnitine) C18:1OH (hydroxyoleylcarnitine)
Carnitine palmitoyltransferase I (CPTI) deficiency	Elevated total carnitine Decreased: C16 (hexadecanoylcarnitine) C18 (octadecanoylcarnitine) C18:1 (octadecenoylcarnitine)
Carnitine palmitoyltransferase II (CPTII) deficiency	Decreased total carnitine Elevated: C16 (hexadecanoylcarnitine) C18:1 (octadecenoylcarnitine)
Carnitine transport defect	Decreased total carnitine

CoA, coenzyme A.

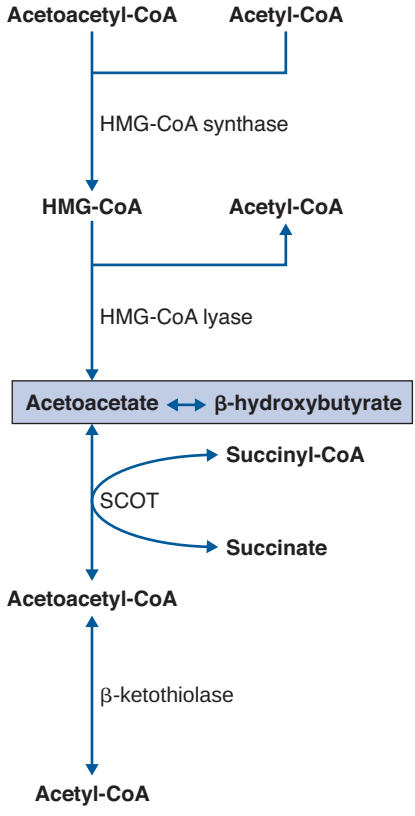

Figure 60.6. Ketone bodies (acetoacetate and β-hydroxybutyrates) synthesis and degradation. CoA,coenzyme A; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; SCOT, succinyl-coenzyme A oxoacid coenzyme A transferase.

B. Disorders of ketone body metabolism. Ketone bodies (acetoacetate and β-hydroxybutyrates) are important fuel for many tissues during fasting. Ketone bodies are synthesized via the enzymes 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) synthase and lyase, whereas succinyl-coenzyme A oxoacid coenzyme A transferase (SCOT) and β-ketothiolase catabolize ketone bodies (Fig. 60.6). Disorders of ketone body synthesis (ketogenesis) typically present with hypoketotic hypoglycemia. On the other hand, disorders of ketone body degradation (ketolysis) present with recurrent episodes of severe ketoacidosis.

1. HMG-CoA synthase deficiency

a. Manifestations. HMG-CoA synthase deficiency can present in infancy with hypoketotic hypoglycemia precipitated by acute illness.

b. Diagnosis. Urine organic acid analysis shows dicarboxylic aciduria without ketosis. The diagnosis can be confirmed molecularly by genetic testing.

c. Management. Hypoglycemia should be avoided by frequent feeding and treated with glucose infusion.

2. **HMG-CoA lyase deficiency**

a. Manifestations. Some affected individuals with HMG-CoA lyase present during the first week of life with vomiting, hypotonia, lethargy, hepatomegaly, hypoketotic hypoglycemia, abnormal liver function tests, elevated lactate, acidosis, and hyperammonemia.

b. Diagnosis. Urine organic acid analysis shows 3-hydroxy-3-methylglutarate (HMG) and methylglutaconate. The diagnosis can be confirmed molecularly by genetic testing. Expanded newborn screening detects this condition.

c. Management. Hypoglycemia should be treated with glucose infusion and acidosis by sodium bicarbonate infusion. Carnitine is also used. Long-term management includes carnitine and low-fat protein-restricted diet with avoidance of fasting.

C. Fructose-1,6-bisphosphatase (FBPase) deficiency. Deficiency of FBPase, a key enzyme in gluconeogenesis, impairs the formation of glucose.

1. **Manifestations.** Infants with FBPase deficiency can present during the first week of life with lactic acidosis, hypoglycemia, ketosis, hepatomegaly, seizures, irritability, lethargy, hypotonia, apnea, and coma.
2. **Diagnosis.** Diagnosis is confirmed by molecular genetic testing with enzyme assay available if necessary.
3. **Management.** The acute presentation can be treated with glucose infusion and bicarbonate to control hypoglycemia and acidosis. Maintenance therapy aims at avoiding fasting by frequent feeding and uncooked starch use. Restriction of fructose and sucrose is also recommended.

D. Glycogen storage disease type I (GSD I). GSD I is caused by the deficiency of glucose-6-phosphatase (G6Pase) activity.

1. **Manifestations.** Some neonates with GSD I present with severe hypoglycemia; however, the common age of presentation is 3 to 4 months with hypoglycemia, lactic acidosis, hepatomegaly, hyperuricemia, hyperlipidemia, growth failure, and hypoglycemic seizures. Hypoglycemia and lactic acidosis can develop after a short fast (2 to 4 hours).
2. **Diagnosis.** Diagnosis can be confirmed by molecular genetic testing with enzyme assay if needed.
3. **Management.** The acute presentation should be treated with glucose infusion and bicarbonate to control the hypoglycemia and the acidosis. Maintenance therapy aims to maintain normal glucose levels by frequent feeding, the use of uncooked cornstarch, and intragastric continuous feeding if needed. The diet should be low in fat, sucrose, and fructose and high in complex carbohydrate.

VII. IEMs WITH NEONATAL SEIZURES.

The possibility of IEMs should always be considered in neonates with unexplained and refractory seizures (see Table 60.1).

A. Biotinidase deficiency

1. Biotinidase is essential for the recycling of the vitamin biotin, which is a cofactor for several essential carboxylase enzymes.
2. **Manifestations.** Untreated children with profound biotinidase deficiency usually present between ages 1 week and 10 years with seizures, hypotonia,

metabolic acidosis, elevated lactate, hyperammonemia, cutaneous symptoms (skin rash, alopecia), and recurrent viral or fungal infections.

3. **Diagnosis.** The diagnosis is established by molecular genetic testing and/or assessing the biotinidase enzyme activity in blood. Newborn screening detects biotinidase deficiency.
4. **Management.** Acute metabolic decompensation can be treated by glucose and sodium bicarbonate infusions. Symptoms typically improve with biotin (5 to 10 mg oral daily) treatment. Children with biotinidase deficiency who are diagnosed before developing symptoms (e.g., by newborn screening) and who are treated with biotin do not typically develop any manifestations.

B. Pyridoxine-dependent epilepsy

1. Pyridoxine-dependent epilepsy is an autosomal recessive disorder that occurs due to the deficiency of the enzyme antiquitin in the lysine metabolism pathway and impairs the metabolism of neurotransmitters.
2. **Manifestations.** Newborns with pyridoxine-dependent epilepsy present soon after birth with seizures that are difficult to control (seizures can begin *in utero*).
3. **Diagnosis.** The diagnosis is established clinically by showing a response to pyridoxine. Administering 100 mg of pyridoxine IV while monitoring the electroencephalogram (EEG) can result in cessation of the clinical seizures with corresponding EEG changes generally over a period of several minutes; however, delayed responses have been described. If a clinical response is not demonstrated, the dose can be repeated up to 500 mg. Oral pyridoxine (30 mg/kg/day) can result in cessation of the seizures within 3 to 5 days. The diagnosis can be confirmed biochemically by demonstrating high levels of pipecolic acid, α-aminoadipic semialdehyde, and piperideine-6-carboxylate and by molecular genetic testing.
4. **Management.** In general, seizures are controlled with 50 to 100 mg of pyridoxine daily.

C. Pyridoxal phosphate–responsive epilepsy

1. Pyridoxal phosphate–responsive epilepsy is an autosomal recessive disorder that results from deficiency of pyridox(am)ine phosphate oxidase (PNPO), an enzyme that interconverts the phosphorylated forms of pyridoxine and pyridoxamine to the biologically active pyridoxal phosphate.
2. **Manifestations.** Neonates with pyridoxal phosphate–responsive epilepsy typically present similarly to those with pyridoxine-dependent epilepsy but do not respond to pyridoxine therapy.
3. **Diagnosis.** Diagnosis is established by demonstrating cessation of seizures with pyridoxal phosphate administration (50 mg orally) with corresponding EEG changes usually within an hour. Glycine and threonine are elevated in plasma and cerebrospinal fluid (CSF), whereas monoamine metabolites and pyridoxal phosphate are low in CSF. Molecular genetic testing is available.
4. **Management.** Seizures can usually be controlled with pyridoxal phosphate 30 to 50 mg/kg/day divided in four doses.

D. Glycine encephalopathy (nonketotic hyperglycinemia)

1. Glycine encephalopathy is an autosomal recessive disorder that occurs due to the deficiency of glycine cleavage enzyme system resulting in defective glycine degradation and glycine accumulation in tissues.
2. **Manifestations.** Individuals with neonatal form of glycine encephalopathy present with lethargy, hypotonia, poor feeding, seizures, and apnea within a few days of birth; symptoms may also begin *in utero* where frequent hiccupping is reported. EEG shows a characteristic burst-suppression pattern. Many infants die within a few weeks of life, typically from apnea; survivors develop profound global developmental delay. In transient glycine encephalopathy, which is secondary to the immaturity of glycine cleavage enzymes, laboratory and clinical abnormalities normalize by 2 to 8 weeks of age.
3. **Diagnosis.** Biochemical diagnosis is based on the demonstration of elevated plasma glycine levels and the CSF-to-plasma glycine ratio (samples of plasma and CSF should be obtained around the same time for accurate calculation of the ratio—normal is $\leq$0.02 and ratios of 0.09 to 0.45 can be seen in the severe form). Molecular genetic testing and enzyme assay can be used to confirm the diagnosis.
4. **Management.** There is no known effective treatment for glycine encephalopathy. Sodium benzoate (250 to 750 mg/kg/day) can be used to reduce glycine levels. The *N*-methyl-D-aspartate (NMDA) receptor antagonists dextromethorphan, memantine, ketamine, and felbamate can be used in an attempt to block the neuroexcitatory effects of glycine on NMDA receptors and possibly improve seizure control. However, these treatments have been of limited benefit to the ultimate neurodevelopmental outcome.

E. Sulfite oxidase deficiency and molybdenum cofactor deficiency

1. Sulfite oxidase deficiency is an autosomal recessive disorder due to deficiency of sulfite oxidase enzyme. Molybdenum is a cofactor for both sulfite oxidase and xanthine oxidase.
2. **Manifestations.** Sulfite oxidase and molybdenum cofactor deficiencies can present with neonatal seizures, lethargy, microcephaly, and progressive psychomotor retardation.
3. **Diagnosis.** The biochemical diagnosis is established by the demonstration of elevated sulfocysteine in urine and decreased homocysteine and cysteine in plasma. In addition, serum uric acid is low in molybdenum cofactor deficiency. Enzyme studies and molecular genetic testing are available for diagnosis confirmation.
4. **Management.** There is no known effective treatment.

F. Purine metabolism disorders. Purine nucleotides are essential cellular constituents, which intervene in energy transfer, metabolic regulation, and synthesis of DNA and RNA. Some disorders of purine metabolism can present with neonatal seizures.

1. **Adenylosuccinate lyase (ADSL) deficiency.** ADSL catalyzes two steps in purine synthesis the conversion of succinylaminoimidazole carboxamide

ribotide (SAICAR) to AICAR and that of adenylosuccinate (S-AMP) to AMP.

a. Manifestations. ADSL can present in intractable seizures starting within the first days to weeks of life. Other manifestations include hypotonia, microcephaly, psychomotor retardation, and brain atrophy, hypomyelination, and cerebellar atrophy in brain imaging.

b. Diagnosis. Biochemical diagnosis is based on the presence of SAICAR and succinyladenosine in CSF and urine. Diagnosis can be confirmed by enzyme assay and molecular genetic testing.

c. Management. There is no known effective treatment.

VIII. IEMs WITH HYPOTONIA.

Hypotonia is a nonspecific finding, although can be a predominant feature of certain IEMs (see Table 60.1).

A. Mitochondrial diseases

1. The principal function of mitochondria is to produce adenosine triphosphate (ATP) from the oxidation of fatty acids and sugars through the electron transport chain. Therefore, tissues that are more dependent on aerobic metabolism, such as brain, muscle, and heart, are more likely to be affected in these disorders.
2. **Manifestations.** Manifestations of mitochondrial diseases can start at any age. Neonates with mitochondrial diseases can present with apnea, lethargy, coma, seizures, hypotonia, spasticity, muscle weakness and atrophy, cardiomyopathy, renal tubulopathy, hepatomegaly, liver dysfunction or failure, lactic acidosis, hypoglycemia, anemia, neutropenia, or pancytopenia. Some infants with mitochondrial diseases display a cluster of clinical features that fall into a discrete clinical syndrome (Table 60.11); however, there is often considerable clinical variability, and many affected individuals do not fit into one particular syndrome.
3. **Diagnosis.** The diagnosis of mitochondrial disorders can be challenging. Biochemical abnormalities in mitochondrial diseases may include lactic acidosis, ketosis, and elevated tricarboxylic acid cycle intermediates in urine organic acid analysis. The histology of affected muscles in older individuals may show ragged red fibers that represent peripheral and intermyofibrillar accumulation of abnormal mitochondria, but this finding is rare in neonates and young children. The enzymatic activity of respiratory chain complexes can be assessed on skeletal muscle, skin fibroblast, or liver tissue, but this may be nondiagnostic. Molecular testing for mitochondrial DNA content and sequencing for mitochondrial DNA and known mitochondrial-related nuclear DNA genes is the preferred mode of testing due to limitations of biochemical and histologic analyses.
4. **Management.** Currently, there are no satisfactory therapies available for the vast majority of mitochondrial disorders. Treatment remains largely symptomatic and does not significantly alter the course of the disease.

B. Zellweger syndrome

1. Zellweger syndrome is a disorder of peroxisomal biogenesis. Peroxisomes are cell organelles that possess anabolic and catabolic functions,

Table 60.11. Mitochondrial Syndromes Associated with Neonatal Presentation
Barth syndrome
■ Hypertrophic cardiomyopathy
■ Skeletal myopathy
■ Neutropenia
■ Affects male individuals (X-linked)
Pearson syndrome
■ Sideroblastic anemia
■ Neutropenia
■ Thrombocytopenia
■ Exocrine pancreatic dysfunction
■ Renal tubulopathy
Hepatocerebral mitochondrial DNA depletion syndromes
■ Hepatic dysfunction or failure
■ Hypotonia
■ Seizures
■ Lactic acidosis
■ Hypoglycemia
Transient infantile liver failure due to mitochondrial translation defect (*TRMU* mutation)
■ Hepatic dysfunction or failure
■ Hepatomegaly
■ Poor feeding and vomiting
■ Lactic acidosis
■ Hypotonia
■ Liver function returns to normal after 3 to 4 months

including synthesizing plasmalogens, which are important constituents of cell membranes and myelin, β-oxidation of VLCFAs, oxidation of phytanic acid, and formation of bile acids.

2. **Manifestations.** Neonates with Zellweger syndrome typically present with severe weakness and hypotonia, poor feeding, widely split sutures, seizures, hepatomegaly, jaundice, elevated transaminases,

short proximal limbs, stippled epiphyses, and distinctive facial features (see Table 60.5).

3. **Diagnosis.** Biochemical abnormalities include elevated phytanic acid and VLCFAs and low plasmalogens. Many proteins are involved in peroxisomal biogenesis and therefore multiple genes are sequenced, in a gene panel or via exome sequencing, to identify the genetic diagnosis.
4. **Management.** There is no effective treatment, and management is largely symptomatic.

IX. IEMs WITH LIVER DYSFUNCTION.

Several IEMs can have hepatic manifestations in the neonatal period (see Table 60.2). Galactosemia is the most common metabolic cause of liver disease in neonates. Some mitochondrial diseases can present with hepatopathy in neonatal period (see Table 60.11).

A. Galactosemia (see Chapter 26)

1. Galactosemia is an autosomal recessive disease due to deficiency of galactose-1-phosphate uridyltransferase (GALT), which functions in the catabolic pathway of galactose.
2. **Manifestations.** Typical symptoms of galactosemia in the newborn develop after ingestion of lactose (glucose–galactose disaccharide) through breast milk or typical infant formulas. Clinical manifestations include vomiting, diarrhea, feeding difficulties, failure to thrive, hypoglycemia, jaundice, hepatomegaly, elevated transaminases, coagulopathy, ascites, liver failure, renal tubulopathy, lethargy, irritability, seizures, cataracts, and increased risk of *Escherichia coli* neonatal sepsis.
3. **Diagnosis.** The biochemical profile of galactosemia includes elevated galactose in plasma, galactose-1-phosphate in red blood cells, and galactitol in urine. Diagnosis is confirmed by enzyme assay and molecular genetic testing. All newborn screening programs screen for galactosemia.
4. **Management.** Lactose-free formula (soy) should be started during the first 3 to 10 days of life for optimal results.

B. Hereditary fructose intolerance

1. Hereditary fructose intolerance is an autosomal recessive disorder due to deficiency of FBPase aldolase (aldolase B), which in part of the catabolic pathway of fructose.
2. **Manifestations.** Clinical manifestations develop when the neonate is exposed to fructose from the sucrose (glucose–fructose disaccharide) in soy-based formulas or later at weaning when the infant is exposed to fructose from fruits and vegetables. Early manifestations include vomiting, hypoglycemia, irritability, seizures, lethargy, coma, hepatomegaly, jaundice, elevated transaminases, coagulopathy, edema, ascites, liver failure, and renal tubulopathy.
3. **Diagnosis.** Diagnosis is established by molecular genetic testing and enzyme assay.
4. **Management.** Management is based on elimination of sucrose, fructose, and sorbitol from the diet.

C. Tyrosinemia type I

1. Tyrosinemia type I is an autosomal recessive disorder due to deficiency of fumarylacetoacetate hydrolase, which functions in the catalytic pathway of tyrosine.
2. **Manifestations.** Tyrosinemia type I can present in early infancy with vomiting, diarrhea, hypoglycemia, septicemia, hepatomegaly, elevated transaminases, jaundice, coagulopathy, ascites, liver failure, renal tubulopathy, and abnormal odor (see Table 60.4).
3. **Diagnosis.** Biochemical abnormalities include elevated urine succinylacetone and tyrosine metabolites (p-hydroxyphenylpyruvate, p-hydroxyphenyllactate, and p-hydroxyphenylacetate) and elevated plasma tyrosine and methionine. Serum α-fetoprotein is markedly elevated. Diagnosis can be confirmed by enzyme assay and molecular genetic testing. Newborn screening programs may screen for tyrosine and/or succinylacetone in the bloodspot to diagnose tyrosinemia; however, many cases may be missed when the screening uses tyrosine alone.
4. **Management.** Nitisinone (NTCB, 1 to 2 mg/kg/day divided in two doses) and a tyrosine-restricted diet are effective at preventing symptoms if instituted early in life.

D. Neonatal intrahepatic cholestasis caused by citrin deficiency (NICCD)

1. NICCD is an autosomal recessive disorder due to deficiency of citrin, which is a mitochondrial aspartate–glutamate carrier (see Fig. 60.3).
2. **Manifestations.** NICCD can present in the neonatal period with transient intrahepatic cholestasis, prolonged jaundice, hepatomegaly, elevated transaminases, hypoproteinemia, coagulopathy, growth failure, hemolytic anemia, and hypoglycemia. NICCD is generally not severe, and most symptoms disappear by age 1 year with appropriate treatment.
3. **Diagnosis.** Biochemical abnormalities include elevated plasma citrulline, arginine, methionine, tyrosine lysine, and increased threonine:serine ratio. Molecular genetic testing is available. Elevated citrulline on newborn screening may lead to the diagnosis.
4. **Management.** Management includes the supplementation of fat-soluble vitamins and the use of lactose-free formula and high MCTs. Subsequently, a diet rich in lipids and protein and low in carbohydrates is recommended.

X. INBORN ERROR OF METABOLISM WITH CARDIOMYOPATHY.

Some metabolic disorders can present predominantly with cardiomyopathy (see Table 60.3).

A. Glycogen storage disease type II (GSD II) (Pompe disease)

1. GSD II is caused by the deficiency of the lysosomal enzyme acid α-glucosidase (GAA, acid maltase). The enzyme defect results in the accumulation of glycogen within the lysosomes in different organs.
2. **Manifestations.** Infants with the classic infantile-onset GSD II typically present in the first 2 months of life with hypotonia, muscle weakness, hepatomegaly, hypertrophic cardiomyopathy, feeding difficulties, failure to thrive, macroglossia, respiratory distress, and hearing loss.

3. **Diagnosis.** Nonspecific tests supporting the diagnosis include elevated serum creatinine kinase level and urinary oligosaccharides. The diagnosis is confirmed by enzyme assay and molecular genetic testing. Certain states now include Pompe disease on the newborn screening panel.
4. **Management.** Enzyme replacement therapy using alglucosidase alfa (Myozyme) should be initiated as soon as the diagnosis is established. The response to enzyme replacement therapy is better for those in whom the therapy is initiated before age 6 months and before the need for ventilatory assistance.

XI. POSTMORTEM DIAGNOSIS. If a genetic metabolic disorder is suspected to underlie an infant death, identifying the diagnosis is important in order to provide the family with information that could help them plan for future children. Genetic testing using exome or genome sequencing now offers the opportunity for molecular diagnosis with minimal tissue requirements, although a full autopsy is also extremely helpful. If a full autopsy is declined by the family, minimally invasive samples may be collected that can help clarify the results of genetic testing. Specimens that should be collected include the following:

A. Blood, both clotted and heparinized. The specimen should be centrifuged and the plasma frozen. Lymphocytes may be saved for culture.

B. Urine, frozen

C. CSF, frozen

D. Skin biopsy for fibroblast culture to be used for DNA analysis or enzyme assay. Two samples should be taken from a well-perfused area in the torso. The skin should be well cleaned with alcohol (not chlorhexidine, which kills cells) and any residual cleaning solution should be washed off with sterile water. The skin can be placed briefly in sterile saline until special media are available.

E. Liver and/or muscle biopsy samples, both premortem samples and generous-size postmortem samples, should be flash-frozen to preserve enzyme integrity as well as tissue histology.

F. Others. Depending on the nature of the disease, other tissues such as cardiac muscle, brain, and kidney should be preserved. Photographs can be taken as well as a full skeletal radiologic screening for infants with dysmorphic features. As previously mentioned, a full autopsy should be done if permitted.

XII. ROUTINE NEWBORN SCREENING. Each state in the United States has its own mandatory newborn screening program, and states now use tandem mass spectrometry (MS/MS) to evaluate newborn screening for a variety of IEMs. The recommended panel can be found here: https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html. Useful information for follow-up of newborn screening ("ACT Sheets") and for confirmation of a disorder identified by newborn screening ("Algorithms") is available on the website of the American College of Medical Genetics: https://www.acmg.net/ACMG/Medical-Genetics-Practice-Resources/ACT_Sheets_and_Algorithms.aspx. Table 60.12 includes the newborn screen analytes and the suspected diagnoses with each analyte.

Table 60.12. Newborn Screen Primary Analytes and the Suspected Diagnoses

Analyte	Condition
Biotinidase enzyme	Biotinidase deficiency
Elevated galactose and/or deficient GALT enzyme	Classical galactosemia
Elevated galactose and normal GALT	Galactokinase deficiency Galactose epimerase deficiency
C0	Carnitine transport defect
C0; C0/C16 + C18	Carnitine palmitoyltransferase I (CPT I) deficiency
C3	Methylmalonic acidemias Propionic acidemia
C3DC	Malonic acidemia
C4	Short-chain acyl-CoA dehydrogenase (SCAD) deficiency Ethylmalonic encephalopathy Isobutyryl-CoA dehydrogenase deficiency
C4OH	Medium-/short-chain hydroxyacyl-CoA dehydrogenase (M/SCHAD) deficiency
C4, C5	Glutaric acidemia 2 Ethylmalonic encephalopathy
C5	Isovaleric acidemia Short-/branched-chain acyl-CoA dehydrogenase deficiency
C5DC	Glutaric acidemia type I
C5OH	β-ketothiolase deficiency Biotinidase deficiency Holocarboxylase deficiency HMG-CoA lyase deficiency Methylcrotonyl-CoA carboxylase (MCC) deficiency
C8, C6, C10	Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency
C14:1	Very long chain acyl-CoA dehydrogenase (VLCAD) deficiency

(continued)

Table 60.12. *(Continued)*

Analyte	Condition
C16 and/or C18:1	Carnitine palmitoyltransferase II (CPT II) deficiency
C16OH ± C18:1-OH	Long-chain hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency Trifunctional protein (TFP) deficiency
Arginine	Argininemia
Citrulline	Argininosuccinate lyase deficiency (argininosuccinic aciduria) Argininosuccinate synthetase deficiency (citrullinemia I) Citrin deficiency (citrullinemia II) Pyruvate carboxylase deficiency
Methionine	Homocystinuria Hypermethioninemia Glycine N-methyltransferase (GNMT) deficiency Adenosylhomocysteine hydrolase deficiency
Leucine	Maple syrup urine disease (MSUD) Hydroxyprolinuria
Phenylalanine	Phenylketonuria (PKU) Biopterin cofactor metabolism defect
Elevated tyrosine and normal succinylacetone	Tyrosinemia II Tyrosinemia III
Tyrosine normal/elevated and succinylacetone elevated	Tyrosinemia I

GALT, galactose-1-phosphate uridyltransferase; DC, dicarboxylic; CoA, coenzyme A; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A.

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61 Thyroid Disorders

Christine E. Cherella and Ari J. Wassner

KEY POINTS

- Women with preexisting hypothyroidism who are treated appropriately typically deliver healthy infants.
- Congenital hypothyroidism is one of the most common preventable causes of intellectual disability.
- Preterm and low birth weight infants are at increased risk for congenital hypothyroidism (CH).
- Fetal and neonatal hyperthyroidism occurs in approximately 1% to 2% of infants born to mothers with Graves disease and is almost always transient.

I. THYROID PHYSIOLOGY IN PREGNANCY. Multiple changes occur in maternal thyroid physiology during normal pregnancy.

A. Increased iodine clearance. Starting early in pregnancy, increased renal blood flow and glomerular filtration lead to increased clearance of iodine from maternal plasma. Iodine is also transported across the placenta to enable iodothyronine synthesis by the fetal thyroid gland, which begins after the first trimester. These processes increase the maternal dietary requirement for iodine but have little impact on maternal plasma iodine concentration or on maternal or fetal thyroid function in iodine-sufficient regions. In contrast, in regions with insufficient iodine intake, increased iodine clearance and transplacental transfer may lead to decreased thyroxine (T_4), increased thyroid-stimulating hormone (TSH), and increased thyroid gland volume in both mother and fetus. Although the United States has historically been considered iodine sufficient, data indicate that half of pregnant women in the United States may have mild iodine deficiency. To ensure adequate intake, supplementation with 150 μg of iodine per day is recommended for all pregnant and lactating women; of note, many prenatal vitamins lack sufficient iodine.

B. Human chorionic gonadotropin (hCG) has weak intrinsic TSH-like activity. The high circulating level of hCG in the first trimester leads to a slight, transient increase in free T_4 accompanied by partial suppression of TSH that resolve by approximately the 14th week of gestation.

C. Increased thyroxine-binding globulin (TBG) levels occur early in pregnancy. TBG doubles by midgestation and then plateaus at a high level. This rise in TBG results largely from diminished hepatic clearance of TBG due to

increased estrogen-stimulated sialylation of the TBG protein. Estrogen also stimulates TBG synthesis in the liver.

D. Increased total triiodothyronine (T_3) and T_4 levels occur early in gestation along with rapidly increasing TBG levels (see section I.C). Free T_4 levels rise much less than total T_4 in early pregnancy (see section I.B) then decline progressively in the second and third trimesters. This physiologic decline is minimal (<10%) in iodine-sufficient regions but may be more pronounced in regions with borderline or deficient iodine intake. Assays that directly measure free T_4 may be affected by changes in TBG and should be used to monitor maternal thyroid function only if assay-specific and trimester-specific normal ranges are available; otherwise, an assay of total T_4 should be used.

E. TSH levels decline in the first trimester in the setting of elevated levels of hCG (see section I.B) and may transiently fall below the normal range for nonpregnant women in approximately 20% of healthy pregnancies. After the first trimester, TSH levels return to the normal, nonpregnant range.

F. The negative feedback control mechanisms of the hypothalamic-pituitary-thyroid (HPT) axis remain intact throughout pregnancy.

G. Placental metabolism and transplacental passage. Iodine and thyrotropin-releasing hormone (TRH) freely cross the placenta. The placenta is also permeable to antithyroid drugs and to TSH receptor–stimulating and TSH receptor–blocking immunoglobulin G (IgG) antibodies, but it is impermeable to TSH. T_4 crosses the placenta in limited amounts due to inactivation by the placental enzyme type 3 deiodinase (D3), which converts T_4 to inactive reverse T_3. T_3 is similarly inactivated by placental D3 and has minimal transplacental passage. In the setting of fetal hypothyroxinemia, maternal–fetal transfer of T_4 is increased, particularly in the second and third trimesters, which helps protect the developing fetus from the effects of fetal hypothyroidism.

II. MATERNAL HYPERTHYROIDISM.

Hyperthyroidism complicates 0.1% to 1% of pregnancies.

A. Graves disease accounts for ≥85% of clinical hyperthyroidism in pregnancy. Hyperemesis gravidarum is associated with transient subclinical or mild hyperthyroidism that may be due to the TSH-like effects of hCG and typically resolves without treatment.

B. Signs and symptoms of hyperthyroidism may include tachycardia, palpitations, increased appetite, tremor, anxiety, and fatigue. The presence of goiter, ophthalmopathy, or myxedema suggests Graves disease.

C. Poorly controlled maternal hyperthyroidism is associated with serious pregnancy complications including spontaneous abortion, preterm delivery, intrauterine growth restriction, fetal demise, preeclampsia, placental abruption, thyroid storm, and congestive heart failure.

D. Treatment of maternal hyperthyroidism substantially reduces the risk of associated maternal and fetal complications.

1. **Antithyroid drugs** are indicated for the treatment of **moderate to severe hyperthyroidism**. In the first trimester, propylthiouracil (PTU) rather than methimazole (MMI) is recommended due to possible

teratogenic effects of MMI, which has been associated with aplasia cutis congenita, tracheoesophageal fistula, and choanal atresia. Although PTU has also been associated with congenital malformations such as face/neck cysts and urinary tract abnormalities, these are less common and generally less severe than those caused by MMI, and PTU remains the drug of choice in the first trimester. However, because PTU can cause severe maternal liver dysfunction, in the second trimester, PTU should be switched to MMI. Both MMI and PTU cross the placenta, and the fetus is more sensitive than the mother to the effects of antithyroid drugs, so fetal hypothyroidism and goiter can occur even with doses in the therapeutic range for the mother. Clinicians should use the lowest possible dose and monitor closely, aiming to maintain T_4 levels in the high-normal range and TSH levels in the low-normal or suppressed range. **Mild hyperthyroidism** can be monitored without treatment.

2. **β-Adrenergic blocking agents** such as propranolol may be useful in controlling hypermetabolic symptoms; however, long-term use should be avoided due to potential neonatal morbidities including hypotension, bradycardia, and impaired response to hypoglycemia.
3. **Surgical thyroidectomy** may be needed to control hyperthyroidism in women who cannot take antithyroid drugs due to allergy or agranulocytosis or in cases of maternal nonadherence to medical therapy. If thyroidectomy is necessary, it should be performed during the second trimester if possible, rather than in the first or third trimesters when risks to the fetus are higher.
4. **Iodine** given at a pharmacologic dose is generally contraindicated because prolonged administration can cause fetal hypothyroidism and goiter. However, a short course of iodine in preparation for thyroidectomy appears to be safe, and clinicians may also use iodine in selected cases in which antithyroid drugs cannot be used. **Radioactive iodine (RAI)** is contraindicated during pregnancy.

E. Fetal and neonatal hyperthyroidism occurs in approximately 1% to 2% of infants born to mothers with Graves disease. In these cases, hyperthyroidism results from transplacental passage of TSH receptor–stimulating antibodies. High levels of these antibodies in maternal serum during the third trimester are predictive of fetal and neonatal hyperthyroidism, as is a maternal history of having a prior child with the condition. All pregnant women with Graves disease should be tested for TSH receptor–stimulating antibodies and monitored for fetal hyperthyroidism through serial measurement of fetal heart rate as well as prenatal ultrasound to assess for fetal goiter and to monitor fetal growth. Fetal hyperthyroidism can be treated by administration of antithyroid drugs to the mother, but excessive treatment can suppress the fetal thyroid gland and cause hypothyroidism.

F. Fetal and neonatal hypothyroidism in maternal Graves disease. Fetal exposure to MMI or PTU can cause transient hypothyroidism that resolves rapidly and usually does not require treatment (see section VI.A.2.a). In mothers with a history of Graves disease, transplacental passage of TSH receptor–blocking antibodies may cause fetal hypothyroidism (see section VI.A.2.e). A rare neonatal outcome of maternal Graves disease is

transient central hypothyroidism, which may be due to pituitary suppression from prolonged intrauterine hyperthyroidism.

G. Infants of mothers with Graves disease can present with thyrotoxicosis or hypothyroidism in the newborn period and require close monitoring after birth (see section VII).

III. MATERNAL HYPOTHYROIDISM. Maternal hypothyroidism in pregnancy can be overt (0.3% to 0.5% of pregnancies) or subclinical (2% to 2.5% of pregnancies).

A. The most common cause of maternal hypothyroidism in iodine-sufficient regions is chronic autoimmune thyroiditis. Other causes include previous treatment of Graves disease or thyroid cancer with surgical thyroidectomy or radioiodine ablation, drug- or radiation-induced hypothyroidism, congenital hypothyroidism (CH), and pituitary dysfunction. Chronic autoimmune thyroiditis is more common in patients with type 1 diabetes mellitus. Occasionally, mothers with a prior history of Graves disease become hypothyroid due to the development of TSH receptor–blocking antibodies.

B. Signs and symptoms of hypothyroidism in pregnancy include weight gain, cold intolerance, dry skin, weakness, fatigue, and constipation. These may go unnoticed in the setting of pregnancy, particularly if hypothyroidism is mild.

C. Unrecognized or untreated hypothyroidism is associated with spontaneous abortion and maternal complications of pregnancy including anemia, preeclampsia, postpartum hemorrhage, placental abruption, and need for cesarean delivery. Associated adverse fetal and neonatal outcomes include preterm birth, intrauterine growth restriction, congenital anomalies, fetal distress in labor, and fetal and perinatal death. However, these complications are avoided with adequate treatment of hypothyroidism, ideally from early in pregnancy. **Affected fetuses may experience neurodevelopmental impairments, particularly if both the fetus and the mother are hypothyroid during gestation** (e.g., iodine deficiency, TSH receptor–blocking antibodies).

D. Women with preexisting hypothyroidism who are treated appropriately typically deliver healthy infants. Such patients should increase their usual L-thyroxine dose by 25% to 30% immediately upon missing a menstrual period or obtaining a positive result on a pregnancy test. Thyroid function tests should be measured as soon as pregnancy is confirmed, every 4 weeks during the first half of pregnancy, at least once between 26 and 32 weeks' gestation, and 4 weeks after any L-thyroxine dose change. The TSH level should be maintained in population-based trimester-specific normal ranges. In the late first trimester (weeks 7 to 12), the lower reference range of TSH can be reduced by approximately 0.4 mU/L, and the upper reference range can be reduced by approximately 0.5 mU/L compared to the nonpregnant range, with a gradual return toward the nonpregnant range in the second and third trimesters. Achieving this goal often requires an L-thyroxine dose of 20% to 50% higher than in the nonpregnant state.

E. Routine thyroid function testing in pregnancy is currently recommended only for women at high risk for hypothyroidism, including those who are

symptomatic; older than 30 years; live in an iodine-deficient area; have a family or personal history of thyroid disease; or have a history of known thyroid antibody positivity, type 1 diabetes, neck irradiation, morbid obesity, use of amiodarone or lithium, multiple prior pregnancies, infertility, miscarriage, or preterm delivery. Because this strategy may miss some women with hypothyroidism, some authors advocate universal screening in early pregnancy, but this has not been shown to improve outcomes, and the topic remains controversial.

F. TSH receptor–blocking antibodies cross the placenta and may cause fetal and transient neonatal hypothyroidism (see section VI.A.2.e).

IV. FETAL AND NEONATAL GOITER

A. Fetal ultrasound by an experienced ultrasonographer is an excellent tool for intrauterine diagnosis and monitoring of fetal goiter.

B. Maternal Graves disease is the most common cause of fetal and neonatal goiter, which results most often from fetal hypothyroidism due to MMI or PTU even when given at relatively low doses. Fetal and neonatal goiter can also result from fetal hyperthyroidism due to TSH receptor–stimulating antibodies. TSH receptor antibodies can be present both in women with active Graves disease and in women previously treated for Graves disease with surgical thyroidectomy or RAI ablation. Maternal history and serum antibody testing is usually diagnostic. Rarely, cord blood sampling is necessary to determine where fetal goiter is due to MMI- or PTU-induced fetal hypothyroidism or to fetal hyperthyroidism induced by TSH receptor–stimulating antibodies. After delivery, neonates exposed *in utero* to PTU or MMI eliminate the drug rapidly. Thyroid function tests usually normalize by 1 week of age, and treatment is not required.

C. Other causes of fetal and neonatal goiter include fetal disorders of thyroid hormonogenesis (usually inherited), excessive maternal iodine ingestion, and maternal iodine deficiency. All of these conditions are associated with fetal or neonatal hypothyroidism, and goiter resolves after normalization of the serum TSH concentration with L-thyroxine treatment.

D. Fetal goiter due to hypothyroidism is usually treated with maternal L-thyroxine administration. Rarely, treatment with intra-amniotic injections of L-thyroxine is used during the third trimester to reduce the size of a fetal goiter when needed to **prevent complications of tracheal/esophageal compression** including polyhydramnios, lung hypoplasia, and airway compromise at birth.

V. THYROID PHYSIOLOGY IN THE FETUS AND NEWBORN

A. The **fetal HPT axis** develops relatively independent of the mother due to the high placental expression of D3, which inactivates most of the T_4 and T_3 presented from the maternal circulation (see section I.G).

B. Thyroid embryogenesis is complete by 10 to 12 weeks' gestation by which time the fetal thyroid gland starts to concentrate iodine and synthesize and to secrete T_3 and T_4. Concentrations of T_4 and TBG increase gradually

throughout gestation. Circulating T_3 levels remains low, although T_3 levels in the brain and pituitary are considerably higher due to local expression of type 2 deiodinase (D2), which converts T_4 to the active thyroid hormone, T_3. In the setting of fetal hypothyroidism, upregulation of D2 activity in the brain maintains the local T_3 concentration, allowing normal development to proceed.

C. TSH from the fetal pituitary gland increases beginning in midgestation. The **negative feedback mechanism of the HPT axis** starts to mature by 26 weeks' gestation. Circulating levels of TRH are high in the fetus relative to the mother, although the physiologic significance of this is unclear.

D. Exogenous iodine suppresses thyroid hormone synthesis, a property known as the Wolff-Chaikoff effect. However, the ability of the thyroid gland to escape from the suppressive effect of an iodine load does not mature until 36 to 40 weeks' gestation. Thus, premature infants are more susceptible than term infants to iodine-induced hypothyroidism.

E. Neonatal physiology. Within 30 minutes after delivery, there is a dramatic surge in serum TSH, with peak levels as high as 80 mU/L at 6 hours of life. TSH then declines rapidly over 24 hours, then more slowly over the first week of life. The TSH surge causes marked stimulation of the neonatal thyroid gland, leading to sharp increases in serum T_3 and T_4 levels, which peak within 24 hours of life and then slowly decline.

F. In the preterm infant, the pattern of postnatal thyroid hormone changes is similar to that seen in the term infant, but the TSH surge is less marked and the resulting T_4 and T_3 increases are blunted. In very preterm infants (<31 weeks' gestation), no TSH surge occurs, and circulating T_4 may fall rather than rise over the first 7 to 10 days. Thyroid hormone levels in umbilical cord blood are related to gestational age and birth weight (Table 61.1).

VI. CONGENITAL HYPOTHYROIDISM

A. CH is one of the **most common preventable causes of intellectual disability**. The incidence of CH varies globally. In the United States, the incidence is approximately 1/2,500 and appears to be rising. CH is more common among Hispanic (1/1,600) and Asian Indian (1/1,757) infants but less common among non-Hispanic black infants (1/11,000). The female-to-male ratio is 2:1. CH is also more common in infants with trisomy 21, congenital heart disease, and other congenital malformations including cleft palate and renal, skeletal, or gastrointestinal anomalies. CH may be permanent or transient. Hypothyroxinemia with delayed TSH rise can be caused by permanent or transient conditions.

1. Causes of **permanent CH** (Table 61.2)

a. Thyroid dysgenesis. Abnormal thyroid gland development is the cause of permanent CH in about 85% of cases. Thyroid dysgenesis includes agenesis, hypoplasia, and ectopy (failure to descend normally into the neck). It is almost always sporadic with no increased risk to subsequent siblings. Rarely, thyroid dysgenesis is associated with a mutation in

Table 61.1. Thyroid Hormone Reference Ranges (*M* ± *SD*) for Full-Term and Preterm Neonates

Gestational Age (Weeks)	Age			
	Birth	7 Days	14 Days	28 Days
Total T_4 (μg/dL)				
23–27	5.4 ± 2.0	4.0 ± 1.8	4.7 ± 2.6	6.1 ± 2.3
28–30	6.3 ± 2.0	6.3 ± 2.1	6.6 ± 2.3	7.5 ± 2.3
31–34	7.6 ± 2.3	9.4 ± 3.4	9.1 ± 3.6	8.9 ± 3.0
≥37	9.2 ± 1.9	12.7 ± 2.9	10.7 ± 1.4	9.7 ± 2.2
Free T_4 (ng/dL)				
23–27	1.3 ± 0.4	1.5 ± 0.6	1.4 ± 0.5	1.5 ± 0.4
28–30	1.4 ± 0.4	1.8 ± 0.7	1.6 ± 0.4	1.7 ± 0.4
31–34	1.5 ± 0.3	2.1 ± 0.6	2.0 ± 0.4	1.9 ± 0.5
≥37	1.4 ± 0.4	2.7 ± 0.6	2.0 ± 0.3	1.6 ± 0.3
Total T_3 (ng/dL)				
23–27	19.5 ± 14.9	32.6 ± 20.2	41.0 ± 24.7	63.1 ± 27.3
28–30	28.6 ± 20.8	56.0 ± 24.1	72.3 ± 28.0	87.2 ± 31.2
31–34	35.2 ± 23.4	91.8 ± 35.8	109.4 ± 41.0	119.8 ± 40.1
≥37	59.9 ± 34.5	147.8 ± 50.1	167.3 ± 31.2	175.8 ± 31.9
TSH (mU/L)				
23–27	6.8 ± 2.9	3.5 ± 2.6	3.9 ± 2.7	3.8 ± 4.7
28–30	7.0 ± 3.7	3.6 ± 2.5	4.9 ± 11.2	3.6 ± 2.5
31–34	7.9 ± 5.2	3.6 ± 4.8	3.8 ± 9.3	3.5 ± 3.4
≥37	6.7 ± 4.8	2.6 ± 1.8	2.5 ± 2.0	1.8 ± 0.9
TBG (mg/dL)				
23–27	0.19 ± 0.06	0.17 ± 0.04	0.19 ± 0.05	0.23 ± 0.06
28–30	0.20 ± 0.05	0.20 ± 0.05	0.21 ± 0.05	0.22 ± 0.06
31–34	0.24 ± 0.08	0.24 ± 0.08	0.23 ± 0.08	0.23 ± 0.08
≥37	0.29 ± 0.06	0.34 ± 0.11	0.28 ± 0.04	0.27 ± 0.07

T_4, thyroxine; T_3, triiodothyronine; TSH, thyroid-stimulating hormone; TBG, thyroxine-binding globulin.

Source: Adapted from Williams FL, Simpson J, Delahunty C, et al. Developmental trends in cord and postpartum serum thyroid hormones in preterm infants. *J Clin Endocrinol Metab* 2004;89(11):5314–5320.

Table 61.2. Interpretation of Thyroid Function Tests and Imaging Results in Congenital Hypothyroidism and Related Disorders

Cause of Hypothyroidism	Total T_4	Free T_4	TSH	TG	Thyroid Imaging	Treatment	Comments
Permanent							
Dysgenesis	↓	↓	↑	↓	Absent, small, or ectopic	Yes	Almost always sporadic
Dyshormonogenesis	↓	↓	↑	*	Normal or large	Yes	Usually autosomal recessive
TSH resistance	Normal or ↓	Normal or ↓	↑	↓	Normal or small	Depends on severity	Autosomal dominant or recessive
Central hypothyroidism	↓	↓	Normal or ↓	↓	Normal	Yes	Not detected on primary TSH NB screen; usually have other pituitary hormone deficiencies
Transient							
Maternal antithyroid medication (MMI, PTU)	↓	↓	↑	Normal or ↑	Normal or large	Not usually	Resolves within 1 week
TSH receptor–blocking antibodies	↓	↓	↑	↓	Normal or small	Yes	Usually resolves within 2–3 months

Hypothyroxinemia of prematurity	↓	↓	Normal	Normal	Normal	Controversial	Some physicians treat infants <27 weeks' gestation
Iodine deficiency	↓	↓	↑	↑	Normal or large	Yes[†]	↓ Urinary iodine
Iodine excess	↓	↓	↑	↑	Normal or large	Yes	↑ Urinary iodine; infants <36 weeks' gestation most susceptible
TBG deficiency	↓	Normal	Normal	Normal	Normal	No	—
Liver hemangioma	↓	↓	↑	↑	Normal	Yes	Rare, usually presents after newborn period May require high doses of L-thyroxine ± T_3

*Absent or ↓ in thyroglobulin (TG) synthetic defect, ↑ in other forms of dyshormonogenesis.

[†]Treat with iodine, not L-thyroxine.

T_4, thyroxine; TSH, thyroid-stimulating hormone; NB, newborn; MMI, methimazole; PTU, propylthiouracil; TBG, thyroxine-binding globulin.

one of the transcription factors necessary for thyroid gland development (*PAX8*, *FOXE1*, *NKX2.1*, *NKX2.5*). Clinically, infants with thyroid dysgenesis have no goiter, low total and free T_4 levels, elevated TSH, and normal TBG. The serum concentration of thyroglobulin (TG) reflects the amount of thyroid tissue present and is low in cases of thyroid agenesis or hypoplasia. Ultrasound confirms the presence or absence of a normally located thyroid gland, whereas scintigraphy with RAI or pertechnetate ($^{99m}TcO4^-$) can locate a normally placed or ectopic gland that is able to concentrate iodine.

b. Defects in thyroid hormone synthesis and secretion (thyroid dyshormonogenesis) are responsible for most of the remaining 15% of permanent CH cases. Most are recessive and carry a 25% recurrence risk in subsequent siblings. The most common defects are abnormal activity of TPO or DUOX2, which result in impaired organification of iodine. Additional defects affect other key steps in thyroid hormone synthesis such as TG synthesis, iodine trapping, and iodotyrosine deiodination. **Pendred syndrome** is an important cause of sensorineural deafness associated with goiter due to a mild organification defect; however, hypothyroidism rarely occurs in the newborn period. In thyroid dyshormonogenesis, goiter may be present. Total and free T_4 levels are low, TSH is elevated, and TBG is normal. Defects in TG synthesis can be distinguished from other abnormalities in thyroid hormone formation by measurement of serum TG, which is low in TG synthetic defects and high in other forms of dyshormonogenesis. Unlike in thyroid dysgenesis, thyroid imaging typically reveals a normally placed thyroid gland that may be normal or large in size.

c. TSH resistance is usually caused by mutations in the TSH receptor. Rarely, it is due to a loss-of-function mutation in the stimulatory $G_s\alpha$ subunit that links TSH binding to TSH receptor action (Albright hereditary osteodystrophy). In TSH resistance, the thyroid gland is small. T_4 is normal or low, and TSH is elevated with the severity of hypothyroidism depending on the degree of TSH resistance.

d. Central (hypothalamic-pituitary) hypothyroidism is less common than primary hypothyroidism. Although previously thought to be rare, this condition may be more common than generally appreciated, with an incidence of between 1/16,000 and 1/50,000 newborns. Although genetic defects in hypothalamic-pituitary signaling can lead to isolated central CH, in most cases, affected infants have other pituitary hormone deficits and may have signs of pituitary dysfunction such as hypoglycemia, microphallus, and midline facial abnormalities. Septo-optic dysplasia is an important cause of central hypothyroidism. Goiter is not present. Total and free T_4 are low, TSH is low or inappropriately normal, and TBG is normal. If central hypothyroidism is suspected, cortisol and growth hormone levels should be measured and magnetic resonance imaging performed to visualize the hypothalamus and pituitary. Failure to identify associated pituitary-hypothalamic defects, particularly adrenocorticotropic and growth hormone deficiencies, may lead to morbidity or mortality.

2. Causes of **transient CH** (see Table 61.2)

a. Antithyroid drugs. As discussed in section IV.B, intrauterine exposure to MMI or PTU can cause transient hypothyroidism that typically resolves within 1 week and does not require treatment. The elimination half-life of MMI is 4 to 6 hours and that of PTU is 1.5 to 5 hours.

b. Iodine excess. Neonates may be exposed to excess iodine in the perinatal or neonatal period. Preterm infants are particularly susceptible to the thyroid-suppressing effects of excess iodine (see section V.D), such as from topical antiseptic solutions (e.g., povidone iodine), radiographic contrast solutions, and medications (e.g., amiodarone). Iodine is excreted into breast milk and can be excessive in mothers who ingest large amounts of iodine (e.g., seaweed). In infants with hypothyroidism due to iodine excess, goiter may be present, T_4 is low, and TSH is elevated. RAI and $^{99m}TcO4^-$ uptake are blocked by excess iodine, and ultrasound shows a normally positioned thyroid gland that may be enlarged.

c. Iodine deficiency is the most common cause of transient hypothyroidism worldwide, particularly in preterm infants but is less common in the United States, a generally iodine-sufficient region. Preterm infants who are not exposed to iodine-containing skin cleansers (e.g., povidone iodine) may be at risk for iodine deficiency due to the low iodine content of their diet including parenteral nutrition, many standard preterm formulas and caloric supplements, and some breast milk (e.g., of women with inadequate dietary iodine intake).

d. Transient hypothyroxinemia of prematurity is most common in infants born before 31 weeks' gestation. Etiologic factors include hypothalamic-pituitary immaturity (particularly in infants <27 weeks' gestation), acute illness, and medications (e.g., dopamine, steroids). T_4 is low, usually with total T_4 more affected than free T_4. Unlike in primary hypothyroidism, TSH is inappropriately normal rather than elevated.

Observational studies in premature infants have demonstrated an association of transient hypothyroxinemia with adverse short- and long-term outcomes, including neonatal death, intraventricular hemorrhage, periventricular leukomalacia, cerebral palsy, intellectual impairment, and academic impairments. However, randomized trials of L-thyroxine supplementation have failed to show a beneficial effect, so the extent to which low T_4 levels directly cause these adverse outcomes is unclear. Treatment is controversial but, if given, may be most beneficial to infants born before 27 weeks' gestation.

e. TSH receptor–blocking antibodies account for 1% to 2% of all cases of CH and occur in 1/180,000 live births, typically in the setting of maternal autoimmune thyroid disease. These IgG antibodies cross the placenta and persist in the neonatal circulation with a half-life of approximately 2 weeks. TSH receptor–blocking and TSH receptor–stimulating antibodies may be present simultaneously, and their relative proportions may change over time. Neonatal hypothyroidism typically persists for 2 to 3 months and depends on the initial titer and the potency of the receptor-blocking activity. In these infants, goiter is not present. T_4 is low, TSH is elevated, and TBG is normal. High concentrations of TSH receptor–blocking antibodies can be measured in maternal and

neonatal serum. Uptake is low or absent on thyroid scintigraphy, but a normally placed thyroid gland is visible by ultrasound.

f. Large liver hemangiomas can be associated with severe, refractory primary hypothyroidism due to massive expression of thyroid hormone–inactivating D3 by the hemangioma. Infants typically present after the newborn period as the hemangioma enlarges. Large doses of L-thyroxine, and occasionally addition of T_3, are required for treatment. Hypothyroidism resolves over time as the hemangioma regresses.

3. **Hypothyroxinemia with delayed TSH elevation (atypical CH)** is often due to recovery from sick euthyroid syndrome but needs to be distinguished from transient hypothyroidism and from a mild form of permanent CH. This condition is most common among extremely low birth weight infants (<1,000 g, reported incidence 1.7% to 3.9%), very low birth weight infants (<1,500 g, reported incidence 1.1% to 2.5%), and in other critically ill newborns including those with congenital heart disease. Monozygotic twins discordant for CH can present with delayed TSH rise because mixing of fetal blood before birth allows the normal twin's thyroid to compensate for CH in the affected twin. Delayed TSH elevation may be missed on the initial newborn screen, particularly in programs using TSH as the primary screen (see section VI.B.1). For infants at high risk for delayed TSH elevation, repeat newborn screening generally is recommended at 2 to 4 weeks of life and again 4 weeks later or at 36 weeks' corrected gestational age, whichever is earlier.

B. Diagnosis. Over 95% of newborns with CH are asymptomatic at birth, but universal newborn screening permits early diagnosis and treatment, resulting in optimal neurodevelopmental outcome. In the United States, 1,600 cases of intellectual disability per year are prevented by newborn screening for CH.

1. **Newborn screening for CH** is routine in most developed countries but is not yet performed in some developing countries. Screening is mandated by law in the United States, but specific screening protocols and cutoff values vary by state. Some programs measure TSH as the primary screen, whereas others measure T_4 as the primary screen, followed by TSH when T_4 is low. Each approach has advantages and disadvantages. A few states measure both T_4 and TSH in the initial screen for all newborns, or for a subset of high-risk newborns, which is an ideal but expensive strategy.

2. A **filter paper blood spot specimen** should be sent from all newborns, ideally between 24 and 72 hours of age, although often, this timing is not feasible due to the early discharge of many healthy newborns. For infants discharged prior to 48 hours of age, a specimen should be sent prior to discharge. Infants tested and discharged before 24 hours of age should be retested at 48 to 72 hours to minimize the risk of false-negative results. For infants transferred to another hospital, the receiving hospital should send a specimen if it cannot be confirmed that the hospital of birth sent one. For infants <1,500 g birth weight, repeat specimens should be sent at 2 to 4 weeks and again 4 weeks later or at

36 weeks' corrected gestational age, whichever is earlier, due to the risk of delayed TSH elevation (see section VI.A.3).

3. **If clinical signs of hypothyroidism** are present (e.g., constipation, hypothermia, poor tone, mottled skin, prolonged jaundice, poor feeding, large tongue, open posterior fontanel), serum thyroid function tests should be sent immediately, **even if the initial screen was normal**. Rarely, screening programs miss cases of CH as a result of early discharge, improper or no specimen collection (e.g., hospital transfers, home births, sick or premature neonates), laboratory error, delayed TSH elevation, or human error in reporting results. Primary TSH screening programs may miss infants with central (pituitary) hypothyroidism. Acquired hypothyroidism (e.g., due to postnatal excess iodine exposure) will also be missed on newborn screening.

4. **Follow-up of newborn screening for CH** in hospitalized preterm infants is outlined in Figure 61.1. Screening protocols and cutoffs for T_4 and TSH levels vary by screening program (see section VI.B.2).
   a. Any infant with abnormal screening results should be evaluated without delay. Consultation with a pediatric endocrinologist is recommended. Maternal and family history should be reviewed and a physical examination performed. TSH and free T4 should be measured in a serum sample within 24 hours. Most infants with an initial TSH level >50 mU/L have a permanent form of CH. Therapy should be initiated as soon as the diagnosis is confirmed. If the newborn screen TSH is >40 mU/L, therapy should be started as soon as confirmatory serum tests are drawn, without waiting for the results. If total T_4 is low but the TSH level is not elevated, a serum free T4 level should be measured to exclude TBG deficiency. Patients with TBG deficiency generally have normal free T_4 levels and are almost always male (the condition is X-linked); this diagnosis should be confirmed by measurement of a serum TBG level. If both total T4 and free T4 are low but TSH is not elevated, central hypothyroidism or transient hypothyroxinemia of prematurity should be suspected. In such cases, consultation with an endocrinologist may be helpful to guide diagnostic evaluation and treatment.
   b. Measurement of serum **TG level** and **thyroid ultrasound and/or thyroid scintigraphy with RAI or $^{99m}TcO4^-$** can help differentiate thyroid dysgenesis from defects in thyroid hormone synthesis, and conditions that may be transient from those likely to be permanent. These tests are not necessary if transient hypothyroxinemia of prematurity is suspected (see section VI.A.2.d). Thyroid scintigraphy is useful to detect dysgenetic or ectopic thyroid tissue as long as the serum TSH level is >30 mU/L at the time of scintigraphy. **Treatment should not be delayed to perform thyroid scintigraphy.** If scintigraphy cannot be performed within 5 days of diagnosis, it should be deferred until the child is 3 years old, at which time thyroid hormone replacement can be safely discontinued for a brief period. Unlike thyroid scintigraphy, ultrasound can be performed at any time, irrespective of the TSH concentration.
   c. Bone age may be helpful in assessing the severity and duration of intrauterine hypothyroidism but does not usually alter management and is performed infrequently.

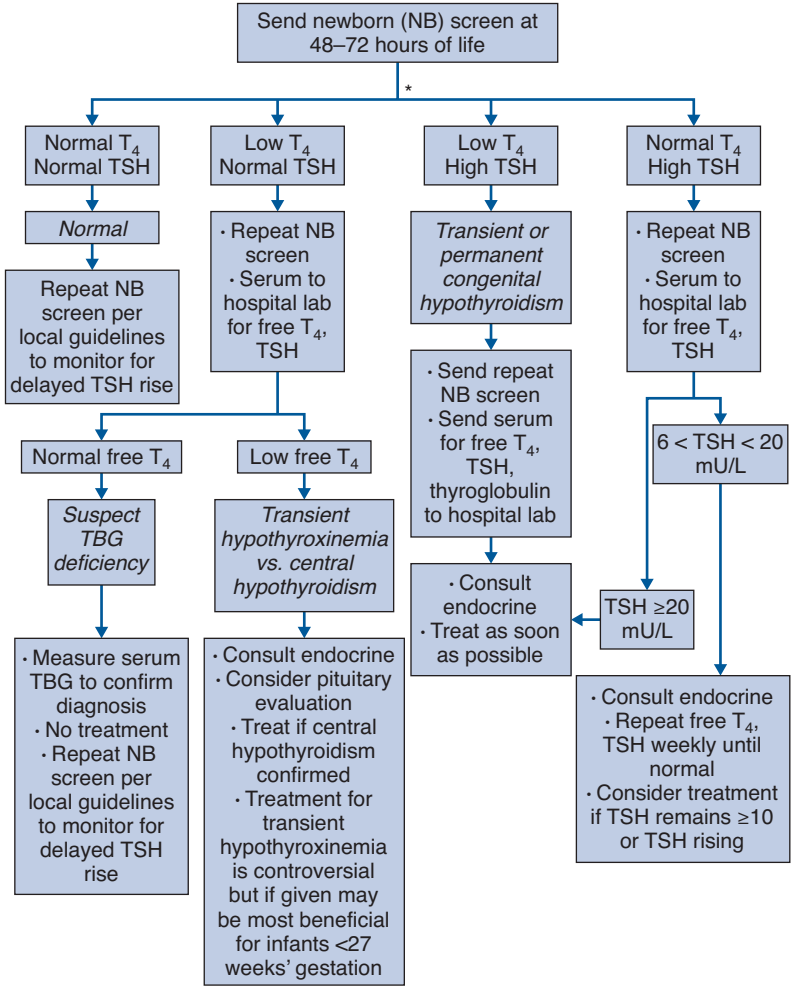

Figure 61.1. Suggested approach to follow-up of newborn screening for hypothyroidism in the hospitalized preterm infant. *In the United States, screening protocols and cutoff values vary slightly by state. T_4, thyroxine; TSH, thyroid-stimulating hormone; TBG, thyroxine-binding globulin. (Modified from Brodsky D, Ouellette MA, eds. *Primary Care of the Premature Infant*. Philadelphia, PA: Elsevier Saunders; 2008).

C. Treatment and monitoring. Optimal neurodevelopmental outcome depends on early, adequate treatment of CH.

1. For **infants with suspected transient or permanent CH**, L-thyroxine should be initiated at **10 to 15 µg/kg/day**, with doses at the higher end of this range used for infants with the lowest T_4 and highest TSH levels.

The goal of treatment is to normalize thyroid hormone levels as soon as possible. Ideally, the T_4 level will normalize within 1 week and the TSH level within 2 weeks of starting therapy. Repeat T_4 and TSH measurements should be performed 1 week after starting therapy, every 1 to 2 weeks until thyroid hormone levels have normalized, 2 to 4 weeks after any dose change, and every 1 to 2 months in the first year of life. Serum thyroid function tests should be drawn at least 4 hours after L-thyroxine dosing and at least 4 hours after medications that can cause assay interference (including aspirin, furosemide, and heparin). Nonadherence to treatment can have serious, permanent neurodevelopmental consequences for the infant and should always be considered when thyroid function tests fail to normalize with treatment.

2. **L-thyroxine** tablets should be crushed and fed directly to the infant, or mixed in a small amount of water, breast milk, or non–soy-based formula. Soy-based formulas, ferrous sulfate, calcium supplements, and fiber interfere with absorption should be administered at least 2 hours apart from the L-thyroxine dose. As of 2017, a pharmaceutical liquid solution of L-thyroxine is FDA approved, but optimal dosing in neonates may differ from that of L-thyroxine tablets.
3. For **preterm infants with transient hypothyroxinemia of prematurity**, treatment decisions are complicated by incomplete data on the risks and benefits of treatment. Although most observational studies have found an association in preterm infants between low serum T_4 concentration with increased morbidity and mortality, at least one study showed in contrast that higher free T_4 levels are associated with poorer developmental outcomes. Moreover, randomized trials have failed to demonstrate a short- or long-term benefit of routine L-thyroxine supplementation for all premature infants. Some physicians prefer to treat infants <27 weeks' gestation due to presumed hypothalamic-pituitary immaturity, but this practice is controversial. If treatment is elected, the starting dose of L-thyroxine is **8 μg/kg/day**, lower than the usual starting dose for CH.
4. For infants with **suspected transient CH**, a brief **trial off medication can be attempted at 3 years of age** after thyroid hormone–dependent brain development is complete. Usually, in infants with transient hypothyroidism, the dose required to maintain normal thyroid function does not increase with age as it generally does in permanent CH.

D. Prognosis. With prompt diagnosis and treatment, the long-term neurodevelopmental outcome is excellent for infants with CH. Subtle defects in visuospatial processing, memory, and sensorimotor function have been reported, particularly in infants with severe CH, but the clinical significance of these differences is controversial. In contrast, infants in whom diagnosis is delayed may have substantial cognitive and behavioral defects ranging from mild to severe, depending on the severity of the CH and the length of delay in starting treatment.

VII. NEONATAL HYPERTHYROIDISM

is uncommon (accounting for <1% of hyperthyroidism in children) and is almost always transient. Most newborns with hyperthyroidism are born to mothers with Graves disease. Rarely,

permanent hyperthyroidism can be caused by an activating mutation of the TSH receptor, a condition that is usually inherited in autosomal dominant fashion and may require thyroid gland removal or ablation.

A. Incidence. The overall incidence of neonatal hyperthyroidism is about 1/25,000. Of infants born to mothers with Graves disease, 1% to 2% develop hyperthyroidism.

B. Pathogenesis. Most neonatal hyperthyroidism results from transplacentally acquired maternal TSH receptor–stimulating antibodies. Rarely, both TSH receptor–stimulating and TSH receptor–blocking antibodies may be present simultaneously. In such cases, infants may present initially with hypothyroidism due to the potent blocking antibodies; hyperthyroidism may emerge later due to the more rapid clearance of blocking antibodies compared to stimulating antibodies. More commonly, neonatal hyperthyroidism due to persistent TSH receptor–stimulating antibodies may follow initial hypothyroidism caused by transplacental passage of MMI or PTU, which are typically cleared within the first week of life.

C. Neonatal hyperthyroidism usually occurs in the setting of active maternal Graves disease but may also occur in infants of mothers with Graves disease who have previously undergone surgical thyroidectomy or RAI ablation. These mothers are no longer hyperthyroid but may continue to produce TSH receptor autoantibodies. High maternal serum levels of TSH receptor–stimulating antibodies increase the risk of hyperthyroidism in the newborn, but precise values differ depending on the sensitivity of the assay used.

D. Clinical findings. Neonatal hyperthyroidism usually presents toward the end of the first week of life as maternal antithyroid medication is cleared from the newborn's circulation but can occur earlier. Clinical manifestations include prematurity, intrauterine growth restriction, tachycardia, irritability, poor weight gain, goiter, prominent eyes, hypertension, and craniosynostosis. Arrhythmias and congestive heart failure can be life-threatening. Rarely, neonatal hyperthyroidism can present with signs and symptoms suggestive of congenital viral infection, including hepatosplenomegaly, petechiae, fulminant hepatic failure, and coagulopathy. Diagnosis is based on maternal history of Graves disease, suppression of TSH, elevation of total and free T_4 levels, and high titers of TSH receptor–stimulating antibodies.

E. Treatment

1. **MMI** (0.5 to 1 mg/kg/day in three divided doses) is used to treat neonatal hyperthyroidism. PTU (5 to 10 mg/kg/day in three divided doses) is also effective but is not recommended as first-line therapy due to the risk of hepatotoxicity.
2. For severe hyperthyroidism, an **iodine preparation** can be used to block the release of T_4 immediately. Lugol's solution (potassium iodide 100 mg/mL and iodine 50 mg/mL) or SSKI (potassium iodide 1 g/mL) can be given at a dose of 1 drop three times per day for 10 to 14 days.
3. **β-Blockade** with propranolol (2 mg/kg/day in three divided doses) is used to control tachycardia. If congestive heart failure develops,

β-blockade should be discontinued and treatment with digoxin considered in consultation with a cardiologist.

4. Additional therapy for severe cases may include **prednisolone** (1 to 2 mg/kg/day).
5. **Supportive care** maintains adequate oxygenation, fluid balance, calorie and nutrient intake for growth, and temperature regulation.
6. **Treatment course.** Thyroid function tests (free T_4, total T_3, and TSH) are repeated every few days initially, and the dose of antithyroid drug is adjusted to maintain levels within the normal range. Treatment is usually required for up to 2 to 3 months but may be needed longer. Once control is achieved, the infant can be discharged with close follow-up. Iodine solutions are given for 10 to 14 days. Infants are weaned off β-blockade as indicated by the heart rate, and then the dose of antithyroid drug is tapered as allowed by the T_4 level and clinical symptoms.

F. Prognosis. Delayed diagnosis and inadequate treatment are associated with serious long-term consequences, including craniosynostosis, failure to thrive, developmental delay, and hyperactivity. Older case series report a 10% to 20% mortality rate, but with early diagnosis and proper treatment, most newborns improve rapidly, and therapy can be withdrawn within 2 to 3 months. Rarely, transient central hypothyroidism may occur as a result of exposure of the fetal hypothalamus and pituitary to high thyroid hormone levels at a critical period in development.

VIII. MATERNAL THYROID MEDICATIONS AND BREASTFEEDING

A. **MMI** and **PTU** are excreted into breast milk but only in small amounts. Breastfeeding is considered safe for mothers taking doses of MMI <30 mg/day or of PTU <300 mg. MMI is preferred over PTU in breastfeeding women due to the risk of hepatotoxicity from PTU.

B. Propranolol is excreted into breast milk only in very small amounts. It is generally considered safe to breastfeed while taking propranolol without any special precautions.

C. L-thyroxine is transferred minimally to breast milk, similarly to endogenous T_4 in euthyroid women. Thus, breastfeeding is safe for women taking L-thyroxine replacement.

D. Iodine is excreted into the breast milk, and **the iodine status of the exclusively breastfed infant is dependent on the iodine status of the mother**. Even in regions considered iodine-sufficient, such as the United States, pregnant and lactating women should take 150 μg daily of supplemental iodine. Of note, many prenatal vitamins do not contain iodine. Preterm infants are particularly susceptible to the thyroid-suppressive effects of excess iodine, which can lead to subclinical or overt hypothyroidism. Excess iodine in the mother can come from the diet (e.g., seaweed) or from exposure to iodine-containing topical antiseptic agents (such as povidone iodine) used during labor and delivery.

Suggested Readings

Alexander EK, Pearce EN, Brent GA, et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid* 2017;27(3):315–389.

Rose SR, Brown RS, Foley T, et al. Update of newborn screening and therapy for congenital hypothyroidism. *Pediatrics* 2006;117(6):2290–2303.

Segni M. Disorders of the thyroid gland in infancy, childhood, and adolescence. http://www.thyroidmanager.org. Updated March 2012. Accessed June 15, 2021.

van Trotsenburg AS, Stoupa A, Léger J, et al. Congenital hypothyroidism: a 2020–2021 consensus guidelines update—an ENDO-European Reference Network initiative endorsed by the European Society for Pediatric Endocrinology and the European Society for Endocrinology. *Thyroid* 2020;31(3):387–419. doi:10.1089/thy.2020.0333.

62 Neonatal Effects of Maternal Diabetes

Karen O'Brien

KEY POINTS

- The majority of infants of diabetic mothers (IDMs) are born to women with gestational diabetes, with pregestational type 2 diabetes rates now eclipsing type 1.
- Pregestational diabetes mellitus (PDGM) has a strong association with congenital abnormalities, perinatal mortality, and prematurity with rates linked to periconception glycemic control.
- Frequent neonatal morbidities associated with diabetes in pregnancy include macrosomia, postnatal hypoglycemia, prematurity, and birth trauma.
- Prenatal hyperglycemia exposure increases longer term metabolic complications including obesity, impaired glucose metabolism, and potential decrements in neurodevelopmental outcomes.

I. BACKGROUND. Diabetes in pregnancy is associated with increased risks of fetal, neonatal, and potentially lifelong complications. Although the adverse effects of diabetes and hyperglycemia in pregnancy have been noted for hundreds of years, the modern history of classification of diabetes in pregnancy began in 1949 with Priscilla White's classification of maternal diabetes, ranging from gestational diabetes to long-standing insulin-dependent diabetes with systemic complications (Table 62.1). Most importantly, White highlighted the relationship between maternal end-organ disease and poor perinatal outcomes. In 1952, Jorgen Pedersen advanced the study of diabetes in pregnant women and their offspring by proposing a mechanism of maternal hyperglycemia leading to fetal hyperinsulinism, explaining many of the neonatal complications. Efforts since have led to improved prenatal monitoring and management of diabetes in pregnancy, reducing the incidence of adverse perinatal outcomes. However, as the incidence of obesity and type 2 diabetes climbs, and as we grow to further understand the long-term metabolic impact of exposure to obesity and diabetes in the developing fetus, we are entering a new era that will require vigilance for both mothers and their offspring.

II. CLASSIFICATION OF DIABETES IN PREGNANCY. Pregnancy itself is characterized by increased insulin resistance as gestation progresses, with peak insulin resistance during the third trimester. A state of relative insulin resistance

Table 62.1. White Classification of Maternal Diabetes

Gestational diabetes (GD):	Diabetes not known to be present before pregnancy
	Abnormal glucose tolerance test in pregnancy
GD diet	Euglycemia maintained by diet alone
GD insulin	Diet alone insufficient; insulin required
Class A:	Chemical diabetes; glucose intolerance before pregnancy; treated by diet alone; rarely seen
	Prediabetes; history of large babies >4 kg or unexplained stillbirths after 28 weeks
Class B:	Insulin-dependent; onset after 20 years of age; duration <10 years
Class C:	C1: Onset at 10–19 years of age
	C2: Duration 10–19 years
Class D:	D1: Onset before 10 years of age
	D2: Duration 20 years
	D3: Calcification of vessels of the leg (macrovascular disease)
	D4: Benign retinopathy (microvascular disease)
	D5: Hypertension (not preeclampsia)
Class F:	Nephropathy with >500 mg/day of proteinuria
Class R:	Proliferative retinopathy or vitreous hemorrhage
Class RF:	Criteria for both classes R and F coexist
Class G:	Many reproductive failures
Class H:	Clinical evidence of arteriosclerotic heart disease
Class T:	Prior renal transplantation

Note: All classes below A require insulin. Classes R, F, RF, H, and T have no criteria for age of onset or duration of disease but usually occur in long-term diabetes.

Source: Modified with permission of John Wiley & Sons; from Hare JW. Gestational diabetes. In: *Diabetes Complicating Pregnancy: The Joslin Clinic Method*. New York, NY: Alan R. Liss; 1989; permission conveyed through Copyright Clearance Center, Inc.

occurs during pregnancy as a result of the actions of various placental hormones including human placental lactogen, progesterone, prolactin, placental growth hormone, and cortisol. Whereas hormones of pregnancy allow an environment for normal development of the fetus, the pregnant state leaves a narrower margin of error in which women's propensity for carbohydrate intolerance can become apparent. This chapter reviews the effects of both diabetes mellitus (DM) diagnosed before conception (pregestational diabetes mellitus [PDGM])

and diabetes diagnosed during pregnancy, most specifically in the second to third trimester (gestational diabetes mellitus [GDM]).

A. PGDM. PGDM complicates 1% to 2% of all pregnancies and comprises 13% to 21% of diabetes in pregnancy. This category of PGDM includes women with type 1 diabetes and type 2 diabetes who have been diagnosed and treated prior to conception. Type 2 PGDM is now more common than type 1 because obesity prevalence and its associations climb. Type 1 DM is typically diagnosed early in life and is characterized by relative or absolute insulin deficiency. Type 2 DM is typically diagnosed later in life and is associated with obesity and peripheral insulin resistance.

Poor early glycemic control correlates with adverse maternal and neonatal outcomes including preeclampsia, macrosomia, fetal congenital anomalies, prematurity, and perinatal mortality. Monitoring glucose control and glycosylated hemoglobin (Hgb A1C) levels is essential to improve maternal and neonatal outcomes. Therefore, preconceptional counseling should be an important part of maternal management for all women with preexisting DM. Unfortunately, less than one-third of women with type 1 or 2 DM actively seek preconceptional counseling. The impacts of PGDM should be discussed during routine gynecologic or primary care visits.

Obstetrical management of women with PGDM includes controlling blood glucoses with a goal of near-normal glucose control (fasting glucose ≤95 mg/dL, 1-hour postprandial glucose ≤140 mg/dL, and 2-hour postprandial glucose ≤120 mg/dL). Most women with PGDM will already be receiving insulin therapy, and insulin requirements will increase from the first to third trimester.

Although women with type 2 DM tend to have milder disturbances in glucose, in general, neonatal outcomes are similar to those with type 1 DM. Women with type 1 DM are more likely to have pregestational microvascular complications, increased risk of hyper- and hypoglycemia, and diabetic ketoacidosis, which all contribute to increased risk of fetal growth restriction.

1. **Maternal complications.** Obstetric complications of PGDM include miscarriage, preeclampsia, gestational hypertension, polyhydramnios, preterm delivery, worsening diabetic retinopathy and nephropathy, and increased risk of requiring a cesarean section. Preterm delivery is not typically associated with preterm labor but rather with signs of fetal distress such as growth restriction or maternal hypertension necessitating preterm delivery.
2. **Congenital malformations.** Congenital malformations occur two- to fourfold higher in PGDM compared with nondiabetics, with incidence for type 1 DM 2.9% to 7.5% of offspring and for type 2 DM 2.1% to 12.3% of offspring. Hyperglycemia during organogenesis (weeks 5 to 8 of gestation) reflected by an increase in Hgb A1C levels correlates directly with frequency of anomalies. The rate of congenital anomalies with Hgb A1C of 5.5% is 2%; this number rises to 2.7% with Hgb A1C 6.2%, 4% with Hgb A1C 7.6%, and up to 20% with Hgb A1C ≥14%. With good glycemic control, the rate of congenital malformations in PGDM can fall to approximate levels of nondiabetic

mothers, and a 30% reduction in risk can occur for every 1% lowering of Hgb A1C.

Congenital anomalies in order of prevalence include congenital heart disease, central nervous system (CNS) defects, urogenital defects, limb defects, orofacial clefts, and rarely, yet highly associated with DM, sacral agenesis/caudal dysplasia (15% to 25% of all cases result from DM). Most prevalent cardiac defects include tetralogy of Fallot, transposition of the great arteries, septal defects, and anomalous pulmonary venous return. CNS defects include anencephaly, spina bifida, encephalocele, hydrocephaly, and anotia/microtia.

3. **Intrauterine growth restriction (IUGR).** Although macrosomia is a risk of DM, a poor intrauterine environment can also lead to growth restriction. In pregnant women with PGDM plus preexisting hypertension or microvascular complications, there is a 6- to 10-fold higher risk relative to those without vascular disease of having a fetus with growth restriction.
4. **Further complications.** The aforementioned complications are more specifically associated with PGDM. Other complications that overlap with diabetic fetopathy that occur due to glycemic derangements later in the pregnancy are addressed later in this chapter.

B. GDM. GDM is defined as any carbohydrate intolerance first diagnosed during pregnancy. This does not exclude the possibility of some undiagnosed PGDM. GDM prevalence has been increasing in association with societal increase in obesity and is directly related to the prevalence of type 2 DM in a given population. GDM currently complicates up to 14% of all pregnancies and accounts for the vast majority of all cases of diabetes in pregnancy. Furthermore, 15% to 50% of women diagnosed with GDM will go on to be diagnosed with type 2 DM later in life. Thus, all women with GDM should be screened postpartum for persistent glucose intolerance.

1. **Screening and diagnosis.** Appropriate screening and diagnosis are crucial first steps to minimize the risks of GDM to the mother and infant. Risk factors for GDM should be screened at the first prenatal visit (Table 62.2). Women at risk for undiagnosed type 2 DM typically warrant screening at the first prenatal visit for potential preexisting glucose intolerance. Screening for all women is by glucose challenge at 24 to 28 weeks. Such screening was first developed by O'Sullivan and Mahan in 1950 with criteria established in 1964. Subsequent modifications have been made to the initial criteria, and controversies exist in the determination of exact thresholds for diabetic screening and diagnosis.

   Currently, in the United States, most women are screened using a two-step method. The first step is a nonfasting 50-g oral glucose load with a 1-hour postprandial cutoff of either ≤140 or ≤130 mg/dL. The cutoffs based on work by Carpenter and Coustan between 130 and 140 mg/dL demonstrate improved sensitivity compared to using the 130-mg/dL limit. It is most important to know your local obstetrical practices in interpreting the prenatal evaluation. For those above the cutoff, the second step is a 100-g oral glucose load after a 12-hour fast, with 1-, 2-, and 3-hour postload glucoses.

Table 62.2. Risk Factors for Gestational Diabetes Mellitus

Advanced maternal age
Maternal obesity
High parity
Previous delivery of a macrosomic infant
Family history of type 2 DM
Maternal short stature
Polycystic ovarian syndrome
Prior GDM
Prior neonatal death
Prior cesarean section
Previous stillbirth or congenital malformations
High blood pressure during pregnancy
Multiple pregnancy

DM, diabetes mellitus; GDM, gestational diabetes mellitus.

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study published in 2008 was the first to link increasing 1- and 2-hour postprandial plasma glucoses with birth weight >90%, primary cesarean section, neonatal hypoglycemia, preterm delivery, shoulder dystocia, neonatal intensive care admission, hyperbilirubinemia, and preeclampsia. Subsequently, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) developed recommendations based on the HAPO study to establish a one-step screening for all women. Their recommendation entailed a fasting 75-g glucose load with 1- and 2-hour postload glucose evaluation. A one-step screening process is relatively standard across the world with support from the World Health Organization (WHO) and the American Diabetes Association (ADA). However, a 2013 National Institutes of Health (NIH) Consensus Development Conference evaluated the current data and supported the continued use of a two-step tiered approach to diagnosis, citing concerns that transition to the current one-step method would certainly increase the diagnosis of GDM with all of its associated costs of increased monitoring and intervention but with unclear benefits to maternal and neonatal outcomes. Thus, the majority of pregnancies in the United States are evaluated by the two-step method. It is important to understand the local obstetrical screening and diagnostic practices for consistency of care from pre- to postnatal.

2. **Treatment.** Standard GDM management has aimed at tight control of maternal glucose levels to diminish the potential for fetal hyperinsulinemia. This can be achieved in three ways, escalating as the clinical scenario dictates, from diet control to oral antidiabetic agents to insulin therapy. Appropriate dietary management includes carefully calculated total daily caloric intake based on body mass index (BMI) as well as managing the dietary components of carbohydrates, protein, and fat to optimize appropriate weight gain during pregnancy. Insulin is recommended as first-line therapy by the ADA for cases refractory to nutrition therapy and exercise. Although multiple decision factors must go into considering insulin use for GDM, fetal abdominal circumference >70% after 29 to 30 weeks' gestation is an indication for the need for insulin therapy. Oral antidiabetic agents are not approved by the U.S. Food and Drug Administration for the treatment of GDM, cross the placenta, and lack long-term neonatal safety data. Nevertheless, although insulin is preferred when pharmacologic treatment of GDM is needed, there may be clinical situations in which oral agents are indicated. These are reasonable alternatives to insulin in the context of discussing safety data and risk of treatment failure ultimately requiring insulin. Glyburide is a sulfonylurea that binds to pancreatic beta cell adenosine triphosphate calcium channel receptors to increase insulin secretion and sensitivity of peripheral tissues. Metformin is a biguanide that inhibits hepatic gluconeogenesis and glucose absorption and stimulates glucose uptake in peripheral tissues.

III. MATERNAL MANAGEMENT AND DELIVERY. Maternal prenatal management is vital to outcomes both for the mother and infant and typically will include the following surveillance:

A. Close follow-up with obstetrician throughout pregnancy, with close attention to glucose management

B. Consultation with a registered dietitian and potentially maternal–fetal medicine and endocrinology based on local referral practices as well as disease severity

C. First trimester prenatal labs including Hgb A1C, TSH, 24-hour urine, electrocardiogram

D. Low-dose aspirin is started at 12 to 18 weeks, optimally prior to 16 weeks

E. Detailed fetal anatomy ultrasound at 18 to 20 weeks, with consideration for fetal echocardiogram

F. Serial fetal growth ultrasounds throughout the third trimester to monitor for macrosomia

G. Fetal monitoring via nonstress testing, or biophysical profiles, typically starting at 32 weeks for patients on insulin

H. Without vascular complications and with well-controlled blood glucose values, most patients with DM are delivered at 39 0/7 to 39 6/7 weeks. If blood glucose values are poorly controlled or in women with vascular complications, delivery is considered at 36 0/7 to 38 6/7 weeks, or earlier in select cases.

I. Cesarean delivery should be considered if the estimated fetal weight is >4,500 g in women with diabetes.

IV. FETAL AND NEONATAL EFFECTS OF MATERNAL DIABETES MELLITUS

A. Fetal effects of maternal DM. In the first trimester, thus primarily in women with PGDM, maternal hyperglycemia increases the risk of diabetic embryopathy resulting in congenital anomalies outlined earlier, as well as increased risk of spontaneous abortion.

Maternal hyperglycemia in the second and third trimesters can result in a diabetic fetopathy characterized by fetal hyperglycemia, hyperinsulinemia, and macrosomia. Chronic fetal hyperinsulinemia increases fetal metabolic rates, leading to increased oxygen consumption. The oxygen needs may not be met by the placental blood flow, resulting in fetal hypoxemia. This sequence of events contributes to increased mortality, metabolic acidosis, and increased erythropoiesis in the fetus. Heightened erythropoietin synthesis causes polycythemia and increased catecholamine production. Elevated catecholamines cause fetal hypertension and cardiac hypertrophy. Furthermore, redistribution of iron stores from developing organs to the red blood cell mass results from polycythemia; in turn, cardiac and neurodevelopment can be affected.

Hyperinsulinemia has been linked to impaired lung maturation, increasing the risk for neonatal respiratory distress. Hyperinsulinemia also stimulates overgrowth of insulin-sensitive tissues including the heart, liver, muscle, and subcutaneous fat, leading to macrosomia with truncal asymmetry, in which there is a disproportionate ratio of the shoulder-to-head or abdomen-to-head ratio (ponderal index). This relative disproportion increases the risk of shoulder dystocia, brachial plexus injury, fractures, and neonatal depression due to difficulty of extraction. One cohort series demonstrated that, due to increased ponderal index, obstetrical and neonatal outcomes are worse in infants of diabetic mothers (IDMs) who are large for gestational age (LGA) relative to infants of nondiabetic mothers who are LGA.

B. Neonatal effects of maternal DM. As explained by the *in utero* mechanisms earlier, the neonatal effects of DM include the following:

1. **Mortality.** IDMs are at increased risk for intrauterine fetal demise or postnatal mortality.
   a. For women with PGDM, the risk of spontaneous abortion, intrauterine demise, and perinatal mortality rises concomitant with elevations Hgb A1C >6. In women with type 1 DM, mortality is largely attributable to complications of prematurity and congenital anomalies. For those with type 2 DM, mortality is attributable to stillbirth, birth asphyxia or hypoxic ischemic encephalopathy, and intra-amniotic infections.
   b. For women with GDM, mortality is more often attributable to intrauterine fetal demise in the setting of poor glycemic control.
2. **Prematurity.** Thirty-six percent of IDMs are born at <38 weeks' gestation, with just over half being born late preterm at 34 to 37 weeks, with the remainder born at <34 weeks. The majority of prematurity is associated with maternal complications of hypertension or preeclampsia, or with fetal IUGR necessitating preterm delivery. In the recent past, more infants were electively induced prior to 39 weeks due to

concern for macrosomia. However, with obstetrical efforts to curtail unnecessary late preterm and early term inductions, the incidence of late preterm IDMs is expected to fall.

3. **LGA.** A large for gestation infant is defined as having a birth weight >90th percentile for gestational age and occurs in 36% to 47% of IDMs, relative to 7% to 9% of infants of nondiabetic women. Because of the distribution of weight in IDMs, there is a 3-fold increased risk of shoulder dystocia and 10-fold increase in brachial plexus injury at the time of delivery.
4. **Respiratory distress** occurs in approximately 30% to 40% of IDMs. This can be partially accounted for by increased rates of prematurity, but IDMs are more likely to develop respiratory distress syndrome (RDS) at any given gestational age as hyperinsulinemia interferes with glucocorticoid induction of surfactant synthesis. Diminished surfactant can lead to increased rates of both RDS and pneumothorax due to less compliant lungs in larger infants. Transient tachypnea of the newborn (TTN) occurs 2 to 3 times more frequently in IDMs, with both increased rates of cesarean section and inherent reduced fluid clearance.
5. **Hypoglycemia** occurs in approximately 25% of IDMs, partly, but not completely, dependent on glycemic control prenatally and peridelivery. Even in rigorously controlled type 1 DM women, 14% of infants experience hypoglycemia after birth. As Pederson noted in 1952 in his hyperglycemia hyperinsulinism hypothesis, maternal hyperglycemia is perpetuated through the placenta to fetal hyperglycemia, which causes hypertrophy of the fetal pancreatic islet tissue with hypersecretion of insulin in a fetal attempt to lower the plasma glucose. At birth, the maternal glucose supply is abruptly discontinued with clamping of the umbilical cord, but the infant cannot acutely decrease the insulin secretion, leading to neonatal hypoglycemia. Onset of hypoglycemia is typically within the first few hours after birth and lasts 2 to 4 days as neonatal insulin levels adjust. These infants frequently need intravenous (IV) glucose supplementation to maintain normal plasma glucose levels. Routine testing of insulin levels is not necessary in the majority of IDMs because the level is known to be initially elevated but will fall appropriately over time. Hence, supportive care and close prefeed glucose monitoring are standard for IDMs. Infants requiring glucose infusion rates exceeding 8 to 10 mg/kg/minute beyond the first week of life require further evaluation of their hypoglycemia, including testing of insulin and cortisol during a period of relative hypoglycemia. Severe, prolonged symptomatic hypoglycemia can result in permanent neurologic injury; thus, timely screening and intervention is important to long-term outcomes (see Chapter 24).
6. **Hypocalcemia.** Defined as total serum calcium <7 μg/dL (1.8 mmol/L) or ionized calcium <4 mg/dL (1 mmol/L), hypocalcemia occurs in 5% to 30% of IDMs. The calcium nadir typically occurs between 24 and 72 hours of life. For the majority of term infants who are feeding well, the hypocalcemia is asymptomatic and resolves

with oral feeding. Thus, routine screening is not necessary for all IDMs. However, evaluation should occur in all infants with jitteriness, respiratory distress or apnea, seizures, neonatal depression, suspected infection, or prematurity (see Chapter 25). For the ill infant for whom enteral supplementation is not possible, calcium can be administered as an IV bolus, typically 200 mg/kg of calcium gluconate or via continuous infusion of IV fluids with calcium.

7. **Hypomagnesemia.** Defined as serum magnesium concentration <1.5 mg/dL (0.75 mmol/L), hypomagnesemia occurs in up to 40% of IDMs within the first 72 hours of life. Contributing factors include maternal hypomagnesemia related to urinary losses and prematurity. With the increased use of maternal magnesium predelivery for neuroprotection in the preterm population, hypomagnesemia is now less common. As with hypocalcemia, this deficiency is typically transient, asymptomatic, and does not require therapy. However, any infant screened for hypocalcemia should also be screened for hypomagnesemia. Hypomagnesemia can reduce parathyroid hormone (PTH) secretion and responsiveness, which in turn will exacerbate hypocalcemia until the hypomagnesemia is corrected.
8. **Hyperbilirubinemia** occurs in approximately 25% of IDMs. Contributing factors include prematurity, macrosomia, and polycythemia. All IDMs should undergo routine screening for jaundice either with transcutaneous or blood testing, with phototherapy as indicated (see Chapter 26).
9. **Polycythemia**, defined as a central venous hematocrit >65%, occurs in 5% of IDMs. In one series, 17% of IDMs had hematocrits >60%. Polycythemia results from increased erythropoietin resulting from chronic fetal hypoxemia. Other contributors can include transfusion of placental blood with maternal or fetal distress around the time of delivery.

   Polycythemia can be associated with hyperviscosity, which can cause vascular sludging, ischemia, and infarction of vital organs. This may explain the increased incidence of renal vein thrombosis (RVT) seen in IDMs. As such, infants of poorly controlled DM should have screening of a central venous hematocrit within 12 hours of birth. Routine hematocrits are not necessary for all IDMs, but infants should be screened if maternal glycemic control was poor, if the infant is notably macrosomic, or if the infant has other clinical signs such as deeply ruddy appearance or early signs of jaundice.
10. **RVT** may occur *in utero* or postpartum due to polycythemia and hyperviscosity. Postnatal presentation includes hematuria, flank mass, hypertension, or embolic phenomena. Whereas half of RVT is associated with prematurity and with central venous lines, IDMs account for almost 15% of cases.
11. **Small left colon syndrome** is a rare form of bowel obstruction highly associated with maternal DM. Forty percent to 50% of all cases of small left colon syndrome occur in IDMs. As presentation is typically abdominal distention with inability to pass stool, an alternated

differential diagnosis includes Hirschsprung disease. Infants with small left colon syndrome have appropriate ganglion cells in the rectum, but the left colon, past the splenic flexure, is small in caliber. Diagnosis is by hyperosmotic contrast enema, which will often also result in evacuation of the colon. Small left colon can often be treated conservatively with enemas.

12. **Hypertrophic cardiomyopathy** is characterized by thickening of the intraventricular septum and/or ventricular walls, with reduction in size of the ventricular chambers of the heart. Hypertrophic cardiomyopathy occurs with increased frequency in PGDM and GDM but has been shown to be more prevalent in PGDM (as high as 40% in one series) even in the setting of strict glycemic control. The hypertrophy can be detected in late second to early third trimester; thus, careful ultrasound screening or fetal echocardiography with concentration on ventricular size is recommended. Fetal hyperinsulinism triggers increased fat and protein synthesis, leading to hypertrophied and disorganized cardiac myocytes. The structural hypertrophy can lead to obstruction of left ventricular outflow. Although most infants with hypertrophic cardiomyopathy are asymptomatic, 5% to 10% may present with respiratory distress, signs of heart failure, or poor cardiac output. The standard for diagnosis is echocardiography, which should be reserved for symptomatic infants or those with notable intraventricular hypertrophy on prenatal ultrasound. For those infants with outflow tract obstruction, supportive care includes increasing ventricular filling by IV fluid administration and propranolol to slow the heart rate to allow better ventricular filling. Inotropes are likely to worsen the outflow obstruction by decreasing the ventricular size, so they should generally be avoided. Most infants will improve with supportive care within 2 to 3 weeks of birth, and most echocardiographic hypertrophy will resolve within 6 to 12 months.

    Less commonly, IDMs may develop a congestive cardiomyopathy with more diffuse hypertrophy related to perinatal hypoxemia or metabolic derangements such as hypoglycemia or hypocalcemia that lead to a poorly contractile heart. Supportive care and correction of metabolic derangements can reverse the congestive cardiomyopathy.

13. **Poor feeding** is a significant issue especially in poorly controlled IDMs, leading to prolonged hospital stays and interruption of parental–infant bonding. Poor feeding can be related to prematurity or respiratory distress associated with IDM; however, it is often present in the absence of other complicating factors. In a series of 150 IDMs at Brigham and Women's Hospital, 37% of IDMs experienced poor feeding.

V. NEONATAL MANAGEMENT OF IDMS.

Just as the prenatal management of a pregnancy complicated by DM is a combined effort of obstetricians, maternal–fetal medicine specialists, endocrinologists, and dietitians, so must the neonatal management of the IDM be a multidisciplinary effort. Seamless communication of prenatally diagnosed anomalies as well as prenatally predicted

complications from the obstetric provider to the pediatric team is imperative. Additional consultation from a neonatologist and other pediatric subspecialists may be warranted prenatally or once the infant has been born to aid in postnatal management. A balance must be made to provide appropriate screening and evaluation while promoting infant–maternal bonding.

A. Delivery room care. Proper assessment of the need for neonatal resuscitation should be made based on gestational age, predicted birth weight, prenatally diagnosed congenital anomalies, mode of delivery, and any complications of labor. The appropriate Neonatal Resuscitation Program (NRP)-trained team should be in attendance to provide care specifically to the infant. The initial evaluation immediately after birth will determine the need for further interventions. If the infant does not require resuscitative measures, the infant should have timely skin-to-skin care and initiation of breastfeeding in the delivery room.

Any infant with cyanosis in the delivery room should have pulse oximetry evaluation with specific attention to the cardiovascular and respiratory systems given the infant's risk of RDS, TTN, congenital heart disease, and hypertrophic cardiomyopathy.

B. Postdelivery management. IDMs are at increased risk for postnatal hypoglycemia and should have systematic evaluation of serum glucose measurements. Infants should feed soon after birth either breast milk or formula, with preference for breastfeeding, with bedside glucose monitoring within the first 1 to 2 hours of life. Prior practices of feeding glucose water were found to actually increase insulin release, and therefore, this is not recommended. The Committee on the Fetus and Newborn provide guidance in their 2011 clinical report on target glucoses in the newborn. Target glucose within the first 24 hours of life is $\geq$45 mg/dL prior to routine feedings. Prefeed glucoses should be followed through the first 36 hours of life with feeding established and normalized glucose levels.

Any infant with lethargy, respiratory distress, jitteriness, apnea, or seizures should have immediate bedside glucose testing as a subset of IDMs will require immediate and aggressive treatment of hypoglycemia. Any low bedside testing should also have serum glucose samples run by the laboratory for confirmation, but such confirmation should not delay timely treatment of hypoglycemia. For infants with glucose $<$25 mg/dL or with persistent glucose $<$40 mg/dL despite adequate feeding within the first 4 hours of life, or $<$35 mg/dL or persistent $<$45 mg/dL after feeding in the first 24 hours of life, warrant administration of IV glucose. Initial boluses of dextrose 10% in water ($D_{10}W$) 2 mL/kg (200 mg/kg) should be administered to bring the glucose into the 40 to 50 mg/dL range. Then, a continuous infusion of $D_{10}W$ should be initiated. An infusion of 60 mL/kg/day of $D_{10}W$ will result in a GIR of approximately 4 mg/kg/minute, and a $D_{10}W$ infusion rate of 100 mL/kg/day will result in a GIR of approximately 7 mg/kg/minute. Of those requiring IV glucose infusion, a small subset will require a GIR in excess of 8 to 10 mg/kg/minute, necessitating placement of a central catheter, typically an umbilical venous catheter, to maintain euglycemia (see Chapter 24).

Following transition from the delivery room, ongoing evaluation of the IDM should include screening for hyperbilirubinemia, polycythemia,

hypocalcemia, and hypomagnesemia as indicated. Venous hematocrit should be obtained within the first 12 hours of life for those at risk. Heightened attention to the potential for jaundice should include close clinical monitoring of bilirubin by either bedside transcutaneous bilirubin screening or serum screening. Many units routinely screen all infants at 36 hours of life with a transcutaneous bilirubinometer, with earlier screening if jaundice is noted. For infants who fall into the high- or high-intermediate risk zone on the bilirubin nomogram, a serum bilirubin is sent for confirmation, and phototherapy is initiated when indicated.

VI. LONG-TERM EFFECTS. Prenatal exposure to hyperglycemia has been shown to increase longer term metabolic and neurodevelopmental outcomes in the offspring of women with DM.

A. Metabolic syndrome is classified as a combination of obesity, hypertension, dyslipidemia, and glucose intolerance. This syndrome was originally described in Pima Indians, a population with high rates of gestational diabetes. In the offspring of these women with GDM, 45% developed type 2 DM by their mid-20s and more than two-thirds by their mid-30s. The increased risk persisted despite accounting for paternal diabetes (factoring in genetic risk), the offspring's BMI, and age of onset of DM in parents, pointing to contribution from the intrauterine environment. Metabolic syndrome has now been shown to have increased incidence in infants who were LGA at birth or born to women with gestational diabetes. Risk of metabolic syndrome was found in a population-based study out of Denmark to be 4 times greater in offspring of GDM women and 2.5 times for offspring of PGDM women.

B. Obesity. Multiple studies have shown an association between DM and obesity in their offspring. Although macrosomia at birth often resolves within the first year of life, later in childhood, IDMs whose mothers had type 1 or 2 DM tend to have higher BMIs than controls. Offspring of women with gestational diabetes have also been shown to have higher BMIs, higher risk of being overweight, and higher fasting insulin levels relative to offspring of nondiabetic women. Overall, the risk of being overweight is approximately twofold for offspring of women with PGDM and GDM.

C. Diabetes. IDMs have an increased risk of developing diabetes later in life. Type 1 and type 2 DM are both known to be influenced by genetics, with type 1 diabetes occurring 4 times more often in offspring of women with type 1 DM. The lifetime risk of a child of a type 2 DM is 5 to 10 times higher than age- and weight-matched controls without a family history. The *in utero* environment has also been shown to contribute to impaired glucose tolerance later in life, with the presence of glucose intolerance correlating with elevated amniotic fluid insulin concentrations during pregnancy.

D. Impaired neurodevelopmental outcomes. Poor maternal glycemic control can adversely affect the developing brain. However, it is important to note that neurodevelopmental outcomes of the well-controlled DM are similar to those of infants of nondiabetic mothers.

Increasing Hgb A1C levels are associated with decreasing head circumference and decreased intellectual performance at 3 years of age. Another study correlated decrements in psychomotor development at 6 to 9 years, with elevated maternal ketone concentrations during the second and third trimesters.

Suggested Readings

American College of Obstetricians and Gynecologists. ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists. Number 60, March 2005. Pregestational diabetes mellitus. *Obstet Gynecol* 2005;105(3):675–685.

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Metzger BE, Lowe LP, Dyer AR, et al; for HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 2008;358(19):1991–2002.

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63 Differences of Sex Development

Jonathan M. Swartz and Yee-Ming Chan

KEY POINTS

- Differences of sex development (DSD) are a heterogeneous group of conditions broadly defined by atypical development of genetic, gonadal, and/or anatomic sex. DSD frequently present in the newborn period with atypical genital appearance.
- The rapid evaluation of infants with atypical genital appearance is critical to identify and, if necessary, treat salt-wasting congenital adrenal hyperplasia (CAH), which is potentially life-threatening.
- The main goal of sex/gender designation in children with DSD is to attempt to match the child's future gender identity. This is a challenging, imperfect, and humbling endeavor.

I. DEFINITION AND NOMENCLATURE. The original term *disorders of sex development* (DSD) was introduced in 2006 to replace older terms such as *ambiguous genitalia*, *pseudohermaphroditism*, and *intersex* to denote atypical development of genetic, gonadal, and/or anatomic sex. However, the term has been criticized for being stigmatizing (leading many to use "differences" in place of "disorders"); surveys of patients and families have demonstrated discomfort with the term, and some patient organizations reject the term entirely. When speaking with an individual patient and the patient's family, it is generally better to refer to the patient's specific condition.

Examples of presenting findings of DSD in the newborn period include the following:

A. Atypical genital appearance

B. A penis and bilaterally nonpalpable testes (cryptorchidism)

C. Unilateral cryptorchidism with hypospadias

D. Severe penoscrotal, scrotal, or perineal hypospadias, with or without microphallus, even if the testes are descended

E. Apparently female appearance with enlarged clitorophallus (clitoromegaly) and/or inguinal hernia(s) or palpable gonad(s)

F. Asymmetry of in size, pigmentation, and/or rugation of labioscrotal folds

G. Discordance of external genital appearance with prenatal karyotype

Because internal genital anatomy, karyotype, and sex/gender designation cannot be determined from a baby's external appearance, a thorough evaluation is required. The evaluation must be expedited because of the possibility of salt-wasting congenital adrenal hyperplasia (CAH), which can be life-threatening within the first week of life, and because of the urgency felt by most parents in designating a sex/gender of rearing.

II. IMMEDIATE POSTNATAL CONSIDERATIONS PRIOR TO SEX DESIGNATION. The discovery of a DSD at birth can be unsettling to parents, even if concern about a possible DSD had been identified prenatally, because birth may be the first time parents truly confront issues raised by the DSD. The care team must balance acknowledging and discussing parents' potential distress with providing appropriate reassurance and validation of their anxiety, concern, and feelings of uncertainty. Different families have different needs, and frequently and explicitly checking in with the parents about the support the team is providing can help with striking and maintaining this balance.

The medical team should avoid telling parents that surgery can "fix" the child's issue because this implies that only anatomic features of the DSD warrant concern and overlooks long-term medical, functional, and psychosocial issues raised by the DSD. Focusing primarily on genital surgery may interfere with counseling about these long-term issues and may make parents feel that their other concerns are being dismissed.

Although delays in sex/gender designation can be distressing for parents, care must be taken to avoid drawing premature conclusions. Until a sex/gender designation is made, it is best to avoid gender-specific names, pronouns, or other references. Prompt consultation with a pediatric endocrinologist will facilitate the evaluation, and in most cases, enough information can be collected in 2 to 4 days to allow initial sex/gender designation, although some cases may take 1 to 2 weeks or longer. The physician should examine the infant's genitalia in the presence of the parents then discuss with them the process of typical genital development, how the development of their child's genitalia occurred differently, and that further tests will be required before a decision can be made regarding the infant's sex. Circumcision is contraindicated until a determination is made concerning the need for surgical repairs.

III. TYPICAL SEX DEVELOPMENT. The process of gonadal differentiation and genital development is depicted in Figure 63.1.

A. Genetic sex refers to the sex chromosome complement.

B. Gonadal sex refers to the development of the gonads as normal or dysgenetic ovaries, testes, or ovotestes. The bilateral genital ridges give rise to undifferentiated gonads around 6 weeks of gestation and begin to differentiate by 7 weeks. *SRY*, which encodes the primary testis-determining transcription factor on the short arm of the Y chromosome, promotes the gonads to develop into testes; in the absence of *SRY*, the gonads typically develop as ovaries. Several genes contribute to testicular and/or ovarian development, including *NR5A1* (*SF1*), *NR0B1* (*DAX1*), *SOX9*, *WNT4*, and *RSPO1*.

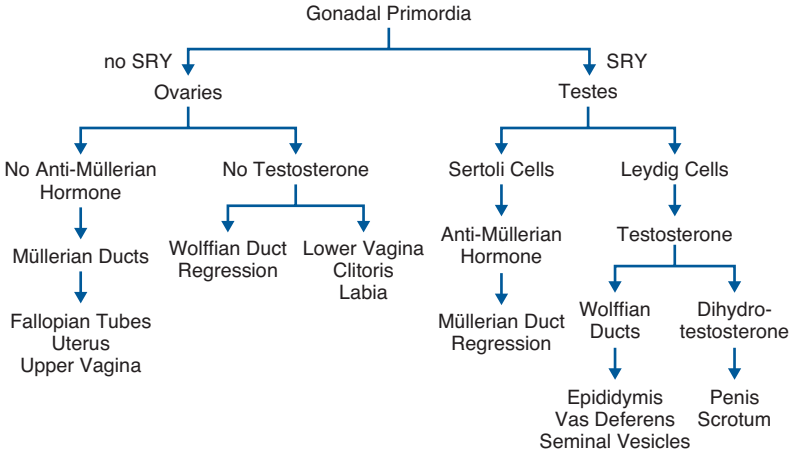

Figure 63.1. The process of gonadal, internal genital, and external genital differentiation. (Reprinted with permission from Holm IA. Ambiguous genitalia in the newborn. In: Emans SJ, Laufer M, Goldstein D, eds. *Pediatric and Adolescent Gynecology*. Philadelphia, PA: Lippincott Williams & Wilkins; 1998:53.)

C. Anatomic sex refers to the external and internal genitalia. The testis secretes two hormones that affect genital development: Sertoli cells produce anti-müllerian hormone (AMH, also called müllerian inhibiting substance or factor, MIS or MIF), and Leydig cells produce testosterone.

1. **Internal genitalia.** The müllerian ducts give rise to the uterus, fallopian tubes, cervix, and upper vagina; AMH causes regression of the müllerian ducts. Testosterone prevents the regression of the wolffian ducts and promotes their development into the vas deferens, seminal vesicles, and epididymis; in the absence of testosterone, the wolffian ducts regress. Müllerian duct regression and wolffian duct development require high *local* concentrations of AMH and testosterone, respectively. Asymmetric absence of these factors on one side (due to absence of a testis or impaired testicular function) may result in ipsilateral retention of müllerian structures and regression of wolffian structures.
2. **External genitalia.** The enzyme 5α-reductase, present in high concentration in genital skin, converts testosterone to dihydrotestosterone (DHT). DHT is the primary hormone responsible for virilizing the external genitalia, including the genital tubercle and labioscrotal folds, which in the presence of DHT give rise to the penis and scrotum, respectively. In the absence of DHT, these structures develop into the clitoris and labia majora. Testicular descent from the abdomen to the inguinal ring requires insulin-like peptide 3 (INSL3), and descent from the inguinal ring into the scrotum requires testosterone. This generally occurs in the last 6 weeks of gestation.

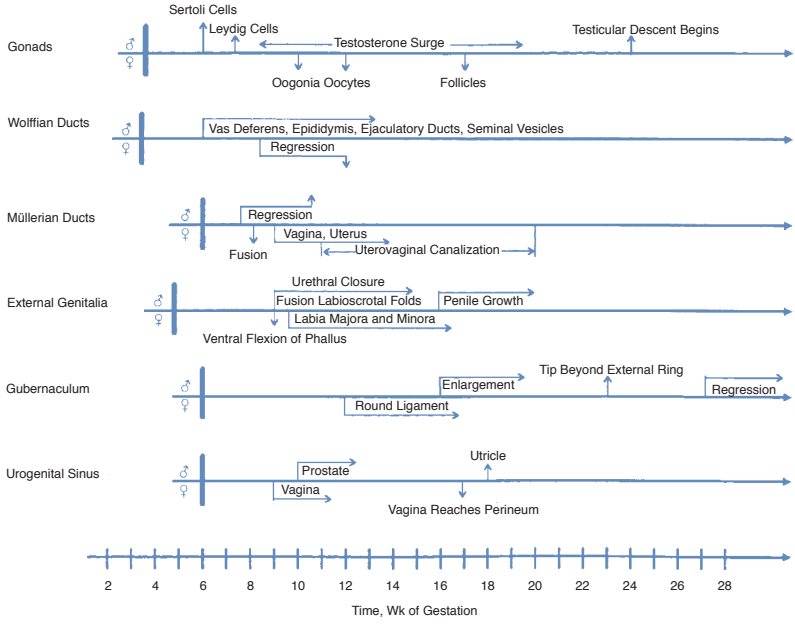

Figure 63.2. Timelines for six aspects of sex differentiation. (Adapted from White PC, Speiser PW. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Endocr Rev* 2000;21[3]:245–291 and Barthold JS, Gonzalez R. Intersex states. In: Gonzalez ET, Bauer SB, eds. *Pediatric Urology Practice*. Philadelphia, PA: Lippincott Williams & Wilkins; 1999:547–578.)

D. Time course. The timeline of fetal sex development is depicted in Figure 63.2 and Table 63.1.

1. **First trimester.** Testicular synthesis of testosterone is stimulated by human chorionic gonadotropin (hCG) produced by the placenta, acting through the common receptor for luteinizing hormone (LH) and hCG. The first trimester is the only period during which the labioscrotal folds are susceptible to fusion. If an XX fetus is exposed to excess androgens during the first trimester, the clitorophallus and labioscrotal folds will virilize and may appear indistinguishable from a normal male penis and scrotum, although the latter will be empty in the absence of gonadal descent.
2. **Second and third trimesters.** Testicular androgen production is stimulated by LH from the fetal pituitary and is responsible for penile growth, scrotal maturation (rugation, pigmentation, and thinning), and testicular descent. High intrauterine concentrations of testosterone are thought to influence brain development and to affect later behavior, sexual orientation, and gender identity.

Table 63.1. Timetable of Typical Male Sex Development

Days after Conception	Events of Sex Development
19	Primordial germ cells migrate to the genital ridge
40	Genital ridge forms an undifferentiated gonad
44	Müllerian ducts appear; testes develop
62	Anti-müllerian hormone (from testes) becomes active
71	Testosterone synthesis begins (induced by placental hCG)
72	Fusion of the labioscrotal swellings
73	Closure of the median raphe
74	Closure of the urethral groove
77	Müllerian regression is complete

hCG, human chorionic gonadotropin.

IV. NURSERY EVALUATION OF A NEWBORN WITH A SUSPECTED DIFFERENCE OF SEX DEVELOPMENT

A. History

1. **Maternal drug exposure** during pregnancy, such as to androgens (e.g., testosterone, danazol), drugs that interfere with androgen synthesis or action (e.g., finasteride, spironolactone), or antiseizure medications (e.g., phenytoin, trimethadione)
2. **Maternal virilization** during pregnancy due to incompletely suppressed maternal CAH, a virilizing adrenal or ovarian tumor, or placental aromatase deficiency
3. **Prenatal findings** of genital ambiguity; sex-chromosome mosaicism/chimerism; a sex-chromosome complement discordant with phenotypic sex (whether assessed on prenatal ultrasound or at birth); and potential DSD-associated conditions, such as oligohydramnios, renal anomalies, or skeletal abnormalities (e.g., campomelic dysplasia associated with *SOX9* mutations)
4. **Family history** of CAH, hypospadias, cryptorchidism, infertility, pubertal delay, genital surgery, genetic syndromes, or consanguinity. Death of a male family member from vomiting and/or dehydration in early infancy may suggest undiagnosed CAH.

B. Physical examination

1. **External genitalia.** The examiner should note the stretched clitorophallic length, width of the corpora, engorgement, presence of chordee (downward curvature), position of the urethral orifice, presence or

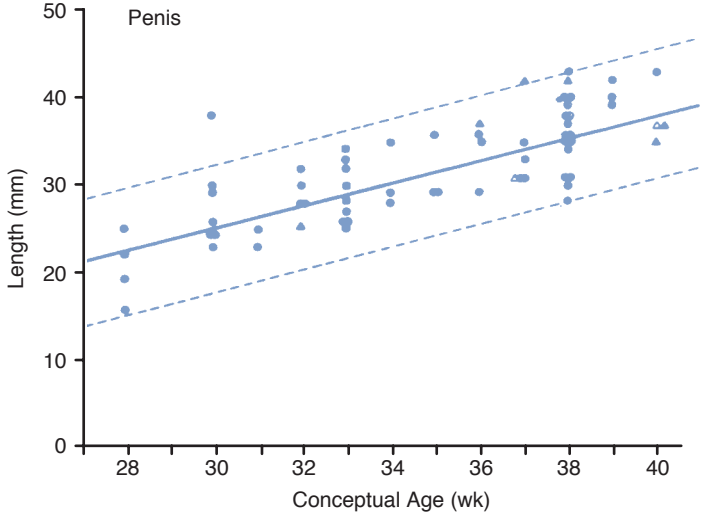

Figure 63.3. Stretched penile length of premature and full-term male babies (*closed circles*), showing lines of mean ±2 standard deviations. Superimposed are data for two small for gestational age infants (*open triangles*), seven large for gestational age infants (*closed triangles*), and four twins (*closed boxes*), all of whom are in the reference range. (Reprinted from Feldman KW, Smith DW. Fetal phallic growth and penile standards for newborn male infants. *J Pediatr* 1975;86[3]:395–398. Copyright © 1975 Elsevier. With permission.)

absence of a distinct vaginal opening, and pigmentation and symmetry of the labioscrotal folds. A full-term male infant typically has a stretched penile length of at least 2.5 cm, measured from the pubic ramus to the tip of the glans (Fig. 63.3), and usually 1 cm or more in width. A full-term female infant typically has a clitoris <1 cm in length and <0.5 cm in width. Posterior fusion of the labioscrotal folds is assessed by determining the **anogenital ratio**, which is the distance between the anus and the posterior fourchette divided by the distance between the anus and the base of the clitorophallus. An anogenital ratio >0.5 indicates first-trimester androgen exposure.

2. **Gonadal size, position, and descent** should be carefully noted. A gonad below the inguinal ligament is usually a testis (normal or dysgenetic) but may be an ovotestis or even a portion of the uterus herniating into the inguinal canal. Atypical genital appearance with bilateral nonpalpable gonads should raise immediate concern for salt-wasting CAH.
3. **Associated anomalies** should be noted. Additional features may indicate a more generalized disorder, although such features may not be present at birth. Denys-Drash syndrome (Wilms tumor and/or diffuse glomerulosclerosis) or WAGR (**W**ilms tumor, **A**niridia, **G**enitourinary anomalies, and mental **R**etardation) syndrome, both due to mutations of *WT1* (11p13), can cause DSD in XY infants. A few examples of other conditions associated with DSD include Smith-Lemli-Opitz,

Robinow, Antley–Bixler, Goldenhar syndromes, campomelic dysplasia, and trisomy 13.

C. Diagnostic tests

1. **Laboratory tests** are tailored to the differential diagnosis.
   a. Karyotype, chromosomal microarray and/or fluorescent *in situ* hybridization (FISH) are options to provide differing but overlapping information about the chromosomal complement of an individual. Turnaround time varies by institution and lab, and choice of test should be tailored to local resources to ensure the fastest turnaround possible. Although a standard karyotype may show XX sex chromosomes, FISH may reveal presence of a translocation of *SRY* to an X chromosome or an autosome. Any chromosomal abnormality detected prenatally should be confirmed after birth.
   b. First-line testing in addition to a chromosomal evaluation should include measurement of 17-hydroxyprogesterone (17-OHP) (part of newborn screens in all U.S. states), LH, testosterone, and AMH on a sample drawn after 48 hours of life. Standard immunoassays for testosterone are inaccurate in neonates due to the presence of interfering substances, and testosterone measurements before 5 days of life should be performed using either mass spectrometry or immunoassay with a prior extraction step. Baseline laboratory studies can also include serum electrolytes, blood urea nitrogen (BUN), and creatinine starting at 3 to 4 days of age (as salt-wasting manifests as early as 5 days of age but not sooner), with electrolytes followed frequently (every 1 to 2 days) to monitor for salt-wasting until salt-wasting CAH is ruled out.
   c. Other tests such as plasma renin activity, follicle-stimulating hormone (FSH), or other adrenal precursors and hormones may be indicated in certain circumstances.
   d. Targeted DSD gene-panel testing and/or chromosomal microarray may identify specific causes of DSD. *SRY*, *SOX9*, *WT1*, *NR5A1* (formerly called *SF1*), and *NR0B1* (formerly called *DAX1*) are a few examples of genes with variants known to be associated with DSD. Duplications in enhancer regions of *SOX9* and *SOX3* have been reported in XX testicular DSD. Targeted genetic testing of one or more specific genes may be appropriate in many cases of DSD. Some institutions are using whole-exome sequencing or DSD gene-panel testing to aid in the diagnosis of DSD. Although cost, insurance coverage, and incomplete knowledge of the genetics of DSD remain limiting factors, genetic testing is uniquely able to establish some diagnoses and may prompt screening for associated clinical issues.
2. **Pelvic ultrasonography**, especially when the bladder is full, can determine whether a uterus is present. However, this determination can be difficult, and both false negatives and false positives are possible even with experienced ultrasonographers. Descended testes can often be visualized by ultrasound, but intra-abdominal gonads are less likely to be identified. Given the association between urologic and genital malformations, ultrasonographic evaluation should include the kidneys, ureters, and bladder. Adrenal hyperplasia can often be found in babies with CAH but is not diagnostic. Magnetic resonance imaging (MRI)

may be needed to locate intra-abdominal gonads or to confirm the presence of a uterus when ultrasonography is indeterminate but may also be inconclusive.

3. **Voiding cystourethrogram (VCUG) or genitogram** may reveal a vagina with a cervix at its apex (indicating the presence of a uterus) or a utricle (a müllerian duct remnant). It may also reveal the presence of a connection between the urinary and genital tracts (e.g., urogenital sinus).

Table 63.2 summarizes causes, and Figure 63.4 describes an approach to patients with DSD.

V. GONADAL DIFFERENTIATION DISORDERS

A. Mixed gonadal dysgenesis (MGD). The hallmark of MGD is the presence of a testis (which may be normal or dysgenetic) on one side of the body and a more markedly dysgenetic gonad (possibly a streak gonad) on the other side. This disorder is most often due to a 45,X/46,XY mosaic karyotype.

1. **Physical findings.** The combination of asymmetric external genitalia and one palpable testis in the labioscrotal fold suggests MGD. However, 45,X/46,XY mosaicism can result in an appearance of the external genitalia ranging from typical male to typical female. In fact, 90% of 45,X/46,XY infants diagnosed prenatally have typical male genital appearance at birth. In patients with MGD, each gonad governs the differentiation of the ipsilateral internal genital structures. A fallopian tube and uterus are frequently present on the side of the streak/dysgenetic gonad, and these structures can herniate into the labioscrotal fold. Children with a mosaic karyotype that includes a 45,X karyotype in some cells may have features of Turner syndrome such as webbed neck, lymphedema, short stature, renal abnormalities, and cardiac defects (e.g., coarctation of the aorta).
2. **Management.** If AMH is measurable, or if hCG stimulation testing causes a significant rise in serum testosterone indicative of testicular tissue, the testis should be sought by imaging and/or surgery. See section VIII for discussion of sex/gender designation. Streak gonads and intra-abdominal dysgenetic testes that produce minimal testosterone and/or AMH should be removed in infancy because germ cell tumors may arise in up to 30% of these children, sometimes within the first few years of life. All children with MGD should be evaluated by a pediatric endocrinologist because many will have poor linear growth and may be candidates for growth hormone therapy.

B. XY gonadal dysgenesis. XY complete gonadal dysgenesis (CGD) is also called Swyer syndrome, which can be a result of abnormal functioning of *SRY* or factors that regulate or are regulated by *SRY*. Bilateral streak gonads are typically present, and internal female reproductive structures are present due to absence of AMH and testosterone. The external genitalia usually have a typical female appearance. These patients are usually raised as girls. Some may not be diagnosed until they fail to initiate puberty and exhibit high gonadotropins consistent with primary gonadal insufficiency. Up to 30% of patients with XY CGD may develop germ cell tumors, so their streak gonads should be removed in infancy.

Table 63.2. Causes of Differences of Sex Development (DSD)

Disorder	Phenotype		Karyotype
	External Genitalia	Gonads	
Atypical gonadal differentiation			
Ovotesticular DSD	Variable	Ovarian and testicular tissue	46,XX; 46,XY; 46,XX/46,XY; others
Mixed gonadal dysgenesis	Variable	Streak gonad and dysgenetic testis	45,X/46,XY; others
XY complete gonadal dysgenesis	Female or atypical	Dysgenetic testes or streak gonads	46,XY
XX testicular DSD	Male or atypical	Testes (normal or dysgenetic)	46,XX
Other XX DSD (atypical virilization)			
Congenital adrenal hyperplasia			
21α-hydroxylase deficiency	Atypical	Ovaries	46,XX
11β-hydroxylase deficiency	Atypical	Ovaries	46,XX
3β-hydroxysteroid dehydrogenase deficiency	Atypical	Ovaries	46,XX
Placental aromatase deficiency	Atypical	Ovaries	46,XX
Maternal androgen excess	Atypical	Ovaries	46,XX
Other XY DSD (incomplete virilization)			
Testicular unresponsiveness to hCG and LH (LH/CG receptor mutation)	Female or atypical	Testes	46,XY

(continued)

Table 63.2. ***(Continued)***

Disorder	Phenotype		Karyotype
	External Genitalia	Gonads	
Disorders of testosterone/dihydrotestosterone synthesis			
Steroidogenic acute regulatory protein deficiency	Female or atypical	Testes	46,XY
Side-chain cleavage enzyme deficiency	Female or atypical	Testes	46,XY
17α-hydroxylase/17,20-lyase deficiency	Female or atypical	Testes	46,XY
3β-hydroxysteroid dehydrogenase deficiency	Atypical	Testes	46,XY
17β-hydroxysteroid dehydrogenase deficiency	Atypical	Testes	46,XY
5α-reductase deficiency	Atypical	Testes	46,XY
End-organ resistance to testosterone			
Complete androgen insensitivity syndrome	Female	Testes	46,XY
Partial androgen insensitivity syndrome	Atypical	Testes	46,XY
Testicular regression syndrome (previously called "vanishing testes syndrome")	Male	Absent gonads	46,XY

hCG, human chorionic gonadotropin; LH, luteinizing hormone; CG, chorionic gonadotropin.

Source: Modified with permission from Wolfsdorf JI, Muglia L. Endocrine disorders. In: Graef JW, ed. *Manual of Pediatric Therapeutics*. Philadelphia, PA: Lippincott-Raven; 1997:381–413.

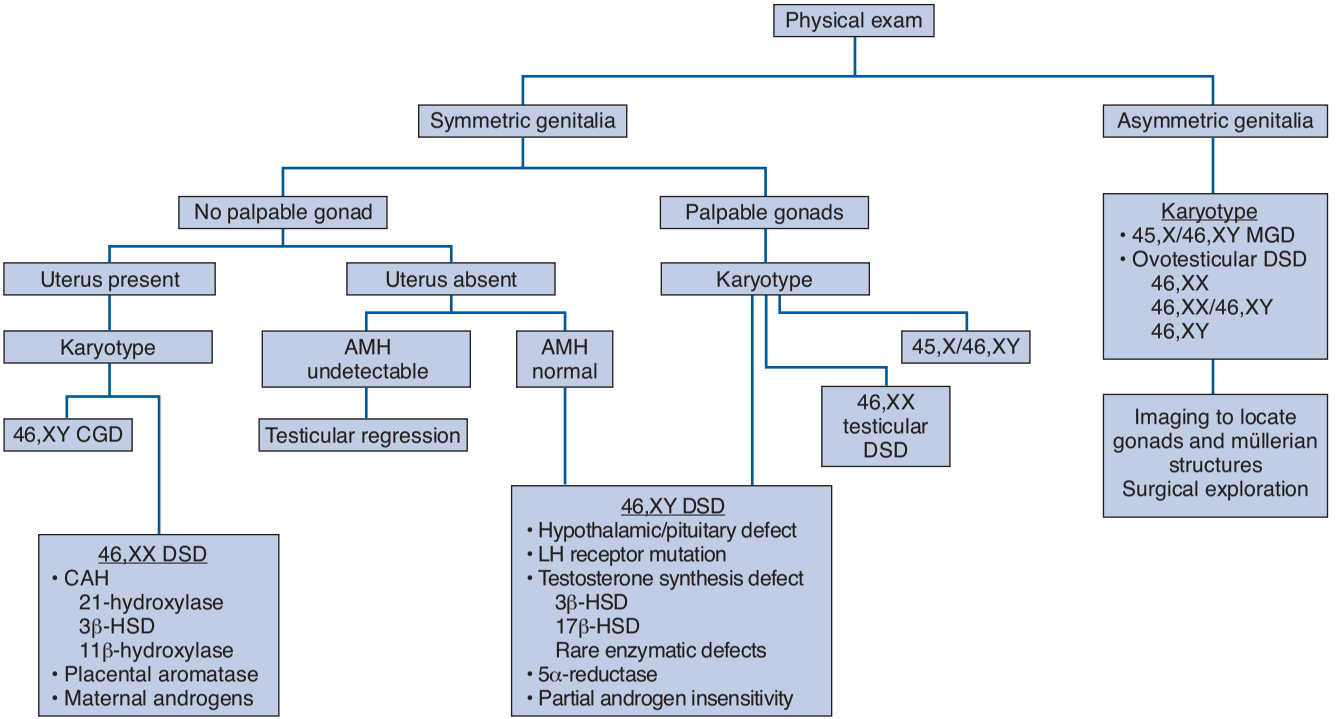

Figure 63.4. Algorithm for the evaluation of differences of sex development (DSDs). CGD, complete gonadal dysgenesis; CAH, congenital adrenal hyperplasia; 3β-HSD, 3β-hydroxysteroid dehydrogenase; AMH, anti-müllerian hormone; LH, luteinizing hormone; 17β-HSD, 17β-hydroxysteroid dehydrogenase; MGD, mixed gonadal dysgenesis.

Partial gonadal dysgenesis occurs when there is partial but incomplete testicular development and/or differentiation, leading to varying degrees of external virilization and müllerian regression depending on the production of testosterone and AMH, respectively. Germ cell tumor risk is also elevated in partial gonadal dysgenesis, but there remains a lack of consensus regarding the degree of tumor risk and whether close monitoring is adequate if the gonad has an extra-abdominal location and thus can be evaluated by physical exam and ultrasound.

C. XX testicular DSD. These individuals may have genitalia that have a typical male appearance or may have atypical genital appearance. Translocation of *SRY* to the X chromosome or an autosome is frequently responsible. In *SRY*-negative individuals, duplication of *SOX9* (17q24) may be detected by FISH. Additional genes associated with testicular or ovotesticular DSD include *SOX3*, *WNT4*, *RSPO1*, and *NR5A1*.

D. Ovotesticular DSD. The sex-chromosomal complement in this rare condition is variable: Seventy percent of patients have XX chromosomes, <10% have XY chromosomes, and the remainder show mosaicism or chimerism with a Y chromosome-containing cell line (most commonly 46,XX/46,XY).

1. **Physical findings.** The external genitalia may have a typical female or male appearance or may show partial labioscrotal fusion, asymmetric labioscrotal folds, and/or hypospadias. Whether the internal structures contain wolffian or müllerian elements depends on the local presence of testosterone and AMH on that side of the abdomen.
2. **Evaluation.** An hCG stimulation test that produces a rise in serum testosterone confirms the presence of Leydig cells, whereas a typical male range AMH level indicates the presence of Sertoli cells. Inhibin A has been proposed as a potential marker of ovarian tissue but may require stimulation by exogenous FSH to be detectable.
3. **Diagnosis** is based on the histology of the gonads, which by definition contain both testicular and ovarian tissue. Laparoscopy, gonadal biopsy, or both may be required for diagnosis.
4. **Management.** Dysgenetic gonadal tissue that contains a Y chromosome should be assessed further by exam and/or imaging. The rate of tumors in ovotestes is lower than with gonadal dysgenesis but may still be elevated from typical testicular tissue. Beyond the tumor risk, hormone production in puberty can be troubling. Girls with intact ovotestes may experience virilization, and boys may undergo breast development. Ideally, this should be carefully addressed by the medical team, family, and patient prior to the onset of puberty. For details of sex/gender designation, see section VIII.

VI. OTHER XX DSD. Infants with XX DSD have undergone virilization due to exposure to excess androgens, which can be of adrenal or gonadal origin (or rarely, maternal or exogenous origin).

A. CAH. The most common DSD presenting in the neonatal period is CAH in an XX infant. The most common form of CAH (>90%) is deficiency of 21-hydroxylase (21-OHase in Fig. 63.5) caused by mutations in *CYP21A2*.

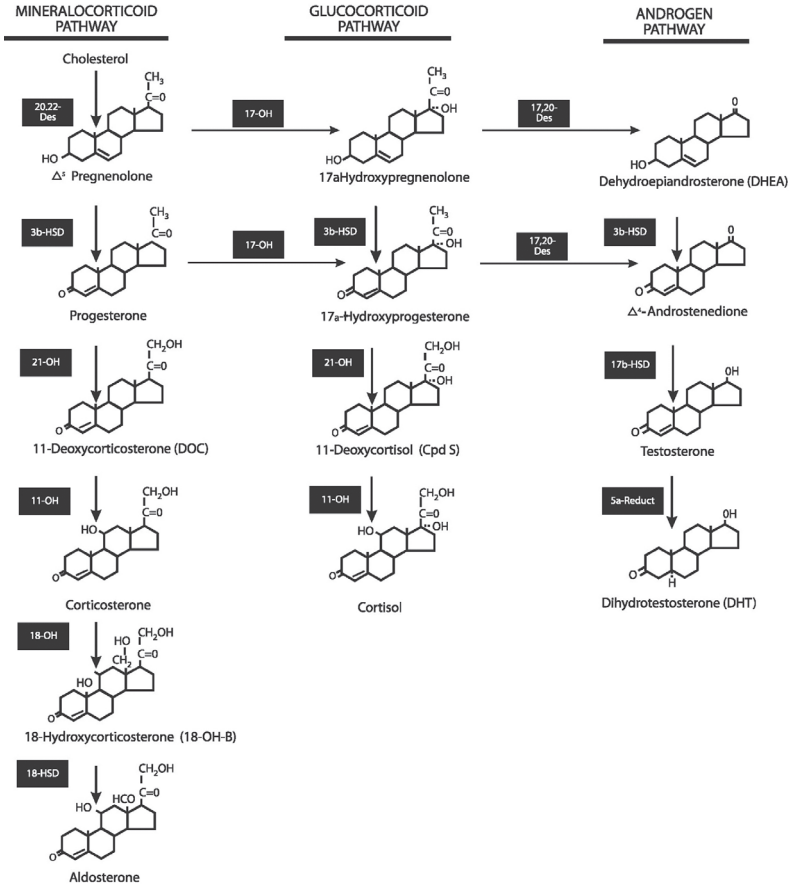

Figure 63.5. Pathways of steroid biosynthesis. 3β-HSD, 3β-hydroxysteroid dehydrogenase; 17β-HSD, 17β-hydroxysteroid dehydrogenase. (From Esoterix, Calabasas Hills, CA.)

Virilization may occur in rarer forms of CAH due to deficiency of 11β-hydroxylase (11-OHase, encoded by *CYP11B1*) or 3β-hydroxysteroid dehydrogenase (3β-HSD, encoded by *HSD3B2*). Individuals with CAH typically do not have testicular tissue and therefore usually have normally developed müllerian structures and no wolffian structures.

1. **Epidemiology.** The incidence of 21-OHase deficiency is 1:16,000 births based on data from worldwide newborn screening programs. Patients with salt-wasting outnumber those with "simple virilizing" CAH by 3:1. The XY:XX sex ratio is 1:1, but XX individuals are more readily detected at birth due to atypical genital development; XY individuals have typical male genital appearance and thus may not come to attention based

on clinical exam (although hyperpigmentation of the scrotum can be a clue).

2. **Diagnosis.** In the United States, all state newborn screening programs include screening for 21-OHase deficiency. Blood spots are obtained on filter paper, ideally between 48 and 72 hours of age, and 17-OHP is measured. Normal values must be determined for each individual screening program because they depend on the filter paper thickness and the immunoassay used. The 17-OHP is elevated on newborn screening in 99% of infants with salt-wasting or simple virilizing 21-OHase deficiency.
   a. False-positive results. Obtaining a blood sample before 48 hours of age can cause a false-positive result. Because normal values for 17-OHP are inversely related to gestational age and birth weight, false-positive results can also occur in premature and low birth weight infants as well as in infants who are acutely ill.
   b. False-negative results. Prenatal administration of steroids (e.g., betamethasone) may suppress 17-OHP levels and cause false-negative results; rescreening of newborns exposed to such medications can reduce false-negative rates.
   c. Rapid evaluation of suspected 21-OHase deficiency is critical to avert salt-wasting crisis from untreated glucocorticoid and mineralocorticoid deficiency, which can arise as early as 5 days of age. Clinical suspicion or abnormal newborn screening results should be confirmed immediately by measurement of serum 17-OHP. An adrenocorticotropic hormone (ACTH) level may aid diagnosis, and measurement of plasma renin activity and aldosterone may help differentiate between salt-wasting and simple virilizing forms. Serum electrolytes should be monitored at least every other day starting around 3 to 4 days of age until salt wasting is confirmed or ruled out.
   d. Rare forms of CAH. In an infant with 11-OHase deficiency, levels of 11-deoxycortisol and 11-deoxycorticosterone are elevated and can cause hypertension. An infant with 3β-HSD deficiency may have mildly elevated 17-OHP on newborn screen; 17-hydroxypregnenolone and the 17-hydroxypregnenolone-to-cortisol ratio are markedly elevated in these infants.
   e. Newborn screening may not detect infants with mild simple-virilizing 21-OHase deficiency. Therefore, in a virilized XX individual suspected of having a form of CAH, or who has equivocal 17-OHP levels, an **ACTH stimulation test** may be necessary to demonstrate the adrenal enzyme defect (see Fig. 63.5).
3. **Management.** In an infant suspected of 21-OHase deficiency, treatment should be started as soon as the laboratory tests mentioned have been obtained.
   a. Glucocorticoids. Hydrocortisone 20 mg/m^2/day, divided into dosing every 8 hours, should be given to all infants suspected of 21-OHase deficiency.

$$\text{Body surface area } (m^2) = \sqrt{\frac{\text{Length (cm)} \times \text{Weight (kg)}}{3{,}600}}$$

b. **Mineralocorticoids.** In cases of salt-wasting CAH, fludrocortisone acetate (Florinef) 0.1 to 0.2 mg daily should be given. Salt-wasting crises usually develop between 5 and 14 days of age but can occur as late as 1 month and may occur even in infants whose virilization is not severe. Weight, fluid balance, and electrolytes must be monitored closely, with blood samples at least every 2 days during the first few weeks of life to detect hyponatremia or hyperkalemia. If salt-wasting occurs, acute fluid losses should be replaced initially with intravenous normal saline with glucose added. Salt-wasting due to aldosterone deficiency typically requires replacement of about 8 mEq/kg/day of sodium. Once the infant is stabilized, sodium chloride (NaCl) 1 to 2 g daily, divided into dosing every 6 hours, should be added to the diet (each gram of NaCl contains 17 mEq of sodium).

B. Maternal hyperandrogenic conditions. Maternal CAH, virilizing tumors of the adrenal or ovary, or exposure to androgenic medications during pregnancy are rare causes of fetal virilization, because the androgen concentrations must be markedly elevated to overcome placental aromatase, which protects the fetus from maternal androgens by converting them to estrogens.

C. Placental aromatase deficiency. The hallmark of this rare disorder is that both mother and infant are virilized due to an inability to convert androgens to estrogens.

D. Cytochrome P450 oxidoreductase (POR) deficiency. Mutations in the *POR* gene lead to a form of CAH. This disorder of steroidogenesis affects multiple microsomal P450 enzymes involved in steroid hormone synthesis including *CYP21A2* (21-OHase), *CYP17A1* (17α-OHase and 17,20-lyase), and *CYP19A1* (aromatase). Patients may have positive newborn screens with elevated 17-OHP levels and may also present with maternal virilization during pregnancy.

E. See section V for discussion of XX ovotesticular and testicular DSD.

VII. OTHER XY DSD.

Evaluation of the infant with XY DSD is complex, and early consultation with a pediatric endocrinologist will help direct the evaluation. Only 20% to 50% of children with XY DSD will receive a specific molecular diagnosis. Even if genetic testing demonstrates Y chromosome material, the parents should not be told hastily that a male sex/gender designation is appropriate.

A. Disorders of testicular development. Gonadal dysgenesis and ovotesticular DSD are discussed in section V.

B. Defects in androgen synthesis or action. These individuals typically have no müllerian structures because AMH production is unaffected.

1. **Leydig-cell hypoplasia.** Impaired Leydig-cell function can be due to unresponsiveness to hCG and LH due to mutations in the LH/chorionic gonadotropin (CG) receptor.

2. **Enzymatic defects in testosterone synthesis** include deficiency of 17β-hydroxysteroid dehydrogenase type 3 (17β-HSD in Fig. 63.5, encoded by *HSD17B3*), 3β-HSD (encoded by *HSD3B2*), 17α-hydroxylase/17,20-lyase

(17-OHase or *CYP17*), isolated 17,20-lyase (17,20 Des in Fig. 63.5), or very rarely side-chain cleavage enzyme (20,22 Des or *CYP11A1*) or steroidogenic acute regulatory protein (StAR).

3. **Defect in testosterone metabolism.** Patients with 5α-reductase type 2 (*SRD5A2*) deficiency have impaired conversion of testosterone to DHT. Although generally uncommon, this defect has a higher prevalence in the Dominican Republic and the Middle East. DHT can also be produced by an alternative, "backdoor" pathway that starts with 17-OHP. Mutations in enzymes in this backdoor pathway have also been reported in XY DSD.
4. **End-organ resistance** to testosterone and DHT is caused by mutations of the androgen receptor. Such mutations are X-linked. The degree of resistance is variable, leading to a clinical spectrum from partial androgen insensitivity syndrome (PAIS) to complete androgen insensitivity syndrome (CAIS).

C. Environmental disorders. Maternal drug ingestion of antiandrogens (e.g., spironolactone) and 5α-reductase inhibitors (e.g., finasteride) can cause atypical genital development. Maternal phenytoin exposure has been associated with atypical genital appearance in rare cases.

D. Evaluation focuses on establishing the presence or absence of testes and their ability to produce androgens.

1. **Presence of testes.** If testes are not palpable, their presence should be determined by imaging and/or measurement of AMH (see sections VII.F and VII.H).
2. **Laboratory evaluation** is focused on determining whether the cause of undervirilization is due to a defect in gonadal development or testosterone synthesis, metabolism, or action. Blood samples should be obtained for measurement of electrolytes, FSH, LH, testosterone, DHT, androstenedione, 17-OHP, 17-hydroxypregnenolone, cortisol, and AMH. Serum electrolytes may reveal hyponatremia and hyperkalemia due to CAH caused by 3β-HSD deficiency.
3. An **hCG stimulation test** may be necessary if the above results do not lead to a diagnosis.
   a. Technique. The hCG is given intramuscularly daily or every 2 days for a total of three doses. Androstenedione, testosterone, and DHT concentrations are measured before the first dose and 24 hours after the final dose of hCG.
   b. Interpretation. Inability to increase the testosterone level in response to hCG is characteristic of testicular dysgenesis, LH/CG receptor mutations, loss of testicular tissue (testicular regression syndrome), or an enzymatic defect in testosterone synthesis. An elevated testosterone:DHT ratio (>20:1) after hCG stimulation suggests 5α-reductase deficiency, whereas a low testosterone:androstenedione ratio (<0.8:1) suggests 17β-HSD deficiency.
4. An **ACTH stimulation test** may be necessary to define defects in enzymatic steps of testosterone synthesis that also affect cortisol synthesis, such as deficiencies of 3β-HSD, side-chain cleavage enzyme, StAR,

or 17-OHase, which result in CAH (see Fig. 63.5). The former three deficiencies are associated with salt wasting; 17-OHase deficiency is associated with salt retention and hypertension, although these are often not present in the newborn period.

5. **Androgen insensitivity syndrome (AIS).** If the initial laboratory tests show high levels of testosterone, and the testosterone-to-androstenedione and testosterone-to-DHT ratios are normal, the infant may have AIS.
   a. Further evaluation may include monthly administration of 25 to 50 mg of intramuscular depot testosterone for 3 months. Failure of the stretched penile length to increase by 1.5 cm supports the diagnosis of AIS.
   b. Genetic studies of the androgen receptor will detect mutations in some but not necessarily all clinical cases of AIS.
   c. Newborns with **CAIS** have normal-appearing female external genitalia (including the lower third of the vagina) and absent müllerian and wolffian structures. They may be identified by an antepartum XY karyotype or by the presence of an apparent inguinal hernia that proves to be a testis. More often, they present in late puberty with primary amenorrhea.

E. Microphallus (<2.5 cm in a full-term infant) with or without cryptorchidism has many causes in addition to those mentioned earlier, including hypothalamic-pituitary disorders of gonadotropin production such as Kallmann syndrome, holoprosencephaly, optic nerve hypoplasia (also referred to as septo-optic dysplasia), and other causes of multiple pituitary hormone deficiencies. Growth hormone deficiency can also be associated with microphallus. Infants with panhypopituitarism often have neonatal hypoglycemia and direct hyperbilirubinemia. Among the many other conditions associated with microphallus are CHARGE syndrome, trisomy 21, Prader-Willi, Robinow, Klinefelter, Carpenter, Meckel-Gruber, Noonan, de Lange, Fanconi, and fetal hydantoin syndromes. Treatment with testosterone enanthate or cypionate 25 to 50 mg intramuscularly given monthly for 3 months may substantially increase penile length in these patients.

F. Bilateral cryptorchidism. Bilateral cryptorchidism at birth occurs in 3:1,000 infants, most of whom are premature. By 1 month of life, the testes are still undescended in 1:1,000 infants.

1. **Imaging.** Either ultrasonography or MRI may reveal inguinal or intra-abdominal gonads; MRI is more sensitive for locating the latter but may still fail to definitely locate abdominal gonads.

2. **Laboratory evaluation.** If testicular tissue cannot be found by exam or imaging, levels of serum FSH, LH, testosterone, and AMH should be measured. The testosterone and gonadotropins dip transiently after birth then recover by 3 to 10 days after birth and remain at pubertal levels until approximately 6 months of age in boys.
   a. Elevated serum gonadotropins with a low testosterone concentration suggests absent or nonfunctioning testes.
   b. Undetectable serum **AMH** is indicative of bilateral anorchia rather than undescended testes (see section VII.H in the following text).

3. **Management.** A urologist should be consulted, and if surgery is indicated, orchidopexy should be performed by 1 year of life. If intra-abdominal testes cannot be brought into the scrotum, removal should be considered because of the 3- to 10-fold increased risk of potentially malignant tumors in cryptorchid testes.
4. **Persistent müllerian duct syndrome (PMDS)** in XY individuals is caused by defects in AMH or its receptor. Cryptorchidism is common in infants with PMDS, who retain a uterus and fallopian tubes but otherwise have typical male genital appearance.
5. **Other conditions** associated with cryptorchidism include trisomy 21; neural tube defects; renal and urinary tract malformations; and numerous syndromes including Prader-Willi, Bardet-Biedl, Aarskog, Cockayne, Fanconi, Noonan, Klinefelter, and fetal hydantoin syndromes.
6. **The presence of any of the following** physical findings also merits evaluation for a DSD:
   a. Unilateral cryptorchidism with hypospadias, especially proximal (e.g., perineoscrotal or penile) hypospadias
   b. Unilateral cryptorchidism with microphallus

G. Testicular regression syndrome, previously known as "vanishing testis syndrome," refers to the absence of functional testicular tissue, presumably secondary to atrophy/loss during fetal life. Spermatic cord structures are present, and the external genitalia have a typical male appearance, consistent with evidence of functional testicular tissue earlier in development. The understanding of the pathophysiology remains incomplete but is presumed to involve vascular or intrinsic abnormalities leading to the tissue loss. Management involves testosterone replacement at the appropriate ages.

H. Use of AMH measurements. The hCG stimulation test is used to assess the presence and function of testicular tissue, specifically Leydig cells, but can be cumbersome and expensive and occasionally requires protracted dosing to stimulate a refractory testis. AMH is an alternative marker of the presence of testicular tissue, specifically Sertoli cells. AMH is produced in a sexually dimorphic manner. Starting at birth, AMH from Sertoli cells rises to above ~60 ng/mL by 6 months of age, remains above ~30 ng/mL through childhood, and then declines during adolescence to an adult male level of 4 ng/mL. In contrast, granulosa cells of the ovary do not make significant amounts of AMH until puberty, when levels in girls also reach approximately 4 ng/mL. Thus, measuring AMH in an infant can distinguish whether testicular tissue is present or absent. AMH above the typical female range has a 100% positive predictive value for the presence of testicular tissue; the predictive value for anorchia is 94% if AMH is undetectable.

VIII. ISSUES OF SEX/GENDER DESIGNATION.

Today, most providers agree that the primary goal in sex/gender designation is to attempt to match the child's future gender identity, but this is a challenging, imperfect, and humbling endeavor. Several factors influence gender identity, including chromosomal sex and fetal (and possibly neonatal) exposure to androgens (the degree of which is

inferred from the appearance of the external genitalia), as well as sex/gender of rearing itself, but there are undoubtedly other, currently unknown factors that affect the formation of gender identity. Data on gender outcomes for various DSD conditions are limited, often relied on rudimentary assessments of gender identity, and may not reflect contemporary concepts related to gender identity and nonbinary gender identities in particular. Some time-honored concepts, e.g., that individuals with XY CAIS universally identify as girls/women, have been challenged by more recent studies.

Other factors to be considered in sex/gender designation include prospects for fertility and considerations for genitoplasty. In the past, a major criterion for raising a child as a boy was a penile size deemed to be adequate for sexual function. XY infants born with little or no penile tissue had traditionally been raised as girls and surgically and hormonally feminized by means of genitoplasty and gonadectomy early in life and estrogen treatment at the age of puberty. However, some individuals changed their gender designation to male, and this practice is no longer routine.

Similarly under debate is the issue of sex/gender designation in the most markedly virilized XX newborns with CAH who have completely fused labioscrotal folds and a penile urethra. A minority opinion recommends male sex/gender designation and eventual gonadectomy, thereby eliminating the need for feminizing genitoplasty. Nevertheless, many geneticists, endocrinologists, and existing guidelines continue to recommend female sex/gender designation, motivated at least in part by the prospect of female fertility.

Another subject of controversy is whether and when to perform gonadal and/or genital surgeries, such as clitoral recession in virilized XX infants being raised female or gonadectomy in infants with CAIS. Opinions of adults with DSD range widely, with some satisfied that surgery was done early in life and others feeling they were harmed by the surgery. One-stage surgical procedures that preserve the neurovascular bundle can be performed in infancy, and outcomes are much improved compared to the clitorectomies routinely performed several decades ago, but there is increasing reluctance to irreversibly remove structures when future gender identity is uncertain. Nevertheless, there is general consensus on the importance of removing a dysgenetic abdominal gonad that contains Y chromosome material because of the high risk of gonadoblastoma. In contrast, removal of gonads in individuals with CAIS is generally deferred until adolescence because the increased risk of germ cell tumors does not emerge until early adulthood.

Parents require a thorough explanation of their child's condition because laboratory and imaging data become available. They should participate with the interdisciplinary team in decision-making regarding the options for medical and surgical therapy, with each treatment option considered separately, discussion of the prospects for genital appearance, sexual functioning, and fertility, and consideration of all possible future gender identities. The full medical team should include a pediatrician/neonatologist, pediatric endocrinologist, pediatric surgeon and/or pediatric urologist, geneticist, and counselor experienced in dealing with DSD. Finally, long-term, unbiased studies of gender identity, sexual functioning, and surgical outcomes in individuals born with various forms of DSD are needed to provide insight into the difficult task of sex/gender designation for these infants.

Suggested Readings

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64 Surgical Conditions in the Newborn

K. Taylor Wild, Natalie E. Rintoul, Mark Puder, and Anne R. Hansen

KEY POINTS

- Bilious emesis is midgut volvulus until proven otherwise and should be treated as a surgical emergency.
- Open lesions (e.g., myelomeningocele [MMC] and abdominal wall defects) require immediate attention to positioning of the infant and lesion with special attention to fluid losses and infection control.
- Patients with known congenital diaphragmatic hernia (CDH) should be intubated immediately after birth and have a catheter inserted for gastric decompression.
- Patients with suspected intestinal obstruction from any cause should have a catheter inserted for gastric decompression.
- Antenatal diagnosis enables families to gain information, prepare for the birth, and ensure that the delivery occurs at a facility able to provide necessary support and interventions for postnatal transition.

I. PRENATAL FINDINGS ASSOCIATED WITH SURGICAL DISEASE

A. Polyhydramnios (amniotic fluid volume >2 L) occurs in 1 in 1,000 births.

1. Gastrointestinal (GI) obstruction (including esophageal atresia [EA]) is the most frequent surgical cause of polyhydramnios.
2. Other causes of polyhydramnios include abdominal wall defects (omphalocele and gastroschisis); anencephaly; congenital diaphragmatic hernia (CDH); maternal diabetes with consequent fetal hyperglycemia and glucosuria; and other conditions impairing the ability of the fetus to concentrate urine, tight nuchal cord and other causes of impaired fetal swallowing, and fetal death.
3. All women with suspected polyhydramnios should have an ultrasonographic examination. This is the study of choice for the diagnosis of intestinal obstruction, abdominal wall defects, CDH, as well as nonsurgical abnormalities leading to an inability of the fetus to swallow.
4. Pediatric surgical consultation should be obtained before delivery.

B. Meconium peritonitis can be diagnosed prenatally by ultrasonography, typically seen as areas of calcification scattered throughout the abdomen.

Postnatally, calcifications are confirmed by plain film of the abdomen. It is usually due to antenatal perforation of the intestinal tract; thus, this diagnosis should prompt an evaluation for a congenital lesion causing intestinal obstruction, either anatomic or functional (see section V.A).

C. Ascites is usually associated with urinary tract anomalies (e.g., lower urinary tract obstruction due to posterior urethral valves). Other possible causes include any severe anemia, peritonitis, thoracic duct obstruction, cardiac disease, hepatic or portal vein obstruction, hepatitis, and congenital infection (e.g., TORCH infections; see Chapters 48 to 53) as well as other causes of hydrops fetalis (see Chapter 26). Prenatal ultrasonography is important and may lead to fetal interventions to alter the natural history of the disease, i.e., bladder decompression with vesicoamniotic shunt to minimize renal parenchymal injury (see Chapters 1 and 28).

II. POTENTIAL PRENATAL INTERVENTIONS TO AVOID POSTNATAL SURGICAL EMERGENCIES

A. Fetal surgery. The potential for surgical intervention during fetal life continues to evolve. It depends heavily on the availability of precise prenatal diagnostic techniques and experience in accurately characterizing disorders including the use of ultrasonography and fast magnetic resonance imaging (MRI). Fetal surgery can involve opening the uterus to operate on the fetus or can be minimally invasive. Minimally invasive options include using small incisions guided by fetoscopy and sonography or percutaneous catheter placement under continuous ultrasonography guidance. For some conditions including complex airway obstructions or large masses, *ex utero* intrapartum treatment (EXIT) may be offered.

Advances in obstetric and anesthesia management have also contributed to the feasibility of performing *in utero* procedures. Medications that reduce uterine irritability have been developed that minimizes risk that the uterus will contract during and after the procedure. The criteria for consideration of a procedure include the following:

1. **Ethical considerations** are important, including balancing both the potential risk and benefit to the fetus with the potential risk to the mother as well as the impact on the family as a whole.
2. **Technical feasibility** depends on the gestational age, the position of the fetus and placenta, and details of the underlying conditions.
3. **Severity of fetal condition.** Initially, most cases dealt with conditions that were life-threatening either resulted in death *in utero* or shortly after birth. Currently, some cases are considered when a condition is not life-threatening, but is severe and either the condition itself is progressive (such as the growth of a large tumor partially obstructing the fetal airway), or the consequences of the condition worsen progressively (such as hydrops secondary to a large teratoma or nerve damage and hindbrain herniation from a large myelomeningocele [MMC]).
4. **Necessary resources.** There must be an experienced maternal–fetal medicine and surgical team to care for the mother and fetus during

surgery as well as an expert postnatal resuscitative team skilled in the care of babies with severe anomalies that have undergone fetal intervention. This team must be in close proximity should the fetus require emergent delivery or prematurely.

5. **Fetal surgical interventions.** There are a growing number of possible fetal interventions. Some of the most common are:
   a. Lung lesion. Fetal surgery has been successfully performed for the removal of enlarging lung lesions, such as congenital pulmonary airway malformations (CPAMs), when these lesions result in life-threatening complications, such as fetal hydrops.
   b. Sacrococcygeal teratoma (SCT). Prenatally diagnosed SCTs have been treated with fetal debulking. Again, this type of intervention is only considered when the lesion is causing life-threatening complications, such as high-output cardiac failure and hydrops. Combined cardiac output should be closely monitored throughout the pregnancy. Combined cardiac output is the sum of the output from the left and right sides of the heart. It is a useful measurement in fetal circulation, where the cardiac output from both sides of the heart work partly in parallel due to the foramen ovale and the ductus arteriosus.
   c. Ureteral obstruction. Progressive fetal urethral obstruction has been ameliorated by the use of percutaneous bladder shunts.
   d. Twin–twin transfusion syndrome (TTTS) or twin reversed arterial perfusion (TRAP). Fetoscopic laser ablation to separate the connecting vessels has been used successfully.
   e. CDH. Fetoscopic endoluminal tracheal occlusion (FETO) is a surgical procedure performed in select cases of severe CDH. The goal of FETO is to promote lung growth by obstructing the outflow of fetal lung fluid. In a FETO procedure, a small incision is made in the uterus between 27 and 30 weeks' gestation, a balloon is surgically inserted into the fetus' trachea and inflated with fluid to occlude the trachea. The balloon is then surgically removed at 34 weeks. FETO is being studied in ongoing clinical trials.
   f. MMC: A multicenter randomized controlled trial comparing *in utero* surgical correction with standard management found that performing prenatal surgery led to better outcomes than postnatal surgery. Significant findings in that report included an increased risk of preterm delivery but decreased need for cerebrospinal fluid shunting at 12 months with reduced hindbrain herniation in the prenatal surgery group. Forty percent of infants with prenatal surgery required a ventriculoperitoneal shunt compared to 82% repaired postnatally. The need for shunting was independent of lesion level and degree of hindbrain herniation. However, prenatal surgery did not decrease the need for shunting in those fetuses with a cerebral ventricular size $\geq$15 mm at initial screening. At 2.5-year follow-up, those treated prenatally demonstrated improved physical development and motor function, such as unassisted walking, compared to those treated after birth. Benefits including improved motor function and decreased number of surgical procedures have persisted into school age. When the diagnosis of MMC is made prenatally, maternal–fetal surgery is a treatment option.

g. Cardiac procedures. Successful fetal cardiac procedures include atrial septostomy, aortic valve dilation for critical aortic stenosis, and stent placement for intact atrial septum with hypoplastic left heart syndrome.
h. EXIT procedures may be considered for complex airway obstruction or intrathoracic lesions that would not allow for a safe transition from the placenta prior to placement of lesion debulking ± placement of a surgical airway.

III. POSTNATAL SURGICAL DISORDERS: DIAGNOSIS BY PRESENTING SYMPTOM

A. Respiratory distress (see sections IV.B and IV.C; see Chapters 29 to 39). Although most etiologies of respiratory distress are treated medically, some respiratory disorders do require surgical intervention.

1. Choanal atresia (see section IV.C.1)
2. Laryngotracheal clefts (see section IV.C.3)
3. Tracheal agenesis
4. EA with or without tracheoesophageal fistula (TEF) (see section IV.A)
5. Congenital lobar emphysema
6. CPAM, pulmonary sequestration
7. CDH (see section IV.B)

B. Scaphoid abdomen

1. CDH (see section IV.B)
2. EA without TEF (see section IV.A)

C. Excessive mucus and salivation. EA with or without TEF (see section IV.A)

D. Abdominal distention can be due to ascites, intestinal obstruction (mechanical or functional), or pneumoperitoneum. Gastric decompression should be considered in all patients with abdominal distension.

1. **Gastric decompression** can be achieved via the orogastric or nasogastric route with various different types of tubes. In general, orogastric tubes are less stable and more prone to displacement but may be preferred if there is concern that occluding a nostril may partially obstruct breathing.
a. A Salem Sump is an enteral tube with two lumens designed specifically for decompression of the stomach. One dominant central lumen (the drainage port) is placed to suction while a smaller side lumen acts as an air vent to prevent tube occlusion and mucosal trauma. There are several drainage holes located along the distal end of the catheter. In a term baby, a 10 or 12 French Salem Sump may be used, in a preterm baby a 6 or 8 French.
b. A Replogle tube also has two lumens, but drainage holes are located more closely together at the distal most tip of the catheter, and all on one side. A Replogle is the preferred tube for continuously draining saliva from a proximal esophageal pouch in TEF, where one lumen is for drainage of saliva and the other functions as an air vent. Adequate drainage of the proximal esophageal pouch is essential to prevent saliva from spilling over into the trachea, which can result in aspiration or pneumonia.

For this purpose, a 10 French Replogle is recommended. A Replogle may also be used for gastric decompression in preterm babies because the close proximity of all of the drainage holes along the distal most end may allow all of the drainage holes to be located within the stomach compared to the Salem Sump where the drainage holes are more widely spaced apart.

c. A Vygon tube is recommended for gastric decompression. The 10 French has five holes on each side, the bottom two vent and the top eight are for suction.

d. A feeding tube should be avoided for the purpose of decompression because it has only a single hole and is prone to blockage.

2. **Pneumoperitoneum** is a surgical emergency that may result from any perforation of the GI tract. Viable bowel may depend on time to intervention (see Chapter 27).

   a. Any portion of the GI tract can potentially perforate for a variety of reasons including poor bowel wall integrity (e.g., necrotizing enterocolitis or localized ischemia of the stomach or small bowel associated with some medications such as indomethacin) and excessive pressure (e.g., obstruction, TEF, or instrumentation [i.e., with a nasogastric tube]). Perforated stomach is associated with large amounts of free intra-abdominal air. Active GI air leak requires urgent surgical closure. It may be necessary to aspirate air from the abdominal cavity to relieve respiratory distress before definitive surgical repair.

   b. Air from a pulmonary air leak may dissect into the peritoneal cavity of infants receiving mechanical ventilation. Treatment of pneumoperitoneum transmitted from pulmonary air leak should focus on managing the pulmonary air leak.

3. **Abdominal compartment syndrome** refers to multiple organ dysfunction that arises as a consequence of increased intra-abdominal pressure. This may occur as a severe consequence of necrotizing enterocolitis. Clinical signs include a taut, tense abdomen with evolving erythema. Immediate surgical intervention is required to reduce intra-abdominal pressure.

4. **Intestinal obstruction**

   a. EA with distal TEF (see section IV.A) can present as abdominal distension. Obstruction of proximal bowel (e.g., complete duodenal atresia) typically results in rapid distension of the left upper quadrant. Obstruction of distal bowel produces more generalized distention, varying with location of obstruction.

   b. Obstruction may be suspected when the progression of the air column through the gut is slowed or halted. Normally, when assessed by plain radiographs, air is seen 1 hour after birth at a point past the stomach and into the upper jejunum; 3 hours after birth, it is at the cecum; 8 to 12 hours after birth, it is at the rectosigmoid. This progression is slower in the premature infant.

E. Vomiting. The causes of vomiting can be differentiated by the presence or absence of bile.

1. **Bilious emesis.** The presence of bile-stained emesis in the newborn should be treated as a life-threatening, surgical emergency. Bilious emesis

may appear yellow or green and occurs in the setting of obstruction distal to the ampulla of Vater. Surgical consultation should be obtained immediately. Of patients with malrotation, volvulus occurs in the first week of life in 30% and in the first month of life in 50%. Plain radiographs are typically normal. In stable infants an upper gastrointestinal (UGI) should be performed to document the location of the duodenum and ligament of Treitz.

Intestinal obstruction may result from malrotation with or without midgut volvulus; duodenal, jejunal, ileal, or colonic atresias; annular pancreas; Hirschsprung disease; aberrant superior mesenteric artery; preduodenal portal vein; peritoneal bands; persistent omphalomesenteric duct; or duodenal duplication.

Bile-stained emesis is occasionally seen in infants without intestinal obstruction who have decreased motility (see section III.E.2.c). In these cases, the bile-stained vomiting will only occur one or two times and will present without abdominal distention. However, a nonsurgical condition is a diagnosis of exclusion; bilious emesis is malrotation with volvulus until proven otherwise.

2. **Nonbilious emesis**
   - **a.** Feeding excessive volume
   - **b.** Milk (human or formula) intolerance
   - **c.** Decreased motility
     - **i.** Prematurity
     - **ii.** Antenatal exposure to magnesium sulfate ($MgSO_4$) or ante-, pre-, or postnatal exposure to narcotics
     - **iii.** Sepsis with ileus
     - **iv.** Central nervous system (CNS) lesion
   - **d.** Lesion above ampulla of Vater
     - **i.** Pyloric stenosis
     - **ii.** Upper duodenal stenosis
     - **iii.** Annular pancreas (rare)

F. Failure to pass meconium can occur in sick and/or premature babies with decreased bowel motility. It also may be the result of the following disorders:

1. Imperforate anus
2. Microcolon
3. Mucous plug
4. Meconium ileus (see section V.D.3)
5. Other causes of intestinal obstruction

G. Failure to develop transitional stools after the passage of meconium

1. Volvulus, other intestinal obstruction

H. Hematemesis or hematochezia

1. **Nonsurgical conditions.** Many patients with hematemesis, and most patients with **hematochezia** (bloody stools), have a nonsurgical condition. Differential diagnosis includes the following:
   - **a.** Milk intolerance/allergy (usually cow's milk protein allergy)
   - **b.** Instrumentation (e.g., nasogastric tube, endotracheal tube)

c. Swallowed maternal blood
   i. Maternal blood is sometimes swallowed by the newborn during labor and delivery. This can be diagnosed by an Apt test performed on blood aspirated from the infant's stomach.
   ii. In breastfed infants, either micro- or macroscopic blood noted several days after birth in either emesis or stool may be due to swallowed blood during breastfeeding in setting of cracked maternal nipples. Inspecting the mother's breasts or expressed milk is usually diagnostic. If not, aspirate the contents of the baby's stomach after a feeding and send the recently swallowed milk for an Apt test.

d. Coagulation disorders including disseminated intravascular coagulation (DIC), lack of postnatal vitamin K injection (see Chapter 43)

2. **Surgical conditions** resulting in hematemesis and bloody stool
   a. Necrotizing enterocolitis (most frequent cause of hematemesis and bloody stool in premature infants; see Chapter 27)
   b. Gastric or duodenal ulcers (due to stress, steroid therapy)
   c. GI obstruction: late sign, concerning for threatened or necrotic bowel
   d. Volvulus
   e. Intussusception
   f. Polyps, hemangiomas
   g. Meckel diverticulum
   h. Duplications of the small intestine

I. **Abdominal masses** (see section IX)
   1. Genitourinary anomalies including distended bladder (see section VIII; see Chapter 28)
   2. Hepatosplenomegaly: may be confused with other masses; requires medical evaluation
   3. Tumors (see section VIII)

J. **Birth trauma** (see Chapter 6)
   1. Fractured clavicle/humerus (see Chapter 58)
   2. Intracranial hemorrhage (see Chapter 54)
   3. Skull fracture
   4. Lacerated solid organs—liver, spleen
   5. Spinal cord transection with quadriplegia

IV. LESIONS CAUSING RESPIRATORY DISTRESS

A. **EA and TEF.** At least 85% of infants with EA also have a TEF. A proximal EA with a distal TEF is most common. Pure EA and EA with proximal TEF may be suspected on prenatal ultrasonography by the absence of a stomach bubble.
   1. **Postnatal presentation** depends on the presence or absence as well as location of a TEF.
      a. Infants often present with excessive salivation and vomiting soon after feedings. They may develop respiratory distress due to the following:
         i. Airway obstruction by excess secretions
         ii. Aspiration of saliva and milk

iii. Compromised pulmonary capacity due to diaphragmatic elevation secondary to abdominal distension

iv. Reflux of gastric contents up the distal esophagus into the lungs through the fistula

b. If there is no fistula, or if the fistula connects the trachea to the esophagus proximal to the atresia, no GI gas will be seen on x-ray examination, and the abdomen will be scaphoid.

c. A fistula distal to the EA allows air to enter the GI tract. Positive pressure ventilation should be avoided in order to avoid distention of the stomach.

d. TEF without EA (H-type fistula) is extremely rare and usually presents after the neonatal period. The diagnosis is suggested by a history of frequent pneumonias or respiratory distress temporally related to meals.

2. **Diagnosis**

a. EA itself is diagnosed by the inability to pass a catheter from the mouth or nose into the stomach. The catheter is inserted into the esophagus until resistance is met. Air is then injected into the catheter while listening (for lack of air) over the stomach. The diagnosis is confirmed by x-ray studies showing the catheter coiled in the upper esophageal pouch. Plain x-ray films may demonstrate a distended blind upper esophageal pouch filled with air that is unable to progress into the stomach. (The plain films may also show associated vertebral anomalies of the cervical or upper thoracic region of the spine.)

b. H-type fistula. This disorder can often be demonstrated with administration of nonionic water-soluble contrast medium (Omnipaque) during cinefluoroscopy. The definitive examination is combined fiberoptic bronchoscopy and esophagoscopy with passage of a fine balloon catheter from the trachea into the esophagus. The H-type fistula is usually high in the trachea (cervical area).

3. **Associated issues and anomalies.** Babies with TEF and EA are often of low birth weight. Other anomalies may be present in up to 50% of patients with TEF and EA, including chromosomal abnormalities and the VACTERL association: **V**ertebral defects, imperforate **A**nus, **C**ardiac defects, **TE**F with EA, **R**enal dysplasia or defects and **L**imb anomalies.

4. **Management.** Preoperative management focuses on minimizing the risk of aspiration and avoiding gaseous distension of the GI tract with positive pressure crossing from the trachea into the esophagus.

a. A multiple end-hole suction catheter (Replogle or Vygon) is placed in the proximal pouch and put to continuous suction immediately after the diagnosis is made. Adequate drainage of the proximal esophageal pouch is essential to prevent saliva from spilling over into the trachea, which can result in aspiration or pneumonia.

b. The head of the bed should be elevated 30 to 45 degrees. This maneuver is to reduce reflux of gastric contents into the fistula and aspiration of oral secretions. These oral secretions may accumulate in the proximal esophageal pouch resulting in gastric distension.

c. If possible, mechanical ventilation of these babies should be avoided until the fistula is controlled because the positive pressure may cause severe abdominal distension compromising respiratory function. If intubation is required, the case should be considered an emergency. Guidelines for intubation are the same as for other types of respiratory distress. Advancement of the endotracheal tube to just above the carina may decrease airflow through the fistula. Most commonly, the fistula connects to the trachea near the carina. Care must be taken to avoid accidental intubation of the fistula. Optimally, if mechanical ventilation is required, it should be done using a relatively high rate and low pressure to minimize GI distention. Heavy sedation should be avoided because it compromises the patient's spontaneous respiratory effort, which generates negative intrathoracic pressure, minimizing passage of air through the fistula into the esophagus resulting in gastric distension.

d. Surgical therapy usually involves immediate placement of a gastrostomy tube. If the patient is of adequate size and stability, the fistula is divided, and if possible, the proximal and distal ends of the esophagus are anastomosed primarily.

e. Coincident prematurity or the presence of associated defects may make it advisable to delay primary repair. Mechanical ventilation and nutritional management may be difficult in these infants due to the TEF. These patients require careful nursing care to prevent aspiration and gastrostomy with G-tube feedings to allow growth until repair is possible. In some cases, the fistula can be divided, with deferral of definitive repair.

f. An echocardiogram (ECHO) is performed preoperatively to determine the side of approach. If the infant has cardiac disease that requires surgery, it is usually best to repair the fistula first. If not, the postoperative ventilatory management can be very difficult.

g. Patients with long-gap EA can be extremely challenging to manage and may require multiple surgical interventions. Transfer to a referral center that specializes in long-gap EA should be considered. Bolus feeds to the stomach are used to promote growth of the distal pouch over months prior to definitive anastomosis. Some centers have developed innovative esophageal growth induction techniques that can allow for primary repairs thereby avoiding the need for gastric, colonic, or jejunal interposition.

B. CDH

1. **Anatomy.** The most common site is the left hemithorax, with a posterior defect in the diaphragm (foramen of Bochdalek), in 70% of infants. It can also occur on the right, with either an anterior or a posterior defect. Bilateral CDH is extremely rare.
2. **Incidence.** CDH occurs in approximately 1 in 2,500 live births. Thirty percent to 40% of these hernias are associated with other malformations, especially cardiac, neural tube, intestinal, skeletal, and renal defects. CDH has been associated with aneuploidies including trisomy 13, trisomy 18, and monosomy X (Turner syndrome), as well as several microdeletions including 22q11.2, 15q26, 8p23.1, and 1q41–42, among

others. CDH has also been reported as part of many syndromes including Goldenhar, Beckwith-Wiedemann syndrome (BWS), Wolf-Hirschhorn (4p deletion), Pallister-Killian (tetrasomy 12p), Fryns, Cornelia de Lange, craniofrontonasal, Donnai-Barrow, Simpson-Golabi-Behmel, Goltz-Gorlin, and congenital rubella. In rare cases, CDH is familial.

3. **Symptoms.** Infants with large a CDH usually present at birth with cyanosis, respiratory distress, a scaphoid abdomen, decreased or absent breath sounds on the side of the hernia, and heart sounds displaced to the side opposite the hernia. Small hernias (both right and left sided), sac-type hernias, eventrations and substernal, central hernias of Morgagni may have a more subtle and/or later presentation, manifested as feeding problems and mild respiratory distress. Associated structural malformations include congenital heart disease (CHD), neural tube defects, skeletal anomalies, intestinal atresias, and renal anomalies.

4. **Diagnosis**

   a. Prenatal diagnosis. CDHs often develop around 10 to 12 weeks of gestation and are most often diagnosed on a routine 20-week anatomy ultrasonography scan. If not detected, the development of polyhydramnios should prompt a later fetal ultrasonography that will detect CDH. Diagnosis earlier in gestation may correlate with a poorer prognosis due to severity of condition. In rare cases, a CDH is diagnosed on a 12-week ultrasound.

   i. The prognostic advantage of prenatal diagnosis is that it generally leads to delivery in a center equipped to optimize chances for survival. If delivery before term is likely, fetal lung maturity should be assessed to evaluate the need for maternal betamethasone therapy (see Chapter 33).

   ii. There are several prenatal markers to assess the severity of pulmonary hypoplasia and predict outcomes in infants with CDH including lung area/head circumference ratio (LHR), observed-to-expected (O/E) LHR, and liver herniation. These are best measured in skilled hands using fetal ultrasound and MRI. LHR is calculated by dividing the two-dimensional area of the contralateral lung (taken at the level of the four-chamber view of the heart) by the head circumference. Although earlier studies used an LHR of 1.4 as a cutoff for poor prognosis, more recent studies have demonstrated an LHR of <1.0 to be a predictor of poor outcomes. Studies on normal fetuses have shown that between 12 and 32 weeks of gestation, there is a 16-fold increase in lung area versus a 4-fold increase in head circumference. To correct for gestational age, LHR is now expressed as a percentage of what can be expected in a normal fetus or O/E LHR, which has been further classified as extreme ($<15\%$), severe (15% to 25%), moderate (26% to 35%), and mild (36% to 45%). Estimation of absolute and relative fetal lung volumes using MRI has also been used to predict survival in fetuses with CDH. Fetuses with a percent predicted lung volume (PPLV) $<15\%$ had significantly higher extracorporeal membrane oxygenation (ECMO) use and poorer outcomes. Based on O/E LHR and liver herniation data from an antenatal

CDH registry in Europe, the overall survival rates for isolated left-sided CDH were approximately 0%, 20%, 30% to 60%, and >75% for extreme, severe, moderate, or mild O/E LHR. ECMO is required in about 30% to 40% of all infants with CDH, including 80% with liver herniation versus 25% without liver herniation.

b. Postnatal diagnosis. The diagnosis is made or confirmed by radiograph.

c. Differential diagnosis. Diaphragmatic eventration, CPAM, pulmonary sequestration, bronchogenic cyst

5. **Treatment**

a. An EXIT procedure with immediate institution of ECMO has been attempted for severe cases of CDH that have been diagnosed before birth but has not been shown to provide survival benefit (see Chapter 39).

b. Intubation. All infants with known CDH are intubated immediately after delivery or at the time of postnatal diagnosis. Bag-and-mask ventilation is contraindicated. Immediately after intubation, a large sump gastric tube should be inserted and attached to **continuous** suction. Care must be taken with assisted ventilation to keep inspiratory pressures low to avoid damage or rupture of the contralateral lung. Some centers place peripheral venous and arterial lines as umbilical lines may require removal during surgery. However, if umbilical lines are the only practical access, these should be placed initially. An umbilical venous line may be difficult to place depending on the position of the liver.

c. Preoperative management is focused on avoiding barotrauma with permissive hypercapnia. The optimal mode of ventilation remains controversial, including the role for high-frequency ventilation. Avoidance of hypoxia and acidosis aids in minimizing pulmonary hypertension. Inhaled nitric oxide treatment has been associated with improved oxygenation and reduced need for ECMO in a subpopulation of patients with CDH and pulmonary hypertension with normal left ventricular systolic function. Thus, a trial of inhaled nitric oxide may be beneficial in certain patients prior to escalating to ECMO. Exogenous surfactant should be reserved for premature delivery.

6. **Surgical repair.** Reduction of the intestines into the abdominal cavity is performed either by an abdominal or a thoracic approach.

7. **Mortality and prognosis**

a. Mortality from CDH is largely related to the degree of pulmonary hypoplasia, the size of diaphragmatic defect, pulmonary hypertension, and any other associated anomalies, especially CHD. The size of the diaphragmatic defect is particularly important; complete diaphragm agenesis is associated with the most severe underlying pulmonary hypoplasia and pulmonary hypertension, which in turn is associated with decreased survival. Overall survival is approximately 65% to 70% nationally, with survival as high as 90% in some tertiary care centers. The degree of underlying pulmonary hypoplasia and pulmonary hypertension are largely responsible for overall mortality (see Chapter 36).

b. Prognosis. Factors associated with better prognosis include herniation of bowel into chest later in gestation, absence of liver herniation, and absence of coexisting anomalies, especially cardiac. The severity of pulmonary hypertension is extremely important in prognosis.

C. Other mechanical causes for respiratory distress

1. **Choanal atresia.** Bilateral atresia presents in the delivery room as respiratory distress that resolves with crying, during which breathing is oral, rather than the usual obligate nasal breathing of infants less than approximately 4 months of age. An oral airway is an effective initial treatment. Definitive therapy involves transnasal removal of the atretic plate with the use of a telescope and small drill or a transpalatal repair with an intra-oral incision through the palate enabling direct visualization and repair. A laser can be used in some settings. Choanal atresia may be associated with various other anomalies and may occur as part of CHARGE syndrome, Treacher Collins syndrome, or Tessier syndrome. CHARGE syndrome, which consists of **C**olobomas, **H**eart disease, **A**tresia choanae, **R**etarded growth and development, **G**enital anomalies, and **E**ar anomalies, is most common and occurs in approximately 25% of infants with bilateral choanal atresia.
2. **Pierre Robin sequence (PRS)** consists of a hypoplastic mandible associated with a secondary U-shaped midline cleft palate. Often, the tongue occludes the airway producing an obstruction. Prone positioning or forcibly pulling the tongue forward will relieve the obstruction. These infants may need continuous positive airway pressure if relatively mild obstructive symptoms or may require intubation if more severe. If the infant can be supported for a few days, he or she will sometimes adapt, and aggressive procedures may be avoided. A polysomnogram can be helpful to determine the degree of obstruction. In some cases, mandibular distraction can avoid the need for continuous positive airway pressure or tracheostomy, or may enable earlier decannulation if tracheostomy is required. A specialized feeder (Breck) facilitates oral feeding the infant, but sometimes, a gastrostomy tube is necessary. Severely affected babies will require a tracheostomy and gastrostomy tube. Infants with PRS will benefit from a multidisciplinary team including plastic surgery, pulmonary medicine, ear, nose, and throat (ENT), and genetics. Approximately 60% of infants with PRS have an associated genetic syndrome, including Stickler syndrome in >30% of infants with PRS. Other common associated syndromes include 22q11.2 microdeletion syndrome and cerebrocostomandibular syndrome.
3. **Laryngotracheal clefts.** During the fourth week of development, the respiratory tract begins to bud from a single tube known as the foregut. The trachea and esophagus are progressively separated from one another, starting caudally and progressing toward the larynx. Disruption of this developmental process may lead to clefting or fistula formation between the two structures. Laryngeal clefts are almost always on the posterior aspect of the larynx and trachea with communication to the esophagus. The length of the cleft determines the symptoms. The diagnosis is made by direct bronchoscopy under anesthesia.
   a. Laryngotracheal clefts are typically divided into five types:
      i. Type I: supraglottic interarytenoid cleft
      ii. Type II: partial cricoid cleft extending below the vocal cords

iii. Type III: complete cricoid cleft extending into the cervical trachea
iv. Type IV: complete cleft extending into the thoracic trachea
v. Type V: cleft to or beyond the carina

b. Although type I clefts may be seen in isolation, more severe laryngotracheal clefts are associated with other anomalies of the tracheobronchial tree, including TEF/EA, focal stenosis of the airway (subglottic stenosis, tracheal stenosis), cysts, or hamartomas. Cleft lip/palate, CHD, and malformations of the GI or genitourinary tract. Laryngotracheal clefts may be seen in association with Down syndrome, Opitz G/BBB syndrome, Pallister-Hall syndrome, and mosaic deletions involving the long arm of chromosome 13.

4. **Laryngeal web occluding the larynx.** Perforation of the web by a stiff endotracheal tube or bronchoscopy instrument may be lifesaving.

5. **Tracheal agenesis.** This rare lesion is suspected when a tube cannot be passed down the trachea. The infant ventilates by way of bronchi coming off the esophagus. Diagnosis is by direct bronchoscopy. Prognosis is poor as tracheal reconstruction is difficult.

6. **Tracheal stenosis** can occur congenitally from tracheal cartilaginous sleeves or from complete tracheal rings. Acquired tracheal stenosis can occur as a result of prolonged or traumatic intubations or other causes of irritation and injury. A few tracheal rings can be surgically resected; however, long segments of complete tracheal rings may require a slide tracheoplasty.

7. **Congenital high airway resistance syndrome (CHAOS)** occurs in patients with laryngeal or tracheal atresia or stenosis. Obstruction may due to teratomas, hemangiomas, or complex cervicofacial lymphatic malformations.

   a. Diagnosis. CHAOS is typically detected via ultrasound findings of polyhydramnios, large and echogenic lungs, a dilated trachea, and a flattened or inverted diaphragm. Ascites and nonimmune hydrops due to severe neck edema may also be present. The lesion can then be confirmed and better characterized on fetal MRI. The obstructed fetal lung field leads to distension of the tracheal bronchial tree and enlarged, echogenic lungs.

   b. Delivery. Due to the high probability of requiring a surgical airway, these patients are typically delivered via an EXIT procedure, allowing placental bypass to oxygenate the neonate while securing the airway. In many instances, endotracheal intubation is performed via rigid bronchoscopy or immediate placement of a tracheostomy. If a patient presents without prenatal diagnosis, rapid tracheostomy is the only treatment option.

   c. Due to the high risk of fetal demise, the true incidence of CHAOS is unknown. It can occur sporadically or as part of a syndrome, most commonly, Fraser syndrome, Cri-du-Chat, short rib polydactyly syndrome, or velocardiofacial syndrome.

8. **Congenital lobar emphysema** may be due to a malformation, a cyst in the bronchus, or a mucous or meconium plug in the bronchus. These lesions produce air trapping, compression of surrounding

structures, and respiratory distress. There may be a primary malformation of the lobe (polyalveolar lobe). Overdistension from mechanical ventilation may result in lobar emphysema. Extrinsic pressure on a bronchus can also cause obstruction. Lower lobes are generally relatively spared. Diagnosis is by chest x-ray.

a. High-frequency ventilation may enable the lobar emphysema to recover (see Chapter 29).

b. Selective intubation. After consultation with a surgeon, selective intubation of the opposite bronchus may be attempted in an effort to decompress the emphysematous lobe if overinflation is thought to be the cause. It should generally be viewed as a temporizing therapy and not be employed for more than a few hours. Many infants will not tolerate this procedure due to both overdistension of the ventilated lung and profound ventilation–perfusion mismatch; therefore, it must be carefully considered and monitored. Rarely, selective intubation is successful and the lobar emphysema does not recur. Much more commonly, even if the selective intubation is initially helpful, the infant develops recurrence and progression of the emphysema and further respiratory compromise. Occasionally, selective suctioning of the bronchus on the side of the emphysema may remove obstructing mucus or meconium.

c. Bronchoscopy, resection. If the infant is symptomatic and conservative measures fail, bronchoscopy should be performed to remove any obstructing material or to rupture a bronchogenic cyst. If this procedure fails, surgical resection of the involved lobe should be considered.

9. **CPAM and bronchopulmonary sequestration (BPS).** Both CPAMs and BPS are nonfunctioning masses of lung tissue. Most CPAMs derive their blood supply from the pulmonary artery and drain via the pulmonary veins. This is in contrast to a BPS, which lacks normal communication with the tracheobronchial tree and receives its arterial blood supply from the systemic circulation. Hybrid lesions, which are a combination of a CPAM and a BPS are characterized by an abnormal blood supply from two sources: an arterial blood vessel branching from the aorta as well as a vessel from the lungs. The type is not as important as the size and how much it enlarges during the pregnancy. Respiratory distress is related to the effect of the mass on the uninvolved lung, which can cause shifting of the mediastinal structures. Depending on the size and effect of the CPAM, it may be resected prenatally with open fetal surgery, at delivery with an EXIT procedure, immediately after delivery or postnatally. If the infant is stable postnatally, resection is often delayed until the infant is approximately 6 to 12 weeks of age. In the absence of respiratory distress, resection is performed to reduce infectious and oncologic risk.

10. **Vascular rings.** The symptomatology of vascular rings is related to the anatomy of the ring. Both respiratory (stridor) and GI (vomiting, difficulty swallowing) symptoms may occur. Barium swallow radiography may be diagnostic. MRI can be useful to more clearly delineate the anatomy, especially in the setting of double aortic arch. An ECHO may be necessary to rule out intracardiac anomalies. Bronchoscopy can be helpful if tracheal stenosis is suspected.

V. LESIONS CAUSING INTESTINAL OBSTRUCTION. The most critical lesion to rule out is malrotation with midgut volvulus. All patients with suspected intestinal obstruction should have a gastric sump catheter placed to continuous suction without delay. Any infant with a GI obstruction is at increased risk for exacerbated hyperbilirubinemia due to increased enterohepatic circulation.

A. Congenital mechanical obstruction

1. Intrinsic types include areas of atresia or stenosis, meconium ileus (most commonly associated with cystic fibrosis [CF]), small left colon syndrome, cysts within the lumen of the bowel, and imperforate anus.
2. Extrinsic forms of congenital mechanical obstruction include congenital peritoneal bands with or without malrotation, annular pancreas, duplications of the intestine, aberrant vessels (usually the mesenteric artery or preduodenal portal vein), hydrometrocolpos, and obstructing bands (persistent omphalomesenteric duct).

B. Acquired mechanical obstruction

1. Malrotation with volvulus
2. Strictures secondary to necrotizing enterocolitis
3. Peritoneal adhesions
   a. After meconium peritonitis
   b. After abdominal surgery
   c. Idiopathic
4. Incarcerated inguinal hernia (relatively common in premature infants)
5. Hypertrophic pyloric stenosis
6. Mesenteric thrombosis
7. Intussusception; unusual in neonatal period

C. Functional intestinal obstruction constitutes the major cause of intestinal obstruction seen in the neonatal unit.

1. Immature bowel motility
2. Defective innervation (Hirschsprung disease) or other intrinsic defects in the bowel wall
3. Paralytic ileus
   a. Induced by medications
      i. Narcotics (pre- or postnatal exposure)
      ii. Hypermagnesemia usually due to prenatal exposure to magnesium sulfate
   b. Septic ileus
4. Meconium ileus, 90% of cases associated with CF
5. Meconium and mucous plugs
6. Formation of abnormal intestinal concretions not associated with CF
7. Endocrine disorders (e.g., hypothyroidism)

D. The more common etiologies of GI obstruction warrant more detailed discussion.

1. **Duodenal atresia.** Seventy percent of cases have other associated malformations, including cardiovascular anomalies and GI anomalies,

such as annular pancreas, EA, malrotation of the small intestine, other small-bowel atresias, and imperforate anus. Twenty-five percent of cases have trisomy 21.

a. There may be a history of polyhydramnios.

b. It is commonly diagnosed prenatally by ultrasonography.

c. Vomiting of bile-stained material usually begins a few hours after birth.

d. Abdominal distention is limited to the upper abdomen.

e. The infant may pass meconium in the first 24 hours of life and then bowel movements cease.

f. The diagnosis is suggested if aspiration of the stomach yields >30 mL of gastric contents before feeding.

g. A plain radiograph of the abdomen will show air in the stomach and upper part of the abdomen ("double bubble") with no air in the small or large bowel. Contrast radiographs of the upper intestine are not mandatory.

h. Preoperative management includes gastric decompression.

i. Surgical repair with duodenoduodenostomy

2. **Jejunal and ileal atresias.** Most are thought to be the result of intrauterine vascular accidents, but as many as 15% to 30% are associated with CF; these patients should therefore be screened (see section V.D.3.b).

3. **Meconium ileus is a frequent cause of meconium peritonitis.** Unlike most other etiologies of obstruction in which flat and upright x-ray films will demonstrate fluid levels, in cases of nonperforated meconium ileus, the distended bowel may be granular in appearance or may show tiny bubbles mixed with meconium.

a. No meconium will pass through the rectum, even after digital stimulation.

b. Ninety percent of babies with meconium ileus have CF. Immunoreactive trypsinogen levels are used to screen newborns for CF on the newborn screen. If elevated, the screen will reflex to testing for the most common CF mutations. However, a sweat test is still the gold standard for diagnosis. Any newborn that weighs >2 kg and is ≥36 weeks' postmenstrual age and ≥10 days chronologic age should have a sweat test performed as soon as possible. Sweat tests on babies who are younger or smaller risk both false-positive results due to the high sodium chloride (NaCl) content of the sweat of newborn babies and false-negative or uninterpretable results when an adequate volume of sweat cannot be obtained. For infants with presumptive CF identified through newborn screening, CF treatment should not be delayed while efforts to establish a diagnosis of CF are initiated.

c. Gastric decompression with continuous suction will minimize further distention. Contrast enemas with water-soluble agents can be both diagnostic and therapeutic. Diluted (1:3 to 1:4) diatrizoate meglumine (Gastrografin) is still used by some radiologists, but more commonly, diatrizoate sodium (Hypaque) is employed. Because these contrast agents are hypertonic, the baby should start the procedure well hydrated, and careful attention should be paid to fluid balance after the procedure. If the diagnosis is certain and the neonate stable,

repeat therapeutic enemas may be administered in an effort to relieve the impaction.

i. Surgical therapy is required if the contrast enema fails to relieve the obstruction.

ii. Microcolon distal to the atresia will generally dilate spontaneously with use.

4. **Imperforate anus.** Fifty percent have other anomalies including those with VACTERL association. Infants with imperforate anus may pass meconium if a rectovaginal or rectourinary fistula exists. A fistula is present in 80% to 90% of affected males and 95% of females. It may take 24 hours for the fistula to become evident. The presence or absence of a visible fistula at the perineum is the critical distinction in the diagnosis and management of imperforate anus.

a. Perineal fistula. Meconium may be visualized on the perineum. It may be found in the rugal folds or scrotum in boys and in the vagina in girls. This fistula may be dilated to allow passage of meconium to temporarily relieve intestinal obstruction. When the infant is beyond the newborn period, the imperforate anus can generally be primarily repaired.

b. No perineal fistula present. There may be a fistula that enters the urinary tract or, for girls, the vagina. The presence of meconium particles in the urine is diagnostic of a rectovesicular fistula. Vaginal examination with a nasal speculum or cystoscope may reveal a fistula. A cystogram may show a fistula and document the level of the distal rectum, which can also be defined by ultrasonography. A temporary colostomy may be necessary in neonates with an imperforate anus without a perineal fistula. Primary repair of these infants without a colostomy is now being performed at some institutions.

5. **Malrotation of the bowel** occurs when the intestines do not rotate counterclockwise upon return to the abdomen in early gestation.

a. Malrotation may be associated with other GI abnormalities such as CDH, annular pancreas, bowel atresias, and omphalocele.

b. After birth, a sudden onset of bilious vomiting in an infant who has passed some normal stools may indicate a volvulus of the malrotated bowel as the cause of intestinal obstruction. This is a surgical emergency because intestinal viability is at stake. **Bilious emesis equals malrotation with midgut volvulus until proven otherwise**. Broad-spectrum antibiotics should be initiated if there is suspicion of volvulus or any question about bowel integrity. If the level of obstruction is high, there may not be much abdominal distension. Signs of shock and sepsis may or may not be present. A radiograph of the abdomen will often show a dilated small bowel, although a normal radiograph does not rule out volvulus and is the most common finding. The volvulus may also be intermittent. The test of choice is an UGI tract radiograph, specifically looking for abnormal position of the ligament of Treitz to assess for malrotation, and bowel obstruction to assess for volvulus. If an infant has an acute abdomen with an unclear diagnosis, a laparotomy may be performed.

6. **Meconium and mucous plug syndrome** is seen in infants who are premature or ill (see section III.F). It may be seen in those with functional immaturity of the bowel with a small left colon, as seen in infants of diabetic mothers or those with Hirschsprung disease (see section V.D.7). CF should also be ruled out. Treatment may simply consist of a glycerin suppository, warm saline enemas (5 to 10 mL/kg), and rectal stimulation with a soft rubber catheter. More typically, and if these maneuvers are unsuccessful, a contrast enema with a hyperosmolar contrast material may be both diagnostic and therapeutic. A normal stooling pattern should follow evacuation of a plug.

7. **Hirschsprung disease** should be suspected in any newborn who fails to pass meconium spontaneously by 24 to 48 hours after birth and who develops distension relieved by rectal stimulation. This is especially so if the infant is neither premature nor born to a diabetic mother. The diagnosis should be considered until future development shows sustained normal bowel function.

   a. When the diagnosis is suspected, every effort should be made to rule the condition in or out. If the diagnosis is considered, but seems very unlikely, parents taking the newborn home must specifically understand the importance of immediately reporting any obstipation, diarrhea, poor feeding, distention, lethargy, or fever. Development of a toxic megacolon may be fatal.

   b. Contrast enema frequently does not show the characteristic transition zone in the newborn, and a follow-up radiograph 24 hours after the initial study may reveal retained contrast material.

   c. Rectal biopsy is obtained to confirm the diagnosis. Absence of ganglion cells and hypertrophic nonmyelinated axons is diagnostic. Histochemical tests of biopsy specimens show an increase in acetylcholine. If the suction biopsy shows ganglion cells in the submucosal zone, the diagnosis is ruled out, and no further testing is indicated. If the suction biopsy is of adequate depth and shows no ganglion cells, this is sufficient evidence to proceed to the operating room. Intraoperative biopsies are sent to determine the extent of resection based on the transition zone between histologically normal and aganglionic bowel.

   d. Obstipation can be relieved by gentle rectal irrigations with warm saline solution. If the patient undergoes a barium enema, gentle rectal saline washes are helpful in removing trapped air and barium. Once the abdomen is decompressed, feedings may be offered.

   e. Infants require surgical intervention when the diagnosis is made. Surgical options include a primary pull-through procedure or a leveling ostomy with delayed reanastomosis. The choice of surgical procedure depends on the amount of colon involved, surgeon preference, and the infant's overall degree of illness. A primary pull-through procedure avoids the need for a colostomy. However, in many institutions, colostomy is still the standard, and it is indicated when there is enterocolitis or adequate decompression cannot be achieved. Definitive repair with reanastomosis is postponed until the infant is of adequate size and stability.

f. Even after the aganglionic segment is removed, the bowel that remains is not completely normal. These patients remain at risk for constipation, encopresis, and even life-threatening enterocolitis (toxic megacolon).

8. **Pyloric stenosis** typically presents with nonbilious vomiting, classically in a firstborn male. Presentation is usually after 2 to 3 weeks of age but has been reported in the first week of life. Radiographic examination will show a large stomach with little or no gas below the duodenum. Often, the pyloric mass, or "olive," can be felt in the newborn, most likely after vomiting. The infant may have associated jaundice and hematemesis. Diagnosis can usually be confirmed by ultrasonography, which limits the need for a UGI series and the consequent radiation exposure.
9. **Annular pancreas** occurs when the second part of the duodenum is surrounded by a ring of pancreatic tissue continuous with the head of the pancreas. This portion of the pancreas can constrict the duodenum and impair intestinal flow. It can present as a high intestinal obstruction or may be nonobstructive, *similar to* duodenal atresia or stenosis.
10. **Hydrometrocolpos.** In this rare condition, a membrane across the vagina prevents fluid drainage and the consequent accumulation causes distension of the uterus and vagina.
    a. The hymen bulges.
    b. Accumulated secretions in the uterus may cause intestinal obstruction by bowel compression.
    c. This intestinal obstruction may, in turn, cause meconium peritonitis or hydronephrosis.
    d. Edema and cyanosis of the legs may be observed.
    e. If hydrometrocolpos is not diagnosed at birth, the secretions will decrease, the bulging will disappear, and the diagnosis will be delayed until puberty.

VI. OTHER GASTROINTESTINAL SURGICAL CONDITIONS

A. Omphalocele. The intestines, liver, and/or other abdominal organs are external and covered in a thin sac. Rarely, the sac can rupture. The diagnosis is often made by prenatal ultrasonography. Cesarean section may prevent rupture of the sac but is not specifically indicated unless the defect is large (>5 cm) or contains liver.

1. **Intact sac.** Emergency treatment includes the following:
   a. Provide continuous gastric sump suction.
   b. Using sterile technique, cover the sac with Xeroform, or Vaseline gauze, and then wrap the sac on the abdomen with Kerlix rolled gauze. Some institutions prefer to encase the intestinal contents in a bowel bag (e.g., Vi-Drape or Lahey isolation bag), prior to transport to a referral hospital for ongoing surgical care. Consider placing the infant in a side-lying position while supporting the abdominal wall defect to prevent compression of blood vessels, especially the vena cava. Take great caution to prevent kinking of the mesenteric blood supply.

c. Do not attempt to reduce the sac because it may rupture, interfere with venous return, or result in respiratory compromise. Bowel viability may be compromised with a small abdominal wall defect and an obstructed segment of eviscerated intestine. In these circumstances, with surgical consultation, it may be necessary before transfer, to enlarge the defect by incising the abdominal wall to relieve the strangulated viscera.

d. Place a reliable intravenous (IV) line in an upper extremity.

e. Monitor temperature, pH, and electrolytes.

f. Start broad-spectrum antibiotics (ampicillin and gentamicin).

g. Obtain a surgical consultation; definitive surgical closure versus staged closure will depend on the infant's pulmonary status. In the presence of other more serious abnormalities (respiratory or cardiac), definitive care can be postponed as long as the sac remains intact.

2. **Ruptured sac.** In the setting of sac compromise, surgery is more emergent, and the bowel should be immediately placed in a bowel bag with warm saline. Antibiotics should also be initiated.

3. **Associated anomalies.** **Occur** in up to 80% of cases; physical examination should include a careful search for phenotypic features of chromosomal defects, particularly trisomy 13, 18, or BWS. BWS includes an omphalocele (typically small), macroglossia, hemihypertrophy, and hypoglycemia. The macroglossia in infants with BWS can range from subtle to overt. In subtle cases, the macroglossia may be difficult to appreciate, but intubation may be challenging. A laryngeal mask airway (LMA) should be available at all omphalocele deliveries. Other associated anomalies include CHD (in up to 50%), genitourinary defects such as cloacal exstrophy, craniofacial, musculoskeletal, vertebral, or limb anomalies.

B. Gastroschisis, by definition, contains no sac, and the intestine is eviscerated.

1. For an uncomplicated gastroschisis, there is no advantage to a specific route of delivery. Preoperative management as per omphalocele with ruptured sac (see section VI.A.2). The infant should be placed in a side-lying position to prevent compression of the mesenteric blood vessels. A gastric sump should be placed to continuous suction, and the infant should be immediately placed in a bowel bag up to the chest to cover the bowel with warm saline.

2. These infants are at increased risk for compromised thermoregulation. Keep the baby warm with a warm resuscitation room, early application of a hat, thermal mattress, and warm blankets to prevent heat loss.

3. Obtain immediate surgical consultation to place the bowel in a silo. Returning the bowel into the abdomen can, at times, be reduced right after delivery. If not, a silo is place and decompressions will occur in the silo over a few days until definitive surgical closure or sutureless closure can occur. Sutureless closure involves leaving the abdominal wall defect open and covering it with a synthetic dressing to allow closure by secondary intention. No randomized studies have described the outcomes of this technique.

4. About 12% of these infants will have other GI anomalies, including volvulus, atresias, intestinal stenosis, or perforation. They have a higher rate of postoperative feeding intolerance compared to patients with omphalocele.
5. Unlike omphalocele, gastroschisis is not commonly associated with anomalies unrelated to the GI tract. All gastroschisis patients have intestinal rotation disorders.

C. Appendicitis is extremely rare in newborns. Its presentation may be that of pneumoperitoneum. The appendix usually perforates before the diagnosis is made; therefore, the baby may present with intestinal obstruction, sepsis, or even DIC related to the intra-abdominal infection. In newborns with perforation of the appendix, evaluation for Hirschsprung disease is indicated.

VII. RENAL DISORDERS (see Chapter 28)

A. Genitourinary abnormalities. The first void should be noted in all infants. Approximately 90% of babies void in the first 24 hours of life and 99% within the first 48 hours. Genitourinary abnormalities should be suspected in babies with abdominal distention, ascites, flank masses, persistently distended bladder, bacteriuria, pyuria, or poor growth. Male infants exhibiting these symptoms should be observed for the normal forceful voiding pattern.

1. **Posterior urethral valves** may produce urethral obstruction. Depending on the degree of lower urinary tract obstruction, oligohydramnios, and pulmonary hypoplasia can develop and range from mild to severe. In severe cases of oligohydramnios, Potter sequence can develop with clubbed feet and cranial anomalies in addition to pulmonary hypoplasia (for fetal interventions, see section II.5.c).
2. **Renal vein thrombosis** should be considered in the setting of hematuria with a flank mass. It is more common among infants of diabetic mothers.
   a. Renal ultrasonography will initially show a large kidney on the side of the thrombosis. Kidney will return to normal size over ensuing weeks to months.
   b. Doppler ultrasonography will show diminished or absent blood flow to the involved kidney.
   c. Current treatment in most centers begins with medical support with the possibility of avoiding surgery. Heparin is generally not indicated, but its use has been advocated by some (see Chapters 28 and 44).
3. **Exstrophy of the bladder** is typically detected on fetal ultrasound by the inability to visualize the bladder, presence of normal amniotic fluid volume, low umbilical cord insertion into the abdomen, and umbilical arteries that enter superiorly to the lower abdominal wall defect. It occurs in approximately in 1:50,000 live births, with a male:female ratio 2 to 5:1. It ranges from an epispadias to complete extrusion of the bladder onto the abdominal wall.
   a. If rupture of the cloacal membrane occurs after the descent of the urorectal septum, then bladder exstrophy occurs. If rupture of the cloacal membrane occurs in the absence of the urorectal septum, then cloacal

exstrophy occurs. In classic bladder exstrophy (CBE), the bladder is open on the lower abdomen with the mucosa fully exposed through a triangular defect in the fascia. The abdominal wall appears elongated because of a low set umbilical cord insertion on the upper edge of the bladder plate. The distance between the umbilical cord insertion and anus is foreshortened. The rectus muscles are diverged distally, attaching to the widely separated pelvic bones. Indirect inguinal hernias are frequent, occurring in >10% of females and >80% of males secondary to wide inguinal rings and the lack of an oblique positioning of the inguinal canal. In the **female**, the clitoris is uniformly bifid with divergent labia superiorly. The vagina is anteriorly displaced. The anus is also anteriorly displaced but maintains a normal sphincter mechanism. In the **male**, the penis is open dorsally as in epispadias. The corpora are shorter and wider than normal. The anus is also anteriorly displaced but maintains a normal sphincter mechanism. Prenatal diagnosis of bladder exstrophy does not alter pregnancy management and vaginal delivery is not contraindicated.

b. Preoperative management

i. Protect the exposed bladder mucosa by covering with saline and clear plastic wrap.
ii. Transport the infant to a facility for definitive care as soon as possible.
iii. Provide adequate hydration in setting of increased insensible losses; monitor electrolytes and renal function.
iv. Obtain renal ultrasonography.

c. Intraoperative management. Careful urologic evaluation after birth is critical to determine whether the abnormality is the classic form of bladder exstrophy or a form of cloacal exstrophy that would require an alternate approach to closure. There are many approaches to closing a bladder exstrophy, including immediate repair within 72 hours after birth to avoid osteotomies, a staged approach to close the bladder initially, and later perform the epispadias repair, and a complete repair with closure of the bladder and epispadias concurrently. There is an ongoing Multi-Institutional Bladder Exstrophy Consortium (MIBEC) that is working to improve outcomes for children with bladder exstrophy. Most centers will perform complete primary repair of the exstrophy with a multidisciplinary team with iliac osteotomies, primary bladder closure, urethroplasty, and genital reconstruction performed in a single stage generally at 6 to 12 weeks of age. This has resulted in improved early bladder cycling such that some patients have achieved continence without the need for bladder neck reconstruction. Creation of a neoumbilicus is also important to many of these patients. Goals of therapy include provision of urinary continence with preservation of renal function and reconstruction of functional and cosmetically acceptable genitalia. Males are often left with a hypospadiac urethra that can be repaired at a later time in order to create the best penile length.

4. **OEIS** (**O**mphalocele, **E**xstrophy of the cloaca, **I**mperforate anus, and **S**pinal defects) **complex** represents the most severe manifestation of exstrophy–epispadias sequence. A portion of the large intestine lies outside of the body, and on either side of it are the two halves of the

bladder. In males, the penis is usually flat and short and each penile half is separated. In females, the clitoris is also separated into a right half and left half with an absent vagina.

a. Preoperative management

i. Gender assignment is an important and controversial debate that is still evolving.

Historically, a genetically male infant with a phallus of inadequate size for reconstruction was often assigned to female gender, performing early orchidectomy with subsequent hormone replacement at puberty. With advances in surgical reconstruction, some advocate for assigning gender based on karyotype. However, better understanding of the long-term psychological effects of these practices has made this decision extremely controversial, and no one approach is correct for all patients. Endocrine consultation is critical when deciding phenotypic gender assignment (see Chapter 63), and decisions should be made only after a collaborative discussion including the parents, urologist, surgeon, endocrinologist, neonatologist, and appropriate counselors.

ii. Gastric decompression relieves partial intestinal obstruction. The infant excretes stool through a vesicointestinal fissure that is often partially obstructed.

iii. A series of complex operations is required in stages to achieve the most satisfactory results.

b. Surgical management

i. The focus is first on separating the GI from the genitourinary tract. The hemibladders are sewn together and closed. A colostomy is created, and the omphalocele is closed.

ii. Later stages focus on bladder reconstruction, often requiring augmentation using intestine or stomach.

iii. Subsequent procedures are designed to reduce the number of stomas and create genitalia, although this remains controversial, as described earlier.

VIII. TUMORS

A. Teratomas are the most common tumor in the neonatal period. Although they are most commonly found in the sacrococcygeal area, they can arise anywhere, including the retroperitoneal area or the ovaries. Approximately 10% contain malignant elements. Prenatal diagnosis is often made by ultrasonography. The possibility of dystocia or airway compromise should be considered prenatally. Masses compromising the airway have been successfully managed with an EXIT procedure (see section IV.B.5.a) with establishment of an airway before complete delivery of the baby. Depending on the size and hemodynamic effects of the teratoma, resection may be performed as an open fetal surgery, as a cesarean section to immediate resection, or as a resection up to a few days following delivery (see section II.5.b).

After delivery, evaluation may include rectal examination, ultrasonography, computed tomography (CT), MRI, as well as serum α-fetoprotein and β-human chorionic gonadotropin measurement. Calcifications are often

seen on plain radiographs. Excessive heat loss and platelet trapping are possible complications.

1. SCTs are classified into the following four types:
   - **a.** Type 1—completely external with a small presacral component
   - **b.** Type 2—predominantly external but has significant intrapelvic portion
   - **c.** Type 3—partially external, predominantly intrapelvic with abdominal extension
   - **d.** Type 4—completely internal with no visible external component

   Resection can be performed as an open fetal surgery, as a cesarean section to immediate resection, or as a resection up to a few days following delivery depending on the size and type of SCT. Combined cardiac output should be closely monitored throughout the pregnancy (see section II.E.2).

B. Neuroblastoma is the most common malignant neonatal tumor, accounting for approximately 50% of malignancies, although the overall incidence is rare. The mass is irregular, hard, and ranges in size from minute to massive. There are many sites of origin; the adrenal–retroperitoneal area is the most common. On rare occasions, this tumor can cause hypertension or diarrhea by the release of tumor by-products, especially catecholamines or vasointestinal peptides. Serum levels of catecholamines and their metabolites should be measured. Calcifications can often be seen on plain radiographs. Ultrasonography is the most useful diagnostic test. Prenatal diagnosis by ultrasonography is associated with improved prognosis. Of note, many neuroblastomas diagnosed prenatally resolve spontaneously before birth. Postnatally, there is also a unique type of neuroblastoma staged as 4S ("Special"), where the tumor cells are isolated to one side of the body and involve no more than 10% of the bone marrow. Children with stage 4S disease have an excellent prognosis and usually experience spontaneous remission without treatment.

C. Wilms tumor is the second most common malignant tumor in the newborn. It presents as a smooth flat mass and may be bilateral. One should palpate gently to avoid rupture. Ultrasonography is the most useful diagnostic test.

D. Hemangiomas are the most common tumor of infancy, although they rarely present in the neonate. Precursors such as bumps or telangiectasia may be seen in newborns. They may occur anywhere on the body, including within solid organs or the GI tract. The incidence is estimated at 4% to 5%, and most are benign and resolve spontaneously. Depending on the size, location (airway, orbit, visceral organs), and growth rate, an infantile hemangioma may be treated with topical or oral propranolol. Other tumors such as lymphatic malformations, hepatoblastomas, hepatomas, hamartomas, and nephromas and sarcoma botryoides may be seen in newborns, but they are extremely rare (see Chapter 66).

IX. ABDOMINAL MASSES

A. Renal masses (see section VII; see Chapter 28) are the most common etiology: polycystic kidneys, multicystic dysplastic kidney, hydronephrosis, and renal vein thrombosis.

B. Other causes of abdominal masses include tumors (see section VIII), adrenal hemorrhage, ovarian tumor or cysts, pancreatic cyst, choledochal cyst,

hydrometrocolpos, mesenteric or omental cyst, intestinal duplications, and hepatosplenomegaly.

X. INGUINAL HERNIAS.

An inguinal hernia is found in 5% of premature infants with a birth weight <1,500 g and as many as 30% of infants with a birth weight <1,000 g. It is more common in small for gestational age infants and male infants. In females, the ovary is often in the sac.

A. Surgical repair.

Inguinal hernia repair is the most common operation performed on infants born prematurely. In general, hernias in this patient population can be repaired shortly before discharge home if they are easily reducible and cause no other problems.

1. **Repair before discharge.** Often, the hernia repair is arranged prior to hospital discharge to avoid the risk of incarceration at home. In a term infant, repair is often scheduled when the diagnosis is made. For stable premature infants, repair is usually delayed until just prior to discharge. An incarcerated hernia can usually be reduced with sedation, steady firm pressure, and elevation of the feet. If a hernia has been incarcerated, it is repaired once the edema has resolved. The operation may be difficult and should be performed by an experienced pediatric surgeon. The use of spinal anesthesia has simplified the postoperative care of some infants with lung disease. As infants born prematurely often develop postoperative apnea, they are monitored in the hospital for at least 24 hours after surgery.
2. **Repair after discharge.** Some infants with CLD may be repaired at a later time when their respiratory status has improved. Some well-instructed parents may bring their infant home and then have them readmitted later for repair. The risks and benefits of this option must be weighed carefully because there is a real risk of the hernia incarcerating at home.

XI. SCROTAL SWELLING

A. Differential diagnosis includes the following:

1. **Testicular torsion.** Approximately 70% of the cases of testicular torsion that are diagnosed in the newborn period actually occur prenatally. In the newborn, testicular torsion is generally extravaginal (the twist occurs outside the tunica vaginalis) and is caused by an incomplete attachment of the gubernaculum to the testis, allowing torsion and infarction.

   a. Diagnosis is made by physical examination. The testicle is generally nontender, firm, indurated, and swollen with a slightly bluish or dusky cast of the affected side of the scrotum. If the torsion is acute, rather than longstanding, it will be extremely tender to palpation. The testicle can have a transverse lie or be high-riding. The overlying skin, limited to the scrotum itself, may be erythematous or edematous. Transillumination is negative, and the cremasteric reflex is absent. Ultrasonography employing Doppler flow studies can be helpful if available, but testing should not delay referral for surgery if there is any possibility that the torsion is recent.

   b. Treatment. In the vast majority of cases, the torsed testicle is already necrotic at birth; therefore, surgical intervention will not salvage

the testicle. However, if there is *any possibility* that the torsion occurred recently, and the infant is otherwise healthy, surgical exploration and detorsion should be performed emergently with a goal within 6 hours. This may result in salvage of the torsed testicle. Because there have been reports of bilateral testicular torsion, surgical exploration should include contralateral orchiopexy. Even if emergency exploration is not indicated because of definitive evidence of chronicity of torsion, exploration should be performed on a nonemergent basis to rule out a tumor with clinical and imaging findings identical to testicular torsion.

c. Prognosis. Testicular protheses are available. Oligospermia has been reported after unilateral testicular torsion.

2. **Hydrocele** is the most common cause of scrotal swelling in the newborn, affecting as many as 2% of infants. Hydrocele forms when fluid remains within the processus vaginalis as the testicle descends into the scrotum during normal development. The fluid may be loculated (noncommunicating) in which case the swelling remains unchanged, or there may be a communication allowing the collected fluid volume (and hydrocele size) to vary over time.
3. **Incarcerated hernias** occur when bowel becomes trapped and can lead to bowel strangulation or obstruction.
4. **Trauma/scrotal hematoma.** Most commonly secondary to breech delivery. This is generally bilateral and may present with hematocele, scrotal swelling, and ecchymoses. Typically, transillumination is negative. Resolution is usually spontaneous, but severe cases may require surgical exploration, evacuation of the hematocele, and repair of the testes.
5. **Torsion of the testicular appendage.** Swelling is usually less marked and may present on palpation or as a blue dot on the scrotum. The cremasteric reflexes are preserved, and Doppler flow ultrasonography may be helpful in ruling out testicular torsion. No treatment is needed.
6. **Spontaneous idiopathic scrotal hemorrhage.** This is most common in large for gestational age (LGA) infants. It is distinguishable from torsion by the appearance of a small but distinct ecchymosis over the superficial inguinal ring.
7. **Tumor.** These are usually nontender, solid, and firm. Transillumination is negative.

XII. NEUROSURGICAL CONDITIONS

A. MMC (see Chapter 57). An MMC occurs when there is incomplete closure of the spinal column leaving a section of the spinal cord and spinal nerves exposed through an opening in the back. The exposed spinal cord and nerves are contained in a sac that is exposed to amniotic fluid. Continuous bathing of the fragile developing spinal cord in amniotic fluid over the course of gestation results in progressive neurologic injury. An MMC is almost always diagnosed prenatally via ultrasonography. A fetal MRI will provide additional information about the level of the lesion and the degree of ventriculomegaly and hindbrain herniation. Many infants will require a ventriculoperitoneal shunt and will have impaired motor function. Fetal

MMC repair results in decreased need for a shunt (40% vs. 82% with postnatal repair) and improved motor outcomes.

1. **Prenatal repair** may be an option for some fetuses depending on a variety of factors including gestational age, the level of the MMC lesion on the spine, presence of a Chiari II malformation, and a number of important maternal health factors. There is an increased risk of premature delivery following fetal surgery with an average delivery at 34 weeks' gestation. If not yet delivered, cesarean sections are scheduled at 37 weeks' gestation (see section II.E.6).
   a. Delivery room management following fetal repair is routine newborn resuscitation. The integrity of the incision should be evaluated. Some repairs are performed with an AlloDerm patch. There is no need to cover the patch unless <30 weeks' gestation, in which case, Xeroform gauze should be placed over the patch.
2. **Postnatal repair** typically occurs between 24 and 48 hours of life, thus infants should be delivered at an institution equipped to perform the repair. A cesarean section is performed at 37 weeks' gestation.
   a. Delivery room management following postnatal repair will often be routine newborn resuscitation. Infants with high thoracic lesions may demonstrate respiratory insufficiency and require intubation. The infant should be placed side-lying or prone while suctioning, drying, and evaluating respiratory effort. If the infant needs to be placed supine for airway or vascular access management, he or she should be placed on a foam positioning "donut" or other support apparatus to prevent sac rupture. The lesion should be dressed with a sterile drape and warmed, saline-soaked sterile gauze. Warm saline should be continually reapplied to keep the lesion moist. Latex supplies should be avoided. The infant should remain nothing by mouth (NPO) with IV fluids until neurosurgical evaluation. There will likely be increased insensible losses. Peripheral IV should be placed, preferably in an upper extremity. Antibiotic coverage with ampicillin and cefotaxime at meningitis dosing should be given as soon as possible. If the sac is ruptured, neurosurgery should be contacted immediately.

XIII. COMMON TESTS USED IN THE DIAGNOSIS OF SURGICAL CONDITIONS

A. Abdominal x-ray examinations. A flat plate radiograph of the abdomen kidney-ureter-bladder (KUB) is sufficient for assessing intraluminal gas patterns and mucosal thickness. A left lateral decubitus or cross-table lateral radiograph is obtained to ascertain the presence of free air in the abdomen.

1. Contrast enema may be diagnostic in suspected cases of Hirschsprung disease. It may reveal microcolon in the infant with complete obstruction of the small intestine and may show a narrow segment in the sigmoid in the infant with meconium plug syndrome due to functional immaturity.
2. UGI series with contrast may be used to demonstrate obstructions of the UGI tract.
3. In patients with suspected malrotation, a combination of contrast studies may be necessary, starting with a UGI contrast study. In combination

with air or contrast media, a UGI series will determine the presence or absence of the normally placed ligament of Treitz. A contrast enema may show malposition of the cecum but will not always rule out malrotation. Neonates with intestinal obstruction presumed secondary to malrotation require urgent surgery to relieve possible volvulus of the midgut.

B. Ultrasonography is the preferred method of evaluating abdominal masses in the newborn. It is useful for defining the presence of masses, together with their size, shape, and consistency.

C. MRI is useful to better define the anatomy and location of masses.

D. CT is a modality that is used with decreasing frequency due to large radiation exposure. It is an excellent modality to evaluate abdominal masses as well as their relation to other organs. Contrast enhancement can outline the intestine, blood vessels, kidneys, ureter, and bladder.

E. Intravenous pyelogram (IVP) should be restricted to evaluating genitourinary anatomy if other modalities (ultrasonography and contrast CT) are not available. The IVP dye is poorly concentrated in the newborn.

F. Radionuclide scan of the kidneys can aid in determining function. This is especially useful in assessing complex genitourinary anomalies and in evaluating the contribution of each kidney to renal function.

XIV. GENERAL PREOPERATIVE MANAGEMENT

A. Preoperative planning is critical to a successful surgery and recovery.

B. Labs. Ideally, labs should be drawn the day prior to surgery to determine optimal preoperative hemoglobin and to optimize electrolytes.

C. Fluids and feeds. Patient should be made NPO. Breast milk is generally considered a clear liquid, and many centers will allow a baby to receive breast milk up until 3 hours preoperatively and formula up until 4 hours preoperatively.

D. Vascular access. At least one, and ideally two sites of IV access should be established.

E. Blood products. If concern for blood loss during surgery, such as in major intrathoracic and intra-abdominal surgeries, blood products should be ordered including packed red blood cells, platelets, and fresh frozen plasma, if indicated.

F. Thermoregulation. Close attention should be paid to thermoregulation for transport to and from the operating room.

G. Location Unstable infants may benefit from having a surgical procedure done at bedside.

XV. GENERAL INTRAOPERATIVE MANAGEMENT

A. Monitoring devices

1. Temperature probe
2. Electrocardiogram (ECG) and/or cardiovascular (CVR) monitor

3. Pulse oximetry responds rapidly to changes in patient condition but is subject to artifacts.
4. Arterial cannula to monitor blood gases and pressure

B. Well-functioning IV line. Babies with omphalocele, gastroschisis, or MMC should have the IV line in the upper extremities, neck, or scalp.

C. Maintenance of body temperature

1. Warmed operating room
2. Humidified, warmed anesthetic agents
3. Warmed blood and other fluids used intraoperatively
4. Cover exposed parts of the baby, especially the head (with a hat); thermal devices (thermal mattress, Bair Hugger, etc.).

D. Fluid replacement

1. Replace ascites loss with normal saline mL per mL to maintain normal blood pressure.
2. The neonate loses approximately 5 mL of fluid per kilogram for each hour that the intestine is exposed. This should generally be replaced by lactated Ringer solution.

E. Anesthetic management of the neonate is reviewed in Chapter 70.

F. Postoperatively, the newborn fluid requirement must be monitored closely, including replacement of estimated losses due to bowel edema, as well as losses through drains.

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65 Skin Care and Conditions

Denise Casey and Arin K. Greene

KEY POINTS

- Primary treatment of intravenous (IV) extravasation injuries is elevation of the affected area.
- Hot or cold packs should not be applied to an extravasation site.
- Evidence proving the efficacy of antidotes for extravasation injuries does not exist.
- IV extravasation rarely causes significant morbidity if skin loss occurs; it heals secondarily with local wound care.

I. INTRODUCTION. The skin performs a vital role in the newborn period. It provides a protective barrier that assists in the prevention of infection, facilitates thermoregulation, and helps control insensible water loss and electrolyte balance. Other functions include tactile sensation and protection against toxins. The neonatal intensive care unit (NICU) environment presents numerous challenges to maintaining skin integrity. Routine care practices including bathing, application of monitoring devices, intravenous (IV) catheter insertion and removal, tape application, and exposure to potentially toxic substances disrupt normal barrier function and predispose both premature and term newborns to skin injury. This chapter describes developmental newborn aspects of skin integrity, skin care practices in the immediate newborn period, and common skin disorders.

II. ANATOMY. The two layers of the skin are the epidermis and dermis. The epidermis is the outermost layer providing the first line of protection against injury. It performs a critical barrier function, retaining heat and fluid and providing protection from infection and environmental toxins. Its structural development has generally occurred by 24 weeks' gestation, but epidermal barrier function is not complete until after birth. Maturation typically takes 2 to 4 weeks following exposure to the extrauterine environment. The epidermis is composed primarily of keratinocytes, which mature to form the stratum corneum. The dermis is composed of collagen and elastin fibers that provide elasticity and connect the dermis to the epidermis. Blood vessels, nerves, sweat glands, and hair follicles are another integral part of the dermis. The subcutaneous layer, composed of fatty connective tissue, provides insulation, protection, and calorie storage.

The premature infant has significantly fewer layers of stratum corneum than term infants and adults, which can be seen by the translucent, ruddy

appearance of their skin. Infants born at <30 weeks may have <2 to 3 layers of stratum corneum compared with 10 to 20 in adults and term newborns. The maturation of the stratum corneum is accelerated following premature birth and improved barrier function, and skin integrity is generally present within 10 to 14 days. Other differences in skin integrity in premature infants include decreased cohesion between the epidermis and dermis, less collagen, and a marked increase in transepidermal water loss.

III. SKIN CARE PRACTICES. Routine assessment, identification, and avoidance of harmful exposures combined with early treatment can eliminate or minimize neonatal skin injury. The identification of potential risk factors for injury and the development of skin care policies and guidelines are an essential part of providing care to both premature and term newborns.

An evidence-based neonatal skin care guideline was created through the collaboration of the National Association of Neonatal Nurses (NANN) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN)[1] in an effort to provide clinical practice recommendations for practitioners caring for newborns from birth to 28 days of age. This guideline provides a comprehensive reference for developing unit-based skin care policies.

A. Assessment

1. Daily inspection and assessment of all skin surfaces is an essential part of neonatal skin care. The use of a validated skin care assessment tool provides a standardized method to perform the assessment and develop appropriate treatment plans. A widely used tool is the Neonatal Skin Condition Score (NSCS) developed and validated as part of the AWHONN/NANN skin care guideline (Table 65.1).
2. Identification of risk factors
   - **a.** Prematurity
   - **b.** Use of monitoring equipment (oxygen saturation probes, electroencephalogram leads, etc.)
   - **c.** Adhesives used to secure central and peripheral access lines, endotracheal tubes
   - **d.** Edema
   - **e.** Immobility secondary to extracorporeal membrane oxygenation (ECMO), neuromuscular blockade, and high-frequency ventilation, which can cause pressure injury
   - **f.** Use of high-risk medications including vasopressors and vesicants (calcium, sodium bicarbonate)
   - **g.** Devices with potential for thermal injury such as radiant warmers. Temperature of any product in contact with the skin should not exceed 41°C/106°F.
3. Avoidance of practices with potential to cause injury

B. Bathing

1. Initial bath should be delayed for 2 to 4 hours after birth when temperature has been stabilized to prevent risk of hypothermia. Provide a controlled environment using warming lights and warm blankets. Bathing is often deferred for the first 24 hours in infants <36 weeks' gestation.

Table 65.1. Association of Women's Health, Obstetric and Neonatal Nurses Neonatal Skin Condition Score

Dryness
1 = Normal, no sign of dry skin
2 = Dry skin, visible scaling
3 = Very dry skin, cracking/fissures
Erythema
1 = No evidence of erythema
2 = Visible erythema, <50% body surface
3 = Visible erythema, ≥50% body surface
Breakdown
1 = None evident
2 = Small, localized areas
3 = Extensive

Note: Perfect score = 3; worst score = 9.

Source: Used with permission from the Association of Women's Health, Obstetric and Neonatal Nurses. *Evidence-Based Clinical Practice Guideline: Neonatal Skin Care*. 4th ed. Copyright 2018 Washington, DC: Association of Women's Health, Obstetric and Neonatal Nurses.

2. Use mild, nonalkaline, preservative-free soap. Avoid the use of dyes or perfumes.
3. Daily bathing is not indicated. Generally, two to three times per week is sufficient. Warm water is sufficient for premature infants during the first few weeks of life.

C. Adhesives

1. Minimize use of adhesives and tape.
2. Use nonadhesive products in conjunction with transparent dressings and double-backed tape to secure IV catheters.
3. Avoid use of adhesive bonding agents that can be absorbed easily through the skin.
4. Pectin barriers should be applied to skin before application of adhesives when securing umbilical lines, endotracheal tubes, feeding tubes, nasal cannulas, and urine bags. Remove carefully using soft gauze or cotton balls soaked in warm water.

5. Use water to remove adhesives from the skin to prevent epidermal stripping. May consider use of no-sting barrier to aid in tape removal.
6. Adhesive removers contain hydrocarbon derivatives or petroleum distillates that can result in toxicity in the preterm and term infants.

D. Cord care

1. Clean umbilical cord area with mild soap and water during first bath. Keep clean and dry. Wipe gently with water if area becomes soiled with stool or urine.
2. Routine application of alcohol is not recommended and may delay cord separation. There is some evidence that chlorohexidine may be of benefit where infection risks are increased, but it may delay cord separation.
3. The routine use of antibiotic ointments and creams are not recommended.
4. Assess for signs of swelling or redness at base of cord.

E. Humidity

1. Consider the use of humidification for infants <32 weeks' gestation and/or <1,200 g to decrease transepidermal water loss, maintain skin integrity, decrease fluid requirements, and minimize electrolyte imbalance. Humidification is typically used for 10 to 14 days of life until the epidermis matures.
2. Recommended relative humidity (RH) is typically set between 60% and 80% dependent on the clinical situation.
3. Humidification requires a gradual wean over a few days. Decrease RH levels by 5% to 10% every 12 hours until reaching 30% and then discontinue. Monitor temperature closely during this time and adjust incubator temperature as necessary to maintain euthermia.
4. Strict equipment cleaning protocols must be in place during humidification (e.g., changing out incubator and humidification chamber weekly, and linen changes every 12 hours).

F. Circumcision care

1. Maintain dressing with petroleum gauze for the first 24 hours.
2. After dressing is removed, clean site with water and dry gently for the first few days.

G. Disinfectants

1. Generally, use alcohol or chlorhexidine as primary disinfectants prior to procedures. In preterm infants, use sterile water to remove residual disinfectant following the procedure to avoid the risk of chemical burns. Current recommendation for chlorhexidine is to use with caution in infants younger than 2 months of age. There is no data to support its use in the premature infant, but it is widely used in NICUs across the country.

   Because of the immaturity of newborn skin, prolonged exposure to povidone iodine has been associated with hypothyroidism. Exposure time should be limited, and if extensive, thyroid function should be monitored.

H. Emollients

1. Emollients are used to prevent and treat skin breakdown and dryness.
2. Emollients should not be used routinely in extremely premature infants because their use may increase the risk of systemic infection.
3. Single-use or patient-specific containers should be used to minimize risk of contamination.
4. Product should not contain perfumes, dyes, or preservatives.

IV. WOUND CARE.

Wounds acquired in the immediate newborn period are most commonly related to surgical procedures, trauma, or excoriation. Skin care protocols and careful attention to positioning can prevent many of the common wounds requiring treatment. Epidermal stripping is common and can be avoided by minimizing adhesive use and applying protective barriers. Routine assessment and prompt treatment maximizes healing.

A. Common causes of neonatal wounds

1. Surgical procedures
2. Trauma
3. Pressure injury
4. IV extravasation
5. Prolonged contact with moisture or chemicals
6. Skin excoriation

B. Three phases of wound healing

1. **Inflammatory phase** (days 1 to 7) begins with hemostasis and leads to inflammation. This phase removes necrotic tissue, debris, and bacteria from the wound.
2. **Proliferative phase** (days 7 to 21) is characterized by collagen production, increase in wound strength, creation of new capillaries, and epithelization.
3. **Remodeling phase** (days 21 to 365) includes collagen remodeling, increase in wound strength, and wound contraction.

C. Treatment.

Accurate assessment followed by immediate, effective treatment promotes wound healing and prevents further damage. Individualized, multidisciplinary care plans should be developed and implemented considering the etiology, type of wound, and the postmenstrual age of the infant. Optimal wound treatment is achieved through proper assessment, cleansing, and dressing choice. Multiple wound care products are currently available to optimize healing and prevent further injury.

1. Wound assessment

a. Assess wound for location, color, depth, size, odor, and exudates along with characterizing tissue type covering the wound base and description of surrounding skin in order to provide consistent, objective documentation.

2. **Wound cleansing**
   a. A surgical incision site that is being closed after an operative procedures mandates sterile technique.
   b. By contrast, wounds that are allowed to heal by secondary intention, whether partial or full thickness, are not sterile and therefore do not require cleaning with sterile materials
   c. Avoid the use of antiseptics in open wounds. Clean tap water and baby shampoo is a preferred choice, using gentle friction or irrigation for cleansing to remove debris and devitalized tissue. The healing process is facilitated by moistening the wound every 4 to 6 hours until the wound surface is cleaned.
   d. Clinical signs of infection (erythema, fever, pain, purulent drainage) may require culture and treatment with local or systemic antibiotics.
3. **Common wound dressings and products**
   a. A full-thickness wound is very unlikely to become infected as long as it is "open" and allowed to drain without occlusive dressings.
   b. Occlusive, nonadherent dressings provide a moist environment to promote healing and protect the site from further injury. These dressings should only be considered for partial-thickness wounds involving only the epidermis and/or dermis. Occlusive dressings should not be used for full-thickness wounds through the dermis.
   c. Gauze
   d. Foam dressings
   e. Hydrocolloids
   f. Hydrogels
   g. Barrier creams

V. IV EXTRAVASATION.

IV extravasation injuries can be minimized with frequent site assessment and prompt intervention.

A. Prevention

1. **Assess and document appearance** of peripheral IV sites hourly.
2. Peripheral IV infusions should not exceed 12.5% dextrose concentrations.
3. Use central access whenever possible for vasopressors and other high-risk medications.

B. Treatment

1. When an infiltration or extravasation occurs, stop the infusion and attempt to aspirate fluid, if possible. Elevate the extremity above the heart to facilitate venous return of the fluid and *do not* apply heat or cold because further tissue damage may occur. Routine use of antidotes are not typically recommended. Convincing evidence that antidotes improve outcomes for extravasation injuries does not exist. Although plastic surgeons generally do not advocate for the use of antidotes, of those that do remain in use, the two that are most commonly chosen are hyaluronidase (used to facilitate subcutaneous diffusion of an extravasate) and phentolamine (used to treat injury caused by extravasation of vasoconstrictive agents such as dopamine, epinephrine, or dobutamine).
2. Consider consultation with plastic surgery for severe injury.

VI. COMMON SKIN LESIONS.

Transient cutaneous lesions are common in the neonatal period. Among the most common are the following:

A. Erythema toxicum

1. Scattering of macules, papules, and even some vesicles or small white or yellow pustules, which not only usually occur on the trunk but also frequently appear on the extremities and face. It occurs in up to 70% of term newborns but rarely in premature infants.
2. Vesicle contents when smeared and stained with Wright stain will show a predominance of eosinophils.
3. The etiology is unknown, and no treatment is necessary.

B. Incontinence-associated dermatitis (IAD)

1. Common skin disorder in infants and children most often affecting the groin, buttocks, perineum, and anal area. It is multifactorial, most often caused by friction or exposure to urine and feces, sensitivity to chemicals contained in detergent, clothing, or diapers. The damp environment increases the skin pH, leading to impaired barrier function and skin breakdown.
2. Prevention is the best treatment, including frequent diaper changes, keeping diaper area clean with warm water, and applying barrier products if needed. Vaseline can be used preventively to intact skin. If signs of IAD are present (redness, excoriation, bleeding), start treatment with barrier products. Cleanse skin with water or pH-balanced cleanser and soft cloths. Reassess ointment regimen every 48 hours; if no improvement, consider alternate regimens. Start with application of thin creams to provide a skin barrier; if skin is not responding, move to thick pastes. If candidal rash is present, use antifungal ointment or powder first and then apply barrier cream. Consider astringent and oatmeal baths to dry out and soothe irritated skin. Dab or gently wipe off excess stool and reapply barrier cream with each diaper change. Remove all barrier products at least once daily to assess skin.

C. Milia

1. Multiple pearly white or pale yellow papules or cysts mainly found on the nose, chin, and forehead in term infants
2. Consists of epidermal cysts up to 1 mm in diameter that develop in connection with the pilosebaceous follicle
   a. Disappears within the first few weeks requiring no treatment

D. Sebaceous gland hyperplasia

1. Similar to milia with smaller, more numerous lesions primarily confined to the nose, upper lip, and chin
2. Rarely occurs in preterm infants
3. Related to maternal androgen stimulation
4. Disappears within the first few weeks requiring no treatment

E. Infection

1. Infections caused by bacterial (especially staphylococcal, *Pseudomonas*, *Listeria*), viral (herpes simplex), or fungal (e.g., candidal) organisms; may also cause vesicular, bullous, or other skin manifestations

VII. VASCULAR ABNORMALITIES (See Chapter 66). Vascular anomalies occur in up to 40% of newborns.

A. Infantile hemangiomas. Affect 5% of infants within the first few weeks of life. Premature infants have a higher incidence, especially those born at <1,000 g. Intervention is only required in the rare instance when the hemangioma interferes with vital functions. Management options for problematic lesions in infancy include topical timolol, intralesional triamcinolone, oral prednisolone, or oral propranolol. Lesions grow for the first 5 months of age and then begin to regress at 12 months of age. They improve until 3.5 years of age. Some leave a deformity requiring intervention in childhood.

B. Fading capillary stains. The most common vascular lesion found in the newborn, occurring in 30% to 40% of infants; also called "angel's kiss" or "stork bite." They are flat, pink macular lesions on the forehead, upper eyelid, nasolabial area, glabella, or nape of the neck. Most resolve by 2 years of age.

C. Capillary malformation (port-wine stain). Pink lesion that can affect any area of integument. The lesion is a vascular malformation of dilated capillaries that do not involute. The association of capillary malformation in the region of the first branch of the trigeminal nerve with cortical lesions of the brain and ocular abnormalities is known as the Sturge-Weber syndrome.

D. Disorders of lymphatic vessels

1. Microcystic lymphatic malformation ("lymphangioma")
2. Macrocystic lymphatic malformation ("cystic hygroma")
3. Lymphedema

VIII. PIGMENTATION ABNORMALITIES. Pigmentary lesions may be present at birth and are most often benign. Some of the most common are briefly described in the following text. A diffuse pattern of hyperpigmentation presenting in the newborn period is unusual and may indicate a variety of hereditary, nutritional, or metabolic disorders. Hypopigmentation presenting in a diffuse pattern may be linked to endocrine, metabolic, or genetic disease.

A. Mongolian spots. Benign pigmented lesions found in 70% to 90% of Black, Hispanic, and Asian infants. The lesions may be small or large and grayish blue or bluish black in color. Caused by the increased presence of melanocytes, most commonly found in the lumbosacral region.

B. Café au lait spots. Flat, brown, round, or oval lesions with smooth edges occurring in 10% of infants. Usually of little or no significance, but they may indicate neurofibromatosis if >4 to 6 cm or >6 are present.

C. Albinism. Most commonly an autosomal recessive condition involving abnormal melanin synthesis leading to a deficiency in pigment production. The only effective treatment is protection from light.

D. Piebaldism (partial albinism). Autosomal dominant disorder present at birth characterized by off-white macules (depigmented lesions with hyperpigmented borders) on the scalp and forehead, trunk, and extremities. The hair may be involved as well. A white "forelock," as in Waardenburg syndrome, is a feature of this disorder.

E. Junctional nevi. Brown or black, flat or slightly raised lesions present at birth occurring at the junction of the dermis and epidermis. They are benign lesions requiring no treatment.

F. Compound nevi. Larger than junctional nevi, involving the dermis and epidermis. Removal is recommended to decrease possibility of later progression to malignant melanoma.

G. Giant nevi. Present at birth, and defined as lesions covering >2% of total body surface area. Neurocutaneous melanosis may be associated with these lesions. Surgical removal is indicated when possible to improve deformity and reduce the risk of malignant melanoma. If the lesion is too difficult to remove, then patients are monitored by a dermatologist annually for signs of malignant changes.

IX. DEVELOPMENTAL ABNORMALITIES OF THE SKIN

A. Skin dimples and sinuses can occur on any part of the body, but they are most common over bony prominences such as the scapula, knee joint, and hip. They may be simple depressions in the skin of no pathologic significance or actual sinus tracts connecting to deeper structures.

1. A pilonidal dimple or sinus may occur in the sacral area. A sinus that is deep but does not communicate with the underlying structures is usually insignificant.
2. Some deep sinuses connect to the central nervous system. Occasionally, a dimple, sometimes accompanied by a nevus or hemangioma, may signify an underlying spinal disorder. These usually require neuroimaging scans for diagnosis.
3. Dermal sinuses or cysts along the cheek or jawline or extending into the neck may represent remnants of the branchial cleft structures of the early embryo.
4. A preauricular sinus is the most common location and may be unilateral or bilateral. It appears in the most anterior upper portion of the tragus of the external ear. The sinus generally causes no problems, but if repeated infections occur later in life, it can be excised.

B. Small **skin tags** can occur on the chest wall near the breast and are of no significance.

C. Aplasia cutis (congenital absence of the skin) occurs most frequently in the midline of the posterior part of the scalp. Treatment involves protection from trauma and infection. Other malformations may be associated, including trisomy 13.

X. OTHER SKIN DISORDERS.

Complete identification and description of all dermatologic disorders is beyond the scope of this chapter; however, the most common developmental and hereditary disorders are the following:

A. Scaling disorders

1. Most common causes of scaling in neonatal period are related to desquamation found in postmature and dysmature infants. The condition is time limited and transient without long-term consequences.

2. Less common scaling disorders that occur within the first month of life include harlequin ichthyosis, collodion baby, X-linked ichthyosis, and bullous ichthyosis.

B. Vesicobullous eruptions

1. Epidermolysis bullosa is a group of genetic disorders characterized by lesions that appear at birth or within the first few weeks. Severity of symptoms ranges from simple, nonscarring bullae to more severe forms with large numerous lesions that result in scarring, contractions, and loss of large areas of epidermis. Specific diagnosis requires skin biopsy. Prevention of infection and protection of fragile skin surfaces is the goal of treatment.

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66 Vascular Anomalies

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KEY POINTS

- Vascular anomalies are relatively common, affecting approximately 5% of the population.
- There are two broad types of vascular anomalies: tumors and malformations.
- Despite improved treatments for vascular anomalies, many lesions continue to cause significant morbidity and are not curable.

I. INTRODUCTION. Vascular anomalies affect approximately 5% of the population and can involve any component of the vasculature. The field is confusing because different lesions may look similar and terminology is difficult. Vascular anomalies are classified based on their clinical behavior and cellular characteristics (Table 66.1). Ninety percent of lesions can be diagnosed by history and physical examination. There are two broad types of vascular anomalies: tumors and malformations. Tumors typically arise postnatally and demonstrate endothelial proliferation. There are four major lesions: (i) infantile hemangioma (IH), (ii) congenital hemangioma, (iii) kaposiform hemangioendothelioma (KHE), and (iv) pyogenic granuloma (PG) (Fig. 66.1). Vascular malformations are errors in vascular development, are present at birth, and have less rapid endothelial turnover. There are four major categories: (i) capillary malformation, (ii) lymphatic malformation, (iii) venous malformation, and (iv) arteriovenous malformation (Fig. 66.2).

II. VASCULAR TUMORS

A. IH. IH is the most common tumor of infancy, affecting approximately 5% of infants. IH is more frequent in premature children and in females. The median age of appearance is 2 weeks. IH is red when it involves the superficial dermis and can appear bluish if it is located beneath the skin. IH grows faster than the child during the first 9 months of age (proliferating phase); 80% of its size is achieved by 3.2 ($\pm$1.7) months. The majority of IH are small, harmless lesions that can be monitored under the watchful eye of a pediatrician. However, a minority of proliferating IH can cause significant deformity or complications. Infants with five or more small ($<$5 mm) tumors are more likely to have IH of the liver, although the risk is low ($\sim$16%). After 12 months, the tumor begins to regress (involuting phase). Involution ceases in most of children by age 4 years (involuted phase). After involution, one-half of children will have a residual deformity.

Table 66.1. Classification of Vascular Anomalies and Their Associated Mutations

Tumors	Malformations		
	Slow-Flow	Fast-Flow	Overgrowth Syndromes
Infantile hemangioma	Capillary malformation (*GNAQ*, *GNA11*, *PIK3CA*)	Arteriovenous malformation (*BRAF*, *HRAS*, *KRAS*, *MAP2K1*)	CLOVES (*PIK3CA*)
Congenital hemangioma (*GNAQ*, *GNA11*)	Lymphatic malformation (*PIK3CA*)		Klippel-Trenaunay (*PIK3CA*)
Kaposiform hemangioendothelioma (*GNA14*)	Venous malformation (*MAP3K3*, *PIK3CA*, *TIE2*)		Parkes Weber (*EPHB4*, *RASA1*)
Pyogenic granuloma (*BRAF*, *NRAS*)			Sturge-Weber (*GNAQ*)

CLOVES, congenital lipomatous overgrowth, vascular malformations, epidermal nevi and scoliosis/skeletal/spinal anomalies.

Most IHs are simply observed. To protect against ulceration, high-risk IHs should be kept moist with hydrated petroleum during the proliferative phase. If ulceration develops, the wound is washed gently with soap and water at least twice daily. Small, superficial areas are managed by the application of topical antibiotic ointment and occasionally with a petroleum gauze barrier. Large, deep ulcers require damp-to-dry dressing changes. Bleeding from an ulcerated IH is usually minor and is treated by applying direct pressure. Ulcerations typically will heal with local wound care within 2 to 3 weeks.

B. A diffuse hemangioma replacing hepatic parenchyma necessitates thyroid-stimulating hormone (TSH) monitoring to prevent potentially devastating and irreversible effects on neurologic function. Hypothyroidism results from the expression of a deiodinase by the hemangioma, which cleaves iodine from thyroid hormone and inactivates it. Massive intravenous thyroid replacement may be necessary until the hemangioma regresses. In contrast to diffuse hepatic hemangioma, a large single hemangioma in the liver is often a rapidly involuting congenital hemangioma (RICH) and does not require intervention. Similarly, multiple small hepatic hemangiomas do not cause morbidity unless significant shunting is present.

1. **Topical pharmacotherapy.** Topical timolol (0.5% gel forming solution) is effective for superficial lesions that are treated early, before 12 weeks of age.

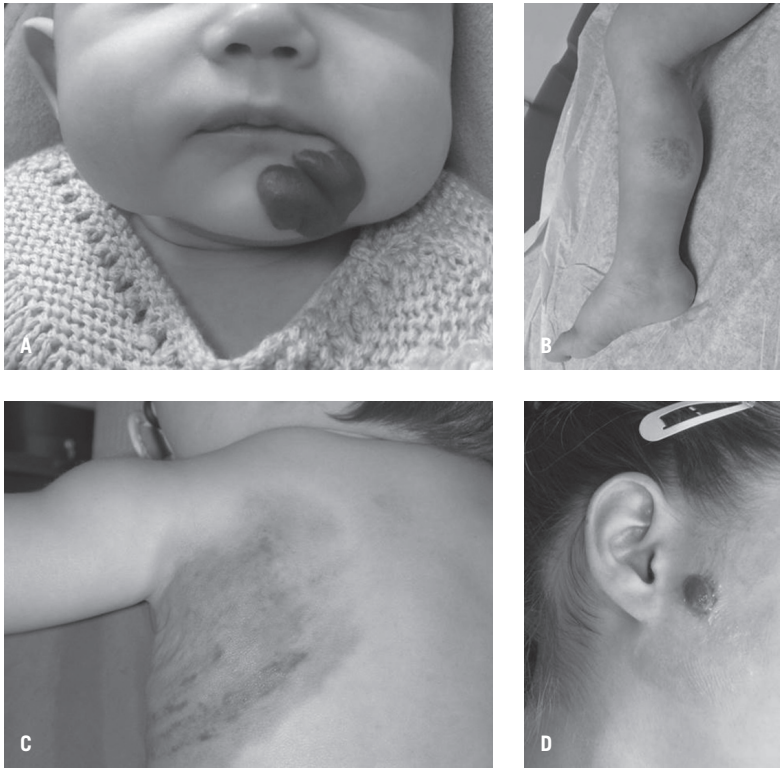

Figure 66.1. Examples of the four major types of vascular tumors. **A:** Infantile hemangioma. **B:** Congenital hemangioma. **C:** Kaposiform hemangioendothelioma. **D:** Pyogenic granuloma.

One drop BID typically is applied to the lesion. The drug will not affect hemangiomas with a subcutaneous component.

2. **Intralesional corticosteroid.** Problematic well-localized (<3 cm) IHs that are not amenable to timolol (i.e., too thick or have a subcutaneous component) are best managed by intralesional corticosteroid. Triamcinolone (not to exceed 3 mg/kg) will stop the growth of the lesion; two-thirds will decrease in size. The corticosteroid lasts 2 to 3 weeks, and thus, infants may require two to three injections during the proliferative phase.
3. **Systemic pharmacotherapy.** Problematic IH that is larger than 3 cm in diameter and unable to be treated with intralesional corticosteroid is managed by oral propranolol. Dosing typically is 2 mg/kg/day. Approximately 90% of tumors will stop growing or regress. Risks (<3%) include bronchospasm, bradycardia, hypotension, hypoglycemia, seizures, and hyperkalemia. Preterm infants and those younger than 3 months of age are more likely to have adverse events. Patients have blood pressure

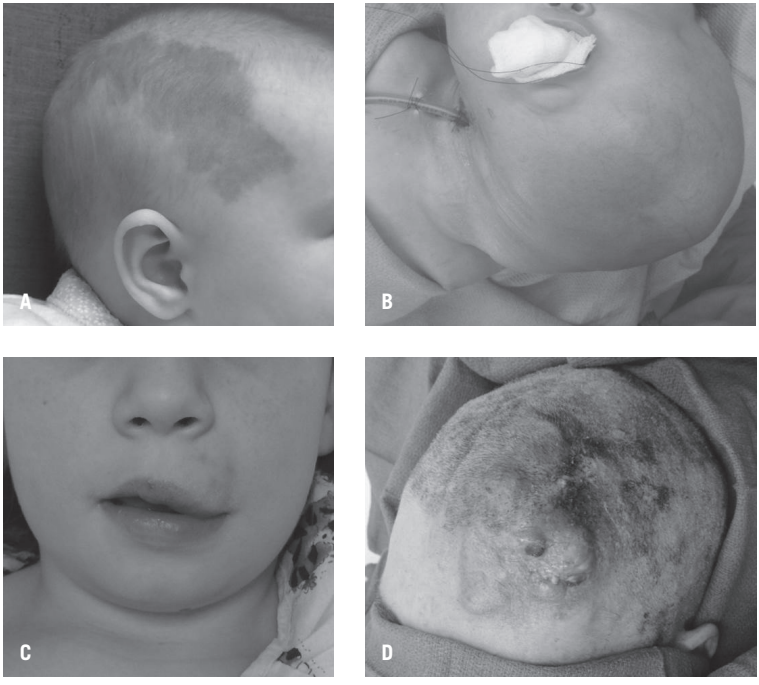

Figure 66.2. Examples of the four major types of vascular malformations. **A:** Capillary malformation. **B:** Lymphatic malformation. **C:** Venous malformation. **D:** Arteriovenous malformation.

and heart rate monitoring during the initiation of treatment. Inpatient initiation of treatment is indicated for infants who are premature or younger than 3 months of age. Potential contraindications include asthma, glucose abnormalities, heart disease, hypotension, bradycardia, or PHACES (posterior fossa, hemangioma, arterial lesions, cardiac abnormalities, eye or endocrine abnormalities) association. Oral prednisone is effective for hemangiomas that fail propranolol or if a contraindication to a beta-blocker is present. Patients are given 3 mg/kg/day for 1 month; the drug is then tapered slowly by volume (0.5 mL every 2 to 4 weeks) until it is discontinued between 10 and 12 months of age. All tumors will stabilize in growth, and 88% will become smaller. Twenty percent of infants will develop a cushingoid appearance that resolves during tapering of therapy. Approximately 12% of infants treated after 3 months of age exhibit decreased gain in height but return to their pretreatment growth curve by 24 months of age.

4. **Laser therapy.** Pulsed-dye laser is not indicated for a proliferating IH. The laser only affects the superficial portion of the tumor. Although lightening may occur, the mass is not affected. Patients have an increased risk of skin atrophy, ulceration, pain, bleeding, scarring, and

hypopigmentation. Pulsed-dye laser is effective during the involuted phase to fade residual telangiectasias.

5. **Resection.** Resection of IH typically is not recommended during the early growth phase. The tumor is highly vascular, and there is a risk of blood loss, iatrogenic injury, and an inferior outcome, compared to excising residual tissue after the tumor has regressed. It is preferable to intervene surgically between 3 and 4 years of age. During this period, the IH will no longer regress significantly, and the procedure is performed before the child's long-term memory and self-esteem begin to form at about 4 years of age.

C. Congenital hemangioma. Congenital hemangiomas are fully grown at birth and do not have postnatal growth. They are red violaceous with a peripheral pale halo. Lesions are more common in the extremities, have an equal sex distribution, and have an average diameter of 5 cm. There are two forms: RICH and *noninvoluting congenital hemangioma* (NICH). RICH involutes rapidly after birth, and 50% of lesions have completed regression by 7 months of age; the remaining tumors are fully involuted by 14 months. NICH, in contrast, does not regress and remains unchanged. RICH usually does not require resection in infancy because it regresses so quickly. After involution, RICH may leave behind atrophic skin and subcutaneous tissue. NICH is rarely problematic in infancy; resection may be indicated to improve the appearance of the area.

D. KHE. KHE is a rare vascular neoplasm that does not metastasize. KHE is present at birth in 50% of patients; has an equal sex distribution; and affects the head/neck (40%), trunk (30%), or an extremity (30%). The tumor is often >5 cm in dimensions and appears as a flat, reddish-purple, edematous lesion. Seventy percent of patients have Kasabach-Merritt phenomenon (KMP) (thrombocytopenia $<25{,}000/mm^3$, petechiae, bleeding). KHE partially regresses after 2 years of age, although it usually persists long term causing chronic pain and stiffness.

Most lesions are extensive, involving multiple tissues, and well beyond the limits of resection. Oral sirolimus is first-line therapy, and vincristine is second-line therapy. Thrombocytopenia is not significantly improved with platelet transfusion which should be avoided unless there is active bleeding or a surgical procedure is planned. By 2 years of age, the tumor usually has undergone partial involution and the platelet count normalized.

E. PG. PG is a solitary, red papule that grows rapidly on a stalk. It is small, with an average diameter of 6 mm; the mean age of onset is 6 years. PG is commonly complicated by bleeding and ulceration. The lesion involves the skin or mucous membranes. It is distributed on the head or neck (62%), trunk (19%), upper extremity (13%), or lower extremity (5%). In the head and neck region, affected sites include cheek (29%), oral cavity (14%), scalp (11%), forehead (10%), eyelid (9%), or lips (9%).

PGs require intervention to control likely ulceration and bleeding. Because the lesion extends into the reticular dermis, treatments such as pulsed-dye laser, cautery, or shave excision have an approximately 50% recurrence rate. Full-thickness excision is definitive treatment.

III. VASCULAR MALFORMATIONS

A. Capillary malformation. Capillary malformation was previously referred to as "port-wine stain." The lesion is obvious at birth, and the pink-purple skin discoloration can cause psychosocial distress. Over time, the lesion darkens and the soft tissue and bone may enlarge underneath the stain. The mainstay of treatment is pulsed-dye laser. Intervention during infancy or early childhood is recommended because superior lightening of the lesion is achieved. Pulsed-dye laser is less effective for capillary malformations that have progressed to a dark color with cutaneous thickening. Surgical procedures are indicated to correct overgrowth caused by the malformation.

B. This birthmark referred to as an "angel kiss" or "stork bite," present in one-half of Caucasian newborns, is located on the forehead, eyelids, nose, upper lip, or posterior neck. This lesion is a fading capillary stain, which lightens over the first 2 years of life.

C. Lymphatic malformation. Lymphatic malformation is defined by the size of its channels: macrocystic, microcystic, or combined. The most commonly affected sites are the neck and axilla. Lymphatic malformation can cause infection, bleeding, and psychosocial morbidity. Macrocystic lesions contain cysts large enough to be accessed by a needle (typically $\geq$5 mm) and are amenable to sclerotherapy. Microcystic lesions have cysts that are too small to be cannulated by a needle (usually $<$5 mm) and thus cannot be treated by sclerotherapy. Approximately one-half of lymphatic malformations contain both macrocysts and microcysts. Small, superficial lymphatic malformations do not require further diagnostic evaluation. Large or deep lesions are evaluated by magnetic resonance imaging (MRI).

Lymphatic malformation is benign, and thus, intervention is not mandatory. Small, asymptomatic lesions may be observed. First-line management for a large or problematic macrocystic/combined lymphatic malformation is sclerotherapy. Generally, sclerotherapy gives superior results and has lower morbidity compared to resection. Resection of a macrocystic lymphatic malformation is indicated if sclerotherapy is no longer possible or if excision may be curative because the lesion is small. Symptomatic microcystic lesions usually are managed by resection which is typically subtotal. Other modalities to treat microcystic lesions include oral sirolimus, carbon dioxide laser, radiofrequency ablation, and intralesional bleomycin injection.

D. Venous malformation. Lesions are blue, soft, and compressible. Hard calcified phleboliths may be palpable. Venous malformations cause psychosocial morbidity as well as pain secondary to congestion, thrombosis, and phlebolith formation. Patients with venous malformations are not at risk for thromboembolism unless a large varicose vein is connected to the deep venous system. Small, superficial venous malformations do not require further diagnostic workup. Large or deep lesions are evaluated by MRI.

Individuals with recurrent discomfort are given low-dose daily aspirin to prevent phlebothrombosis. Intervention is reserved for symptomatic lesions or asymptomatic phlebectatic areas at risk for thromboembolism. If possible, intervention should be postponed until after 12 months of age when the risk of anesthesia is lowest. Therapy for venous malformations

causing a deformity should be considered before 4 years of age to limit psychological morbidity. Sclerotherapy typically is first-line treatment and is generally safer and more effective than resection. Resection of a venous malformation should be considered for small lesions that can be completely removed or for persistent symptoms after completion of sclerotherapy.

E. Arteriovenous malformation. Arteriovenous malformation has an absent capillary bed which causes shunting of blood directly from the arterial to venous circulation through a fistula (direct connection of an artery to a vein) or nidus (abnormal channels bridging the feeding artery to the draining veins). Lesions have a pink-red cutaneous stain, are warm, and can have palpable pulsations. Patients are at risk for disfigurement, destruction of tissues, pain, ulceration, bleeding, and congestive heart failure. Doppler examination shows fast flow. MRI usually is obtained to confirm the diagnosis and determine the extent of the lesion. An angiogram is obtained if the diagnosis remains unclear following ultrasound and MRI or if embolization is planned. Because the lesion is often diffuse and involves multiple tissue planes, cure is rare. An asymptomatic arteriovenous malformation should be observed unless it can be removed for possible cure with minimal morbidity. Embolization is generally first-line therapy for a symptomatic lesion. Embolization is not curative, and most arteriovenous malformations will reexpand following treatment.

Resection of an arteriovenous malformation has a lower recurrence rate than embolization. Indications for resection include (i) a well-localized lesion, (ii) correction of a focal deformity, or (iii) a symptomatic arteriovenous malformation that has failed embolization. When excision is planned, preoperative embolization will facilitate the procedure by minimizing blood loss. Excision should be carried out within a week after embolization, before recanalization restores blood flow to the lesion.

ACKNOWLEDGMENTS

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67 Retinopathy of Prematurity

Kristen T. Leeman and Deborah K. VanderVeen

KEY POINTS

- Retinopathy of prematurity (ROP) typically develops in premature infants ≤30 weeks' gestation and/or weighing ≤1,500 g at birth. Other risk factors include prolonged or labile oxygen exposure and increased illness severity.
- The risk of ROP increases with decreasing gestational age (GA).
- The timing of first screening by an ophthalmologist is critical and based on postmenstrual age.

GENERAL PRINCIPLES

I. DEFINITION. **Retinopathy of prematurity (ROP)** is a multifactorial vasoproliferative retinal disorder that increases in incidence with decreasing gestational age (GA). Under current screening guidelines, about 43% of infants develop ROP, and 12.5% develop severe ROP. However, the risk is higher for those with lower birth weight (BW) and earlier GA (e.g., >95% of infants with BW of ≤900 g or GA ≤24 weeks develop ROP).

II. PATHOGENESIS

A. Normal development. After the sclera and choroid have developed, retinal elements, including nerve fibers, ganglion cells, and photoreceptors, migrate from the optic disc at the posterior pole of the eye and move toward the periphery. The photoreceptors have progressed 80% of the distance to their resting place at the ora serrata by 28 weeks' gestation. Before the retinal vessels develop, the avascular retina receives its oxygen supply by diffusion across the retina from the choroidal vessels. The retinal vessels, which arise from the spindle cells of the adventitia of the hyaloid vessels at the optic disc, begin to migrate outward at 16 weeks' gestation. Migration is complete by 36 weeks on the nasal side and by 40 weeks on the temporal side.

B. Possible mechanisms of injury. Although many factors contribute to development and severity, ROP is primarily an oxygen-driven retinopathy. Clinical observations suggest that the onset of ROP consists of two stages:

1. The **first stage** involves an initial insult or insults, such as hyperoxia, hypoxia, or hypotension, at a critical point in retinal vascularization that

results in vasoconstriction and decreased blood flow to the developing retina, with a subsequent arrest in vascular development. The relative hyperoxia after birth is hypothesized to downregulate the production of growth factors, such as vascular endothelial growth factor (VEGF), that are essential for the normal development of the retinal vessels.

2. During the **second stage**, neovascularization occurs. This aberrant retinal vessel growth is thought to be driven by excess angiogenic factors (such as VEGF) upregulated by the hypoxic avascular retina. New vessels grow within the retina and into the vitreous. These vessels are permeable; therefore, hemorrhage and edema can occur. Extensive and severe extraretinal fibrovascular proliferation can lead to retinal detachment and abnormal retinal function. In most affected infants, fortunately, the disease process is mild and regresses spontaneously.

C. Risk factors. ROP has been consistently associated with low GA, low BW, and prolonged oxygen exposure. In addition, potential or confirmed risk factors include lability in oxygen requirement as well as markers of neonatal illness severity, such as mechanical ventilation, systemic infection, blood transfusion, intraventricular hemorrhage, and poor postnatal weight gain. In lower resourced settings, severe ROP can occur with less severe prematurity, primarily due to administration of unblended oxygen, and thus, screening criteria need to be modified. In this chapter, we primarily refer to studies and guidelines in the United States and other well-resourced countries.

III. DIAGNOSIS

A. Screening. Because no extraocular signs or symptoms indicate developing ROP, timely and regular retinal examination is necessary. The timing of the occurrence of ROP is related to the maturity of retinal vessels and therefore to postnatal age. The Postnatal Growth and Retinopathy of Prematurity (G-ROP) study reported the incidence of ROP and severe ROP in a large North American cohort of premature infants who met current screening criteria during the years 2006 to 2011. Overall, 43.1% of infants developed any ROP, and there was an inverse relationship between GA or BW and incidence and severity of ROP. Of the ~12.5% of the study cohort who developed severe ROP, it occurred almost exclusively among those with a BW ≤1,250 g. All large multicenter studies have shown that the onset of ROP and severe ROP are correlated with postmenstrual age (PMA). In the G-ROP study, stages 1, 2, and 3 ROP were first diagnosed at a mean PMA of 34.8 ± 2.9, 35.5 ± 2.7, and 36.4 ± 2.6 weeks, respectively. Similarly, the mean PMA at the time of diagnosis of type 1 ROP was 36.4 weeks' PMA. This information has led to the current screening recommendations outlined in the following text. Because ROP that meets treatment criteria may be reached after discharge from the neonatal intensive care unit (NICU), all preterm infants who meet screening criteria and are discharged before they show resolution of the ROP or have mature retinal vasculature must continue to have ophthalmologic examinations on an outpatient basis.

B. Diagnosis. ROP is diagnosed by retinal examination with indirect ophthalmoscopy; this should be performed by an ophthalmologist with expertise in

ROP screening. In some NICU settings, screening is performed by digital imaging, and a bedside exam using indirect ophthalmoscopy is only performed when concerning imaging findings are noted. The current recommendation is to screen all infants with a BW ≤1,500 g or GA ≤30 weeks. Infants who are born after 30 weeks' GA may be considered for screening if they have been ill (e.g., have had severe respiratory distress syndrome, hypotension requiring pressor support, or surgery in the first several weeks of life). Because the timing of ROP is related to PMA, infants who are born at ≤27 weeks' gestation are examined at a PMA of 31 weeks, but those born at ≥28 weeks are screened at a chronologic age of 4 weeks. Patients with no ROP on indirect ophthalmoscopy are examined every 2 weeks until their vessels have grown out to the ora serrata, and the retina is considered mature. Infants undergoing telescreening usually have weekly imaging unless they are considered to be very low risk (e.g., infants ≥30 weeks' GA). If ROP is diagnosed, the frequency of the screening examination depends on the severity and rapidity of progression of the disease.

IV. CLASSIFICATION AND DEFINITIONS

A. Classification. The International Classification of Retinopathy of Prematurity (ICROP) is used to classify ROP. This classification system consists of four components (Fig. 67.1).

1. **Location** refers to how far the developing retinal blood vessels have progressed. The retina is divided into three concentric circles or zones.
   a. Zone 1 consists of an imaginary circle with the optic nerve at the center and a radius of twice the distance from the optic nerve to the macula.
   b. Zone 2 extends from the edge of zone 1 to the ora serrata on the nasal side of the eye and approximately half the distance to the ora serrata on the temporal side.
   c. Zone 3 consists of the outer crescent-shaped area extending from zone 2 out to the ora serrata temporally.
2. Severity refers to the **stage** of disease.
   a. Stage 1. A demarcation line appears as a thin white line that separates the normal retina from the undeveloped avascular retina.
   b. Stage 2. A ridge of fibrovascular tissue with height and width replaces the line of stage 1. It extends inward from the plane of the retina.
   c. Stage 3. The ridge has extraretinal fibrovascular proliferation as abnormal blood vessels and fibrous tissue develop on the edge of the ridge and extend into the vitreous.
   d. Stage 4. Partial retinal detachment may result when fibrovascular tissue pulls on the retina. Stage 4A is partial detachment not involving the macula so that there is still a chance for good vision. Stage 4B is partial detachment that involves the macula, thereby limiting the likelihood of good vision in that eye.
   e. Stage 5. Complete retinal detachment occurs. The retina assumes a funnel-shaped appearance and is described as either open or closed in the anterior and posterior regions.
3. **Extent** refers to the circumferential location of disease and is reported as clock hours in the appropriate zone.

Children's Hospital Boston

OPHTHALMOLOGIC CONSULTATION FOR RETINOPATHY OF PREMATURITY (ROP)

USE PLATE OR PRINT

NAME _____ (LAST) (FIRST)

DATE _____ DIV _____

MED. REC. NO. _____

Gestational age (weeks) _____ Birth weight _____ gm

Date of exam _____ Adjusted age (weeks) _____

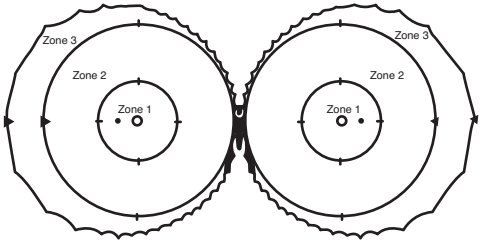
Ophthalmologist _____ MD
(PRINT NAME)

EXAMINATION:

☐ Pertinent record reviewed

Extended Ophthalmoscopy

Right Eye **Left Eye**



Penlight examination (both eyes)

☐ External ☐ Anterior chamber
☐ Lids ☐ Iris
☐ Conjunctiva ☐ Lens
☐ Cornea ☐ _____

COMMENTS: _____

Right eye	Other findings (mark with an "X")	Left eye
_____	Dilatation/Tortuosity	_____
❒	Mild	❒
❒	Moderate	❒
❒	Severe	❒
_____	Iris vessel dilatation	_____
_____	Pupil rigidity	_____
_____	Vitreous haze	_____
_____	Hemorrhages	_____
	Neovascular tufts posterior to ridge	
_____		_____
	Neovascular cylinders posterior to ridge	
_____		_____

Right eye	Summary diagnosis	Left eye
_____	Mature retina	_____
_____ Zone	Immature, no ROP	_____ Zone

ROP

Stage	Zone	Number of clock hours	Stage	Zone	Number of clock hours

Other: _____

Plan: Repeat exam in: _____

Examined by: _____, M.D.
(Signature)

Physician I.D. # ☐☐☐☐☐

03241 25/pkg 05/06

Figure 67.1. Sample of form for ophthalmologic consultation. (From Boston Children's Hospital, Ophthalmology Department.)

4. **Plus disease** is an additional designation that refers to the presence of vascular dilatation and tortuosity of the posterior retinal vessels in at least two quadrants. This indicates a more severe degree of ROP and may also be associated with iris vascular engorgement, pupillary rigidity, and vitreous haze. **Preplus disease** describes vascular abnormalities of the posterior pole (mild venous dilatation or arterial tortuosity) that are present but are insufficient for the diagnosis of plus disease.

B. Definitions

1. **Aggressive posterior ROP** is an uncommon, rapidly progressing, severe form of ROP characterized by its posterior location (usually zone 1) and prominence of plus disease out of proportion to the peripheral retinopathy. Stage 3 ROP may appear as a flat, intraretinal network of neovascularization. When untreated, this type of ROP usually progresses to stage 5.
2. **Threshold ROP** is a historic term used for classification of ROP requiring treatment under old guidelines, but currently treatment is recommended for "prethreshold" ROP. In the Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) study, treatment was recommended if five or more contiguous or eight cumulative clock hours (30-degree sectors) of stage 3 with plus disease in either zone 1 or 2 were present. The risk of blindness was predicted to be at least 50% with "threshold" ROP, and the CRYO-ROP study showed that the risk of blindness could be reduced to approximately 25% with treatment.
3. **Prethreshold ROP** is any ROP in zone 1 less than threshold ROP, and in zone 2, stage 2 ROP with plus disease, stage 3 without plus disease, or stage 3 with plus disease but fewer than the requisite clock hours that define threshold ROP. Currently, severe ROP is categorized into type 1 and type 2 ROP as follows:
   a. **Type 1 ROP** includes (e.g., Fig. 67.2):
      i. In zone 1, any ROP and plus disease or stage 3 with or without plus disease
      ii. In zone 2, stage 2 or 3 ROP with plus disease
   b. **Type 2 ROP** includes:
      i. In zone 1, stage 1 or 2 ROP without plus disease
      ii. In zone 2, stage 3 ROP without plus disease

V. TIMING OF TREATMENT

A. Current recommendations are to consider treatment for eyes with **type 1 ROP** based on the Early Treatment for ROP (ETROP) randomized trial that showed a significant benefit in visual and anatomic outcomes for treatment of eyes with type 1 ROP compared to eyes receiving treatment only if threshold ROP developed.

B. Close observation is currently recommended for **type 2 ROP**. Treatment should be considered for an eye with type 2 ROP when progression to type 1 ROP occurs. Approximately 15% of type 2 eyes progress to type 1 ROP.

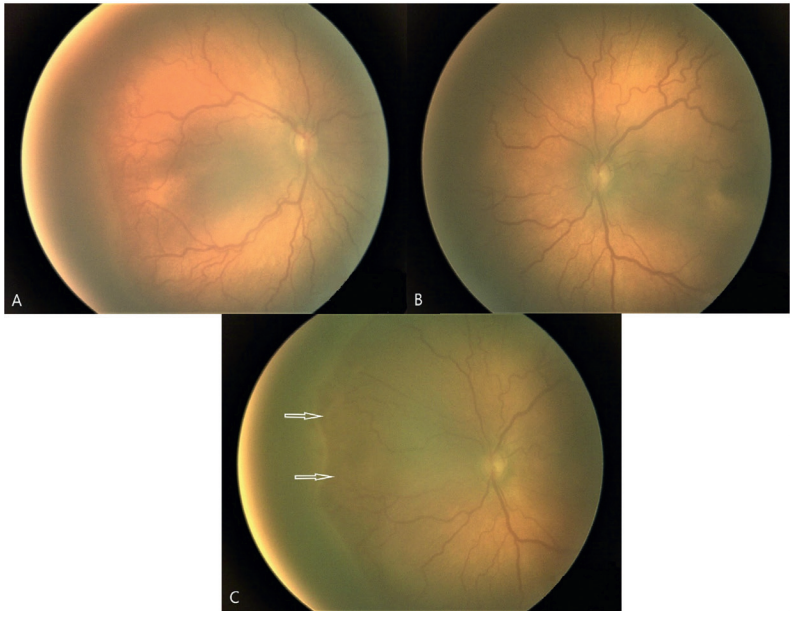


Figure 67.2. Digital images of type 1 retinopathy of prematurity. Former 25 2/7 week 650-g female infant at postmenstrual age of 36 3/7 weeks. (**A,B**) Plus disease is present in both right and left eyes, with stage 2 retinopathy of prematurity in zone 2. (**C**) *Arrows* show examples of preretinal fibrovascular tissue posterior to the stage 2 ridge at the end of the retinal vessels.

VI. PROGNOSIS

A. Short-term prognosis. Risk factors for ROP requiring treatment include posterior location (zone 1 or posterior zone 2), presence of ROP on the first properly timed examination, increasing severity of stage, circumferential involvement, the presence of plus disease, and rapid progression of disease. Most infants with stage 1 or 2 ROP will experience spontaneous regression. Treatment is recommended for type 1 eyes, and in the ETROP study, this reduced unfavorable visual outcomes from 33% to 25%. Unfortunately, only 35% of patients maintained visual acuity at 6 years of age of 20/40 or better, suggesting more work to prevent development of ROP is needed. Any zone 3 disease has an excellent prognosis for complete recovery.

B. Long-term prognosis. Infants with significant ROP have an increased risk of myopia, anisometropia, astigmatism, strabismus, amblyopia, late retinal detachment, and glaucoma. **Cicatricial disease** refers to residual scarring in the retina and may be associated with retinal detachment years later. The prognosis for stage 4 ROP depends on the involvement of the macula; the chance for good vision is greater when the macula is not involved. Once the retina has detached, the prognosis for good vision is poor even with surgical reattachment, although some useful vision may be preserved. All premature

infants who meet screening criteria regardless of the diagnosis of ROP are at risk for long-term vision problems, from either ocular or neurologic abnormalities. We recommend a follow-up evaluation by an ophthalmologist with expertise in neonatal sequelae at approximately 1 year of age or sooner if ocular or visual abnormalities have been noted.

VII. PREVENTION.

Currently, no proven methods are available to prevent ROP. Multiple large clinical trials to prevent ROP have been performed evaluating the use of prophylactic vitamin E therapy, reduced exposure to bright light, and administration of penicillamine, but none of these have shown clear benefit. Nonrandomized studies suggested that lower or more tightly regulated oxygen saturation limits in the early neonatal course may reduce the severity of ROP without adverse effects on mortality, bronchopulmonary dysplasia, or neurologic sequelae. However, more recent meta-analyses have suggested that in the group of infants with restricted oxygen there is a higher mortality rate. Although the meta-analyses also confirmed higher rates of ROP requiring treatment for infants in the higher oxygen saturation target range, this was not associated with a higher rate of blindness by 24 months.

VIII. TREATMENT

A. Laser therapy. Laser photocoagulation therapy for ROP has been the preferred initial treatment in most centers. Laser treatment is delivered through an indirect ophthalmoscope and is applied for 360 degrees to the avascular retina, anterior to the ridge of extraretinal fibrovascular proliferation. An average of 1,000 spots are placed in each eye, but the number may range from a few hundred to approximately 2,000. The procedure can be performed in the NICU, and usually with local anesthesia and sedation, avoiding the potential adverse effects of general anesthesia. Clinical observations and comparative studies suggest that laser therapy is at least as effective as cryotherapy in achieving favorable visual outcomes, and while the success rate is good with regard to causing ROP regression, neither is 100% effective. Known complications include the development of cataracts, glaucoma, or anterior segment ischemia following laser surgery or cryotherapy.

B. Anti-VEGF therapy. Intravitreal injection of VEGF inhibitors is commonly used for ROP in zone 1 or posterior zone 2, aggressive posterior ROP (AP-ROP), as salvage treatment after laser therapy, or in conjunction with vitreoretinal surgery. Although use of these agents for ROP treatment is off-label, several studies have shown the efficacy of this treatment. However, some concerns remain as to which agent and dose should be used because systemic absorption can result in reduced systemic VEGF and potentially impede normal vascularization of other developing organs such as the brain or lungs and can delay wound healing for surgical patients. Furthermore, the retina may never become fully vascularized, requiring long-term close follow-up after discharge from the NICU, with a risk of late reactivation. For this reason, many ophthalmologists plan to perform laser treatment after anti-VEGF therapy. Nevertheless, the ocular safety profile is reasonably good, although endophthalmitis is a rare but potentially devastating

complication. Some benefits of intravitreal injection are short procedure time, less stress/discomfort requiring only topical anesthesia, and potential long-term benefits such as lower rates of high myopia.

C. Cryotherapy. A cryoprobe is applied to the external surface of the sclera, and areas peripheral to the ridge of the ROP are frozen until the entire anterior avascular retina has been treated. Approximately 35 to 75 applications are required for each eye when performed as monotherapy. The procedure is usually performed under general anesthesia. Cryotherapy causes more inflammation and requires more analgesia than laser therapy but may be necessary in special cases.

D. Retinal reattachment. Once the macula detaches in stage 4B or 5 ROP, retinal surgery may be performed in an attempt to reattach the retina. Vitrectomy with or without lensectomy, and membrane peeling if necessary, is performed to remove tractional forces causing the retinal detachment. A scleral buckling procedure may be useful for more peripheral detachments, with drainage of subretinal fluid for effusional detachments. Repeat operations for recurrent detachment of the retina are common. Even if the retina can be successfully attached, with rare exception, the visual outcome is in the range of legal blindness. Despite the low visual acuity measurement, children find any amount of vision useful, and untreated stage 5 ROP eventually leads to no light perception vision. The achievement of even minimal vision can result in a large difference in a child's overall quality of life.

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68 Hearing Health in Neonatal Intensive Care Unit Graduates

Arielle Spellun, Jane E. Stewart, and Jennifer E. Bentley

KEY POINTS

- 1-3-6 Guidelines: screened before 1 month, diagnosed before 3 months, language-based intervention initiated before 6 months
- Neonatal intensive care unit (NICU) graduates are at increased risk for elevated hearing thresholds.
- Even mildly elevated bilateral and any elevation of unilateral hearing thresholds can cause significant developmental delays as a result of limited access to spoken language.
- Children with risk factors of late-onset and progressive hearing loss should be monitored by an audiologist.
- The earlier interventions aimed at restoring access to language start, the better the child's chance of achieving age-appropriate language and communication skills.

I. DEFINITION

A. Terminology. In order to convey culturally sensitive language throughout in this chapter, the authors replaced commonly used terms such as "*hearing loss*" or "*hearing impairment*" with terminology such as "hearing thresholds in the mild, moderate, severe, or profound range" and "elevated hearing thresholds." Elevated hearing thresholds refer to the softest level of detectable sound being within the mild, moderate, severe, or profound range on the audiogram (see Fig. 68.1 for audiogram reference). The term "hearing loss" may be used in relation to audiologic concepts, late-onset, or progressive changes in hearing thresholds.

Neonatal intensive care unit (NICU) graduates have an increased risk of congenital hearing thresholds within the mild, moderate, severe, or profound range as well as developing hearing loss postnatally. When undetected, elevated hearing thresholds can delay language, communication, and cognitive development.

Hearing is defined by type, degree, and configuration.

1. Type refers to the relationship between hearing by air conduction (through the outer, middle, and inner ear/central system) and hearing

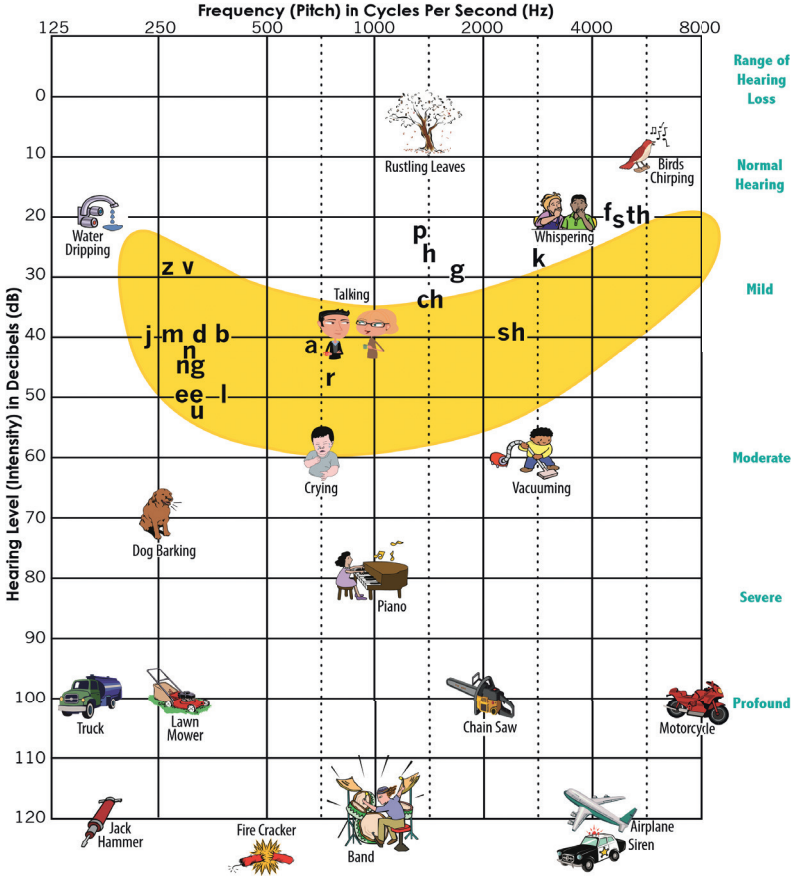

Figure 68.1. Audiogram of familiar sounds. (Adapted from American Academy of Audiology, www.audiology.org, and Northern, J. & Downs, M. (2002). Audiogram of familiar sounds; and Ling, D. & Ling, A (1978). Aural Habilitation. Reprinted with permission from John Tracy Center, www.jtc.org. Available at https://s3.amazonaws.com/www.jtc.org/Ideas-Advice/hearing-loss/New+Audiogram+of+FS+English+2019.pdf.)

by bone conduction (inner ear/central system only). There are five major categories of hearing loss type:

a. Sensorineural loss is the result of abnormal development or damage to the cochlear hair cells (sensory end organ) or auditory nerve.

b. Conductive loss is the result of interference in the transmission of sound from the external auditory canal to the inner ear. The most common cause of conductive hearing loss is fluid in the middle ear or middle ear effusion. Less common are anatomic causes such as microtia, canal

stenosis, or stapes fixation that often occur in infants with craniofacial malformations.

c. Auditory dyssynchrony or auditory neuropathy is rare accounting for only 10% of children diagnosed with severe permanent hearing loss. The inner ear or cochlea appears to receive sounds normally; however, the transfer of the signal from the cochlea to the auditory nerve is abnormal. Although the etiology of this disorder is not well understood, babies who have a history of extreme prematurity, hypoxia, severe hyperbilirubinemia, and immune disorders are at increased risk. In approximately 40% of cases, there is a genetic basis for their auditory dyssynchrony.

d. Central hearing loss occurs despite an intact auditory canal and inner ear and normal neurosensory pathways because of abnormal auditory processing at higher levels of the central nervous system.

e. Mixed hearing loss occurs when there is an interference with the transmission of sound through both the conductive and sensorineural system.

2. **Degree** is categorized by the intensity decibel (dB) level of hearing thresholds (Table 68.1). Hearing thresholds are the measurement of the softest sound (in dB) that is reliably detected at each frequency. Thresholds are graphed on an audiogram (see Fig. 68.1) based on intensity and frequency of the sound. On the audiogram, intensity is softest at the top (around 0 dB) and gets louder at the bottom (around 110 dB). Frequencies have more bass to the left (250 Hz) and increase in treble toward the right (8,000 Hz).
3. **Configuration** refers to the overall shape of the thresholds across the audiometric frequency range (i.e., rising = greater elevation in thresholds in the low frequencies than in the high, cookie-bite [referring to the shape of the audiogram] = greater elevation in thresholds around the midfrequencies).

Table 68.1. Degree and Severity of Hearing Thresholds

Degree of Hearing Threshold	Hearing Range (dB HL)
Typical	−10–15
Slight	16–25
Mild	26–40
Moderate	41–55
Moderately severe	56–70
Severe	71–90
Profound	91+

dB, decibel; HL, hearing loss.

Source: Reprinted from Clark JG. Uses and abuses of hearing loss classification. *ASHA* 1981;23(7):493–500. With permission.

II. INCIDENCE. The overall incidence of elevated congenital hearing thresholds is 1 to 3 per 1,000 live births. However, 20 to 40 per 1,000 infants surviving neonatal intensive care have hearing within the mild, moderate, severe, or profound range.

III. ETIOLOGY

A. Genetic. Approximately 50% of the etiologies linked to being deaf or hard of hearing is thought to be of genetic origin (30% syndromic and 70% nonsyndromic). Of the nonsyndromic, 75% to 85% are autosomal recessive, 15% to 24% autosomal dominant, and 1% to 2% X-linked. The most common nonsyndromic autosomal recessive genetic cause is a mutation in the **connexin 26 (Cx26) gene (GJB2)**, located on chromosome 13q11–12 (at least 90 deletions have been associated with elevated hearing thresholds). The carrier rate for a Cx26 mutation is 3%, and it accounts for elevated hearing thresholds in approximately 20% to 30% of that population. Deletion of the **mitochondrial gene** 12SrRNA, A1555G, is associated with a predisposition for elevated hearing thresholds after exposure to aminoglycoside antibiotics. Approximately 30% of infants who are deaf or hard of hearing have other associated medical problems that are part of a **syndrome**. More than 400 syndromes are known to be associated with elevated hearing thresholds (e.g., Robin sequence, Usher, Waardenburg syndrome, neurofibromatosis type 2, branchio-oto-renal syndrome, trisomy 21). Infants identified with a syndrome that has an associated congenital or progressive hearing loss should be seen for a diagnostic hearing evaluation by 9 months of age Joint Committee on Infant Hearing (JCIH).

B. Nongenetic. In approximately 25% of children who are deaf or hard of hearing, a nongenetic cause is identified. Elevated hearing thresholds are thought to be secondary to injury to the developing auditory system in the intrapartum or perinatal period. This injury may result from infection, hypoxia, ischemia, metabolic disease, hyperbilirubinemia, or ototoxic medication. Preterm infants and infants who require admission to a newborn intensive care or a special care nursery are often exposed to these factors.

1. **Cytomegalovirus (CMV)** congenital infection is the most common cause of nonhereditary sensorineural hearing loss. Approximately 1% of all infants in the United States are born with CMV infection. Of these ~40,000 infants per year, 10% have clinical signs of infection at birth (small for gestational age, hepatosplenomegaly, jaundice, thrombocytopenia, neutropenia, intracranial calcifications, or skin rash), and 50% to 60% of these infants develop elevated hearing thresholds or other neurodevelopmental sequela. Although most (90%) infants born with CMV infection have no clinical signs of infection, hearing loss still develops in 10% to 15% of these infants, and it is often progressive. Treatment with the antiviral agent valganciclovir given orally for 6 months after birth is associated with improved long-term hearing function as well as improved neurodevelopmental outcomes at 2 years of life. Infants must be tested within the first 3 weeks to distinguish between congenital and acquired infection. Prompt diagnosis of congenital CMV is essential to determine if the infant is a possible candidate for treatment; ideally,

treatment is initiated within 1 month after birth. Screening for CMV with urine or saliva in all babies who fail their newborn hearing screen has been implemented by many hospitals to facilitate making this diagnosis. Universal screening will hopefully be feasible in the near future so that asymptomatic infants who pass their first hearing screen are detected in the newborn period. Educating women on strategies to avoid CMV exposure during pregnancy is equally important. All infants diagnosed with congenital CMV whose initial hearing thresholds are normal should have their hearing monitored closely by a pediatric audiologist for at least the first 4 years of life.

C. Risk factors. The JCIH lists risk indicators associated with early childhood hearing loss. Recommended surveillance schedules and methods are summarized in Table 68.2, adapted from the JCIH 2019 position statement. All infants with one or more risk factors should have ongoing developmentally appropriate hearing screening and at least one diagnostic audiology assessment no later than 3 to 9 months of age, as outlined in Table 68.2. Risk factors that are highly associated with late-onset hearing loss or progressive hearing loss such as congenital CMV or treatment with hypothermia for hypoxic ischemic encephalopathy (HIE) warrant earlier and more frequent follow-up.

IV. SCREENING TESTS.

The currently acceptable methods for physiologic hearing screening in newborns are auditory brainstem response (ABR) and evoked otoacoustic emissions (EOAEs). A threshold of ≥35 dB has been established as a screening cutoff that prompts further testing.

Universal newborn hearing screening is recommended to determine hearing function as early as possible. The JCIH and the American Academy of Pediatrics (AAP) endorse a goal of testing 100% of infants during their hospital birth admission. The percentage of infants screened in the United States prior to 1 month of age has increased from 46% in 1999 to 98% in 2017.

A. ABRs measure the electroencephalographic waves generated by the auditory system in response to clicks through three electrodes placed on the infant's scalp. The characteristic waveform recorded from the electrodes becomes more well-defined with increasing postnatal age. ABR is reliable after 34 weeks' postmenstrual age. The automated version of ABR allows this test to be performed quickly and easily by trained hospital staff. Although the otoacoustic emission (OAE) is acceptable for routine screening of low-risk infants, the AAP recommends the ABR over the OAE in high-risk infants including NICU patients and graduates. This is because the ABR tests the auditory pathway beyond the cochlea and picks up neural dysfunction including auditory dyssynchrony.

B. EOAEs record acoustic "feedback" from the cochlea through the ossicles to the tympanic membrane and ear canal following a click or tone burst stimulus. EOAE is even quicker to perform than ABR. However, EOAE is more likely to be affected by debris or fluid in the external and middle ear, resulting in higher referral rates. Furthermore, EOAE is unable to detect some forms of neural dysfunction including auditory dyssynchrony. EOAE is often combined with automated ABR in a two-step screening system.

Table 68.2. Recommended Surveillance Schedules

Risk Indicator	Recommended Diagnostic Follow-Up Time
Caregiver concern regarding hearing, speech, language, or developmental delay	Immediate referral
Extracorporeal membrane oxygenation (ECMO)	No later than 3 months after occurrence
In utero infections with CMV	No later than 3 months after occurrence
Culture-positive postnatal infections associated with sensorineural hearing loss, including bacterial and viral (especially herpes viruses and varicella) meningitis	No later than 3 months after occurrence
Head trauma, especially basal skull/temporal bone fractures that require hospitalization	No later than 3 months after occurrence
Chemotherapy	No later than 3 months after occurrence
In utero infections with Zika (mother and infant)	Screen with ABR by 1 month; diagnostic by 4–6 months
Neonatal intensive care of >5 days	By 9 months
Hyperbilirubinemia that requires exchange transfusion (regardless of length of stay)	By 9 months
Aminoglycoside administration for >5 days	By 9 months
Asphyxia or hypoxic ischemic encephalopathy (HIE) particularly if requiring hypothermia treatment	By 9 months
In utero infections such as herpes, rubella, syphilis, or toxoplasmosis	By 9 months
Craniofacial anomalies, including those that involve the pinna, ear canal, ear tags, ear pits, and temporal bone anomalies such as microtia/atresia, ear dysplasia, microphthalmia, microcephaly, congenital or acquired hydrocephalus or temporal bone abnormalities	By 9 months

(continued)

Table 68.2. Recommended Surveillance Schedules *(Continued)*

Risk Indicator	Recommended Diagnostic Follow-Up Time
Syndromes associated with progressive or late-onset hearing loss such as neurofibromatosis, osteopetrosis, and Usher syndrome. Other frequently identified syndromes include Waardenburg, Alport, Pendred, and Jervell and Lange-Nielsen.	By 9 months

CMV, cytomegalovirus; ABR, auditory brainstem response.

Source: Reprinted with permission from Year 2019 position statement: principles and guidelines for early hearing detection and intervention programs. *J Early Hear Detect Interv* 2019;4(2):1–44. doi:10.15142/fptk-b748.

V. FOLLOW-UP TESTING. Follow-up diagnostic testing of infants who fail their newborn screen is critical and should ideally be completed by 3 months of age according to 1-3-6 guidelines. Despite the high success in screening of newborns at 98%, most recent data indicate 26% of infants who do not pass their initial hearing screen are lost to follow-up and do not receive a diagnosis. Almost 18% of those who do receive a diagnosis are lost to follow-up and are not enrolled in early intervention. Family issues associated with poor follow-up include age of mother, insurance status, poverty level, and lack of family education regarding screening. Loss to follow-up also varies geographically. Newborns born at home or in more remote areas are more likely to miss or forgo hearing screening and follow-up services.

Infants who fail the screen should have a diagnostic ABR performed by a pediatric audiology specialist within 3 weeks of their initial test. For infants who remain hospitalized and require further hearing testing, diagnostic evaluations should be completed by the hospital audiology department within the same time frame or immediately following discharge if no audiology department is available. The diagnostic testing format should include measures to rule out or identify auditory dyssynchrony, sensorineural, or conductive hearing loss. Testing should include a full diagnostic frequency-specific ABR to measure hearing thresholds, EOAEs, and evaluation of middle ear function (tympanometry using a 1,000-Hz probe tone). Observation of the infant's behavioral response to sound and parental report of emerging communication and auditory behaviors should also be included.

A. Definitions of the degree and severity of hearing thresholds are listed in Table 68.1.

B. Infants who have risk factors of progressive or delayed-onset sensorineural and/or conductive hearing loss require continued surveillance, even if the initial newborn hearing screening is passed. Recommended surveillance schedules and methods are summarized in Table 68.2, adapted from the JCIH 2019 position statement.

C. Infants with **mildly elevated bilateral or any elevation of unilateral hearing thresholds** should also be monitored closely with repeat audiology evaluations and provided with early intervention services because they are at increased risk for both progressive hearing loss and delayed and abnormal development of language and communication skills.

D. All infants should be monitored by their primary care providers for typical hearing and language development.

VI. MEDICAL EVALUATION.

An infant diagnosed with hearing thresholds in the mild, moderate, severe, or profound range should have the following additional evaluations:

A. Complete evaluation should be performed by an otolaryngologist or otologist who has experience with infants. Referral for radiologic imaging with computed tomography (CT) or magnetic resonance imaging (MRI) should occur when needed.

B. Genetic evaluation and counseling should be provided.

C. Examination should be performed by a pediatric ophthalmologist to detect eye abnormalities that may be associated with elevated hearing thresholds.

D. Developmental pediatrics, neurology, cardiology, and nephrology referral should be made as indicated.

VII. INTERVENTIONS FOR OPTIMIZING LANGUAGE DEVELOPMENT

A. Early intervention. Infants with confirmed elevation of hearing thresholds, regardless of degree or laterality, should be referred for early intervention services to enhance the child's acquisition of developmentally appropriate language skills.

1. Referral to early intervention constitutes the final step of the 1-3-6 guidelines and should occur as soon as possible after identification and before 6 months of age for optimal developmental outcomes.
2. Appropriate early intervention services should include therapy from speech and language pathologists, audiologists, and developmental specialists with knowledge of deaf education and sign languages.
3. Early intervention resources and information for parents to make decisions regarding communication opportunities should be provided as promptly as possible.

B. Amplification and hearing technologies. If parents consent, infants who are appropriate candidates for personal amplification systems (i.e., hearing aids or bone-anchored hearing aid [BAHA]) should be fitted for hearing technologies as soon as possible. Children with severe to profound bilateral hearing thresholds may be candidates for cochlear implants by 9 months of age and, if desired by parents, should be evaluated by specialized otolaryngologists for this procedure.

1. The ability of a child who is deaf or hard of hearing to develop language using hearing technologies is dependent on whether or not

those technologies restore complete access to the elements of spoken language (all frequencies for a majority of the time).

2. For English, the key phonologic elements of speech required to access spoken language are designated in Figure 68.1 by the shaded area. Failure to access the elements of speech within this shaded region may result in inadequate language development and subsequently poor outcomes across developmental domains. There are also a number of assistive listening devices available to help in classrooms, homes, and public venues. Frequency modulation, infrared, and inductive loop systems allow for minimization of background noise and can help override poor acoustics.

C. Sign languages. In addition to hearing technologies, visual linguistic supports are a key intervention in assuring early language access for children who are deaf or hard of hearing.

1. One example is sign languages, such as American Sign Language, that are complete natural languages that activate neurologic structures for language without impeding spoken language development in children with intact visual abilities.
2. Other examples include Signing Exact English, Manually Coded English, and Simultaneous Communication (known as Sim-Com) that are manual forms of spoken English and are meant to complement spoken English learning instruction but alone do not provide linguistic access for neurologic activation and development.

D. Language access. Given what is known about language development occurring from day 1 of life, the inclusion of an accessible sign language during the first months to 1 year of life, prior to and in addition to other hearing technologies as desired by a family, may be beneficial to general cognitive development.

1. Emerging evidence has shown improved developmental outcomes for children with complete early sign language access from fluent language models.
2. Auditory perception and speech production develop similarly in both children who learn oral and manual modes of communication together and those who focus only on oral. There are no risks in providing access to sign languages and likely only benefits in ensuring children who are deaf or hard of hearing do not experience any periods without linguistic stimulation.
3. There are risks of poor developmental, cognitive, linguistic, and psychologic outcomes if children do not have adequate linguistic access, either through spoken or signed languages; efforts must be made to prioritize accessible language in early intervention goals.

VIII. OUTCOMES.

Outcomes depend largely on the degree of elevated hearing thresholds, the time of diagnosis, and provision of language access, as well as the presence of syndromes or other congenital anomalies. For optimal auditory brain development, normal maturation of the central auditory pathways depends on the early maximizing of auditory input. In addition, to optimize

development of linguistic brain structures, complete access to language in either signed or spoken modalities is required. The earlier habilitation starts, the better the child's chance of achieving age-appropriate language and communication skills. Fitting of hearing aids by the age of 6 months has been associated with improved speech outcomes. Language and communication outcomes for children receiving early cochlear implants, the accompanying intensive multidisciplinary team therapy, and early complete access to sign language are also very promising. Initiation of early intervention services before 3 months of age has also been associated with improved cognitive developmental outcomes at 3 years. Finally, family involvement is critical to success. Early identification, together with early intervention and an actively involved family, result in improved developmental and language outcomes at age 5 years.

Suggested Readings

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Online Resources

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69 Neonatal Procedures: Basic Principles and Considerations

Anne Ades and Kristen T. Leeman

KEY POINTS

- Performance of procedures in neonates requires diligent attention to maintenance of patient care principles including risk–benefit profile of the procedure, knowledge of the critical steps and potential complications of the procedure, monitoring of the patient during the procedure, and appropriate analgesic management (pharmacologic and nonpharmacologic).
- All procedures should be performed with strict attention to safety and infection control practices.
- Procedural care should be individualized based on patient and clinical context.

I. INTRODUCTION. Invasive procedures are a necessary and risk-laden part of newborn intensive care. To provide maximum benefit and minimal harm, procedures must be performed using evidence and safety-based guidelines.

II. GENERAL PRINCIPLES

A. Consideration of alternatives. For each procedure, all alternatives should be considered and risk–benefit ratios evaluated. For example, after assessment of patient-specific procedure risks and benefits, providers may choose a less invasive procedure such as a needle thoracentesis rather than placement of a thoracostomy tube. Many procedures involve the placement of indwelling devices made of plastic. Polyvinylchloride-based devices leach a plasticizer, di(2-ethylhexyl)-phthalate (DEHP), which may be toxic over long-term exposure. Alternatives exist, and devices that are DEHP-free should be used for procedures on neonates whenever possible. In addition, several indwelling catheters may contain latex; thus, care should be taken when selecting catheters for invasive procedures in a population at high-risk for developing latex allergies such as patients with myelomeningocele.

B. Infection control. For any procedure, care should be taken to ensure antisepsis. Most units have specific guidelines for appropriate antisepsis agents

at their institution. These guidelines should include the antiseptic of choice specific to the procedure as well as the application time and dry time. Other considerations include the routine management of the indwelling devices such as specifics for dressing and securement of the devices as well as for dressing changes. The optimal agent to use for infants is not clear; chlorhexidine solutions, alcohol, and povidone-iodine are the usual options. Any skin reactions thought to be due to the antiseptic used should be clearly documented, and alternatives should be discussed. As formulations of solutions, such as chlorhexidine, change frequently allowing for use in more preterm newborns with less mature skin, it is difficult to recommend one method over another except in unique circumstances. Other infection control considerations include use of full sterile coverage of the field as appropriate; use of sterile gloves, masks, and gowns; and wearing of head coverings depending on the procedure.

C. Monitoring and homeostasis. Ideally, the operator should delegate another care provider to be responsible for the ongoing monitoring and management of the patient during a procedure. This person's primary focus should be on the patient rather than the procedure being performed. They must assess cardiorespiratory and thermoregulatory stability throughout the procedure. Continuous cardiorespiratory monitoring can be accomplished through a combination of invasive (e.g., arterial blood pressure monitoring) or noninvasive (e.g., oximeter) techniques. For sterile procedures, a particularly important function of this second care provider is ensuring the integrity of the sterile field.

D. Pain control. Treatment of procedure-associated discomfort can be accomplished with pharmacologic and nonpharmacologic approaches (see Chapter 70). The potential negative impact of any medication on the patient's cardiorespiratory status should be considered. Oral sucrose (e.g., 24% solution, 0.2 to 0.4 mL/kg) is very effective in reducing pain of minor procedures including blood drawing. It can also be used as adjunctive therapy for more painful procedures when the patient can tolerate oral medication. Either morphine or fentanyl is commonly administered before beginning potentially painful procedures. In addition, topical lidocaine preparations or intradermal lidocaine can be used depending on the procedure as well as the patient's skin integrity for the use of topical lidocaine preparations. The use of age-appropriate pain scales to assess the need for medication is recommended.

E. Informing the family. Other than during true emergencies, parents should be notified of the need for invasive procedures in their child's care before they are performed. Institutional and unit-based guidelines should specify whether assent or consent is needed based on the procedure being performed. For example, some institutions only require assent for lumbar punctures where others might require an informed consent. In any case, the discussion with the family should be documented and any signed consents saved in the patient's chart. In emergencies, when informing the family is not possible, the family should be notified after of any procedures that were attempted. In some cases where the performance of invasive procedures is anticipated but there are concerns with the ultimate patient prognosis, it

is useful to have preemptive conversations with the family to discuss any limitations of care.

F. Personal protective equipment (PPE). The operator should use universal precautions to prevent exposure to blood and bodily fluids that may be contaminated with infectious agents. At minimum, this should include wearing gloves with the addition of impermeable gowns, masks, and eye protection depending on the procedure being performed. In addition, any provider in the immediate patient care area, frequently defined as within 6 ft of the patient, should also be wearing personal PPE.

G. Time out and checklists. Before beginning any procedure, the entire team should take a "time out" or "safety pause" to ascertain that the correct procedure is to be performed on the correct patient and, if appropriate, on the correct side. This pause should be incorporated into a complete checklist that includes all the steps of the procedure. Use of such a list helps ensure that a key step or assessment is not inadvertently omitted.

H. Education and supervision. Individuals should be trained in the conduct of procedures both from a teamwork and psychomotor skill perspective before performing the procedure on patients. This training should include a discussion of indications, contraindications, possible complications and their treatment, and the techniques to be used. For some procedures, there are mannequins or other options for simulation training, which also offer the opportunity to refine team and psychomotor skills. Experienced operators should be available at all times to provide guidance and needed assistance. For rare procedures or where the person performing the procedure has not done the procedure frequently or recently, "just in time" training is beneficial as a refresher if time allows. The balance of minimizing patient exposure to multiple procedural attempts with the need for trainee experience is very challenging. The number of attempts allowed per provider should be considered at the individual provider, patient, and procedure level.

I. Documentation. Careful documentation of procedures enhances patient care. For example, noting difficulties encountered at intubation or the size and insertion depth of an endotracheal tube (ETT) provides important information if the procedure must be repeated. Documentation should include the date and time, the indication for the chosen procedure, the analgesia and antisepsis used, the number of attempts (successful and unsuccessful), the equipment and technique used, any complications encountered, documentation of positioning of device if appropriate, and any follow-up/radiologic studies done/pending (Fig. 69.1).

J. Maximizing success. Measures that can enhance successful performance should be undertaken. These include pharmacologic measures including chemical paralysis (with respiratory support) where appropriate, attention paid to patient positioning, adequate support staff including appropriate supervision of providers who are not yet ready for independent practice as well as use of other tools. These other tools could include transilluminators and ultrasounds for vascular access, ultrasound identification of location and/or guidance (lumbar punctures, para-, pericardio-, thoracentesis), and video laryngoscopy for intubation.

TRACHEAL INTUBATION PROCEDURE NOTE

General Fields	Examples of Data to Populate in the Fields
Indication:	Hypoxemia, respiratory failure, congenital diaphragmatic hernia in the delivery room
Monitoring:	Cardiac, pulse oximetry, transcutaneous carbon dioxide monitoring
Anesthesia/analgesia:	
Neuromuscular blockade:	Nondepolarizing or depolarizing
Other drugs:	Sedatives
Number of attempts:	
Size of endotracheal tube and cuff present or not:	
Depth at lip/gum:	
Equipment used:	Video laryngoscopy, stylet use, etc.
Position confirmed by:	Auscultation, capnography (qualitative of quantitative), chest x-ray
Chest x-ray findings:	
Comments:	"Procedure well tolerated without any significant events" or "Bradycardia with first attempt, attempt aborted with recovery of heart rate prior to next attempt"
Consent obtained:	Yes/no/not applicable
Preprocedure checklist (time out):	Yes
Difficult to bag-mask-ventilate:	Yes/no and if yes success if adjuncts used to improve
Difficult or critical airway:	Yes/no and if yes why and what should be done next time

Figure 69.1. Example procedure note.

III. BLOOD DRAWING. The choice of location, technique, site, and preparation for the procedure of withdrawing blood depend on considerations such as type of studies needed, patient size, frequency, and volume of blood needed.

A. Analgesic considerations. Procedures that involve breaks in the skin and/or squeezing of an extremity (particularly heel stick specimens) are painful.

Pain reducing measures such as the use of oral sucrose solutions, topical lidocaine preparations, swaddling, and other nonpharmacologic measures should be provided. Only rarely are medications such as opiates given.

B. Antisepsis. In general, alcohol (70% isopropyl alcohol) can be used to clean the anticipated site of puncture and surrounding skin. If blood cultures are to be obtained, then the site should be cleaned with povidone-iodine or chlorhexidine gluconate. If blood cultures are being obtained, then a new sterile needle or needle-free system should be used to insert the blood into the culture bottle(s).

C. Types of blood draws

1. **Capillary blood** is drawn when there is not a need for large volume of blood (usually only 1 to 2 mL at a time). Most frequently, this is drawn from the heels of neonatal patients; only infrequently would a capillary specimen be obtained from a finger.
   - **a. Technique**
     - **i.** Capillary punctures of the foot should be performed on the medial or lateral side of the heel, avoiding previous sites if possible (Fig. 69.2).

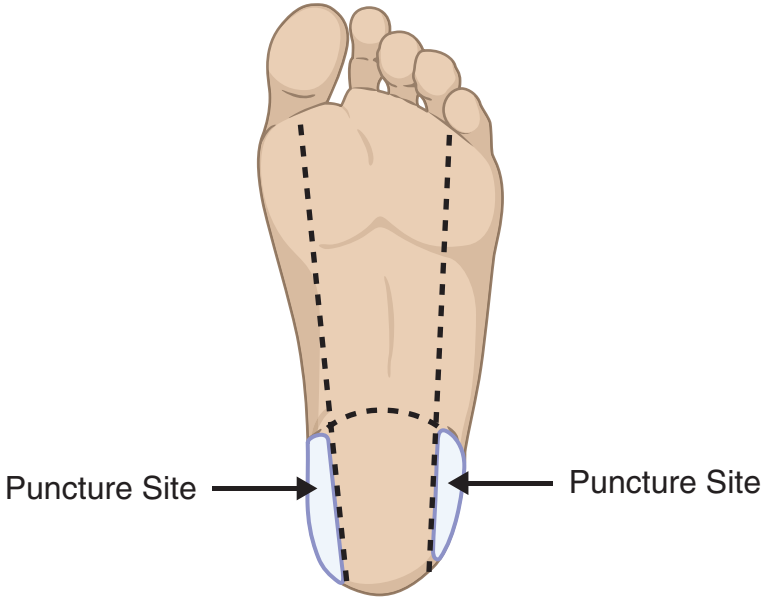

Figure 69.2. Site locations for capillary puncture of the heel. A *line* extending from a point between the 4th and 5th toes running parallel to the lateral heel and a *line* from the middle of the big toe running parallel to the medial heel are landmarks. Heel sticks are recommended to be performed in the *blue shaded* regions. (Adapted from Jain A, Rutter N. Ultrasound study of heel to calcaneum depth in neonates. *Arch Dis Child Fetal Neonatal Ed* 1999;80[3]:F243–F245.)

ii. The extremity to be used should be warmed to increase peripheral blood flow using approved devices.
iii. The skin should be cleaned carefully with an antiseptic before puncture to avoid infection of soft tissue or underlying bone. If using an alcohol-based solution, allowing the appropriate dry time is critical to avoid hemolysis of the specimen due to residual alcohol.
iv. A spring-loaded lancet should be used because it minimizes pain while ensuring a puncture adequate for obtaining blood. The appropriately sized lancet based on the patient's weight should be used. The blood should flow freely, with minimal or no squeezing. This will ensure the most accurate laboratory values.

2. **Venous blood** can be obtained from a peripheral vein when larger blood volumes are needed and/or for blood cultures and some metabolic labs. It is useful to have an assistant to help prevent the patient from withdrawing or excessively moving the extremity to decrease the risk for accidental dislodgment of the needle. This assistant can also assist in aspirating from the syringe once blood is obtained.
   a. **Technique**
      i. The hand dorsal veins, antecubital, and saphenous veins are frequently used sites.
      ii. Butterfly safety needles of 23G or 25G attached to a T-connector and syringe are generally used.
      iii. A tourniquet is placed proximal to the site of anticipated needle entry. This should be released prior to withdrawal of blood for specimens when a free-flow of blood is needed such as lactate and ammonia levels.
      iv. Visualization of the vein can be assisted with transillumination if it is not easily visible by sight alone. Ultrasound is a useful adjunct to aid in successful venipuncture.
      v. The skin should be cleansed with the desired agent following hospital and manufacturer guidelines for length of cleansing and dry times.
      vi. The needle is introduced usually at an approximately 15-degree angle to the skin until there is flashback of blood. Then, the person performing the procedure or an assistant should draw back gently on the syringe until the appropriate volume of blood is obtained.
      vii. Once the appropriate volume of blood is obtained, the tourniquet should be released (if still tied) and the needle removed from the skin. Gentle pressure should be held to ensure hemostasis.

3. **Arterial blood** may be needed for blood gases, some metabolic studies, and when the volume of blood required would be difficult to obtain from a peripheral vein and no indwelling catheter is available. It is useful to have an assistant to help prevent the patient from withdrawing or excessively moving the extremity to decrease the risk for accidental dislodgement of the needle. This assistant can also assist in aspirating from the syringe once blood is obtained.
   a. **Technique**
      i. The radial or posterior tibial artery are common sites for arterial puncture. Rarely, the potential risk of brachial artery puncture

may be justified when no other site is available. Traditionally, an Allen test is performed to ensure collateral perfusion.

ii. Butterfly safety needles of 23G or 25G attached to a T-connector and syringe are generally used.

iii. Visualization of the artery can be assisted with transillumination if sight alone is insufficient. Ultrasound is becoming an increasingly useful adjunct to aid in successful arterial puncture.

iv. The skin should be cleansed with the desired agent following hospital and manufacturer guidelines for length of cleansing and dry times.

v. The artery is identified and entered with the bevel of the needle facing up and at a 15-degree angle against the direction of flow. Once there is flashback of blood, then the syringe should be gently aspirated until the appropriate volume of blood is obtained.

vi. Once the needle is removed from the skin, gentle pressure should be held to ensure hemostasis.

Complications with the earlier procedures include need for repeated punctures if inadequate blood volume obtained, hemolyzed specimens (highest incidence with capillary specimens), hematomas, infection, bruising, accidental puncture of a wrong vessel (i.e., artery rather than a vein), and long-term sequela with sensitization.

D. Catheter blood samples

1. **Umbilical artery or radial artery catheters** are often used for repetitive blood samples, especially for blood gas studies.

2. **Technique**

a. A needleless system for blood sampling from arterial catheters should be used. Specific techniques for use vary with the product; the manufacturer's guidelines should be followed.

b. The catheter must be adequately cleared of infusate before withdrawing samples to avoid false readings. After the sample is drawn, blood should be cleared from the catheter by infusing a small volume of heparinized saline-flushing solution.

c. For blood gas studies, a specially designed blood gas syringe or a 1-mL preheparinized syringe is used to withdraw the sample unless a point of care device is being used. If a point of care device is used for the blood gas sample, then a heparinized syringe is not necessary. The rate of sample withdrawal should be performed slowly to avoid altering downstream arterial perfusion.

IV. VASCULAR CATHETERIZATION (See Fig. 69.3 for diagrams of the newborn venous and arterial systems.)

A. Peripheral intravenous (IV) catheter placement.

The insertion and management of IV catheters requires great care. Sites of placement for peripheral IV catheters include dorsal hand veins, veins in the antecubital fossa, dorsal foot veins, or saphenous veins. If there are no other options, use of a scalp vein can be considered. Transillumination and ultrasound are both useful adjuncts to aid in successful placement.

1. **Indications and contraindications.** Peripheral IV catheters are indicated for short-term use for IV fluid or pharmacologic therapy, especially

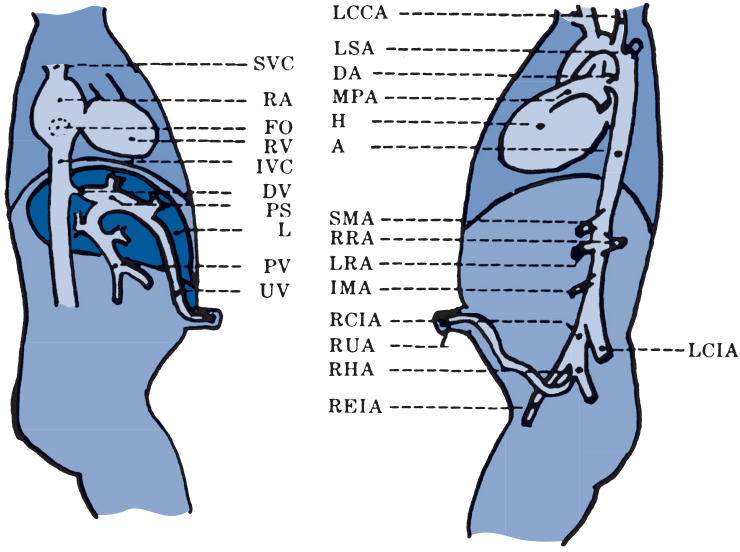

Figure 69.3. **A:** Diagram of the newborn umbilical venous system. SVC, superior vena cava; RA, right atrium; FO, foramen ovale; RV, right ventricle; IVC, inferior vena cava; DV, ductus venosus; PS, portal sinus; L, liver; PV, portal vein; UV, umbilical vein. **B:** Diagram of the newborn arterial system, including the umbilical artery. LCCA, left common carotid artery; LSA, left subclavian artery; DA, ductus arteriosus; MPA, main pulmonary artery; H, heart; A, aorta; SMA, superior mesenteric artery; RRA, right renal artery; LRA, left renal artery; IMA, inferior mesenteric artery; RCIA, right common iliac artery; LCIA, left common iliac artery; RUA, right umbilical artery; RHA, right hypogastric artery; REIA, right external iliac artery. (Reprinted from Kitterman JA, Phibbs RH, Tooley WH. Catheterization of umbilical vessels in newborn infants. *Pediatr Clin North Am* 1970;17[4]:895–912. Copyright © 1970 Elsevier. With permission.)

intermittent medications. They are also used for transfusion of blood products if an adequately sized central venous catheter is not present. Contraindications include use with high-risk extravasant or irritant medications.

2. **Analgesic considerations.** Oral sucrose and swaddling excluding the extremity being accessed for the attempt can be used. If time allows and the patient does not meet contraindications, a topical lidocaine preparation can help minimize pain.
3. **Technique.** The technique to place a peripheral IV catheter follows the technique for venous blood withdrawal except as follows:
   a. Use of specifically designed peripheral IV catheter size of 22G or 24G.
   b. Once blood flashback is seen, the catheter is advanced over the introducer needle. Then, a preflushed T-connector is attached to the hub of the catheter and flushed into the catheter slowly to ensure it infuses smoothly. The catheter should be secured with a silicon adhesive.
4. **Complications** include extravasation of infusate with subsequent skin damage, air embolus, and rarely infection. Close assessment of catheter patency is required to avoid the significant risk of peripheral IV infiltration.

B. Umbilical artery catheterization (UACs)

1. **Indications and contraindications.** UACs are used for continuous monitoring of arterial blood pressure, frequent monitoring of arterial blood gases, exchange transfusion, or as a temporary route for infusion of some parenteral fluids if no alternative vascular access is available. Vasopressors should not be administered through a UAC. Contraindications include omphalitis, abdominal wall defects (e.g., omphalocele), vascular compromise to lower body, peritonitis, and necrotizing enterocolitis. Alternative methods for blood sampling, including arterial puncture and noninvasive blood pressure monitoring, should be considered as a first option; only critically ill patients requiring continuous arterial access should have a UAC placed.

2. **Technique**

   a. Determine catheter size and length. Arterial catheter size should be determined based on patient size. In infants with birthweight of <1.5 kg, usually a 3.5 French single-lumen catheter is used. In larger infants, a 3.5 or 5 French single-lumen catheter may be used depending on the vessel size. To determine length of insertion, two common methods are used. One method is to use external measurements (Fig. 69.4). For a "high" UAC, the distance is usually (umbilicus-to-shoulder) +2 cm plus the length of the stump. Alternatively, the calculation of UAC depth of insertion (cm) = [birthweight (kg) × 3] + 9 plus the length of the umbilical stump. The goal tip position for a "high UAC" is between the 6th and 10th thoracic vertebrae. UACs placed in the high position are associated with less vascular complications than UACs placed in lower vessel positions, with tip between the 3rd and 4th lumbar vertebrae.

   b. Catheter is prepared according to unit guidelines. Two examples are (i) attaching a three-way stopcock and (ii) attaching a T-connecter to the catheter hub. No matter what method is used, the catheter and attachments should be flushed with a sterile saline solution. The catheter should never be left open to the atmosphere because negative intrathoracic pressure could cause an air embolism. In some cases, nonheparinized solutions may be used for flush, but continuous infusions are typically heparinized.

   c. Patient is positioned supine and swaddled to help limit contamination of the sterile field. Sterile technique is used including provider hand washing and PPE for all staff in the procedural area.

   d. The umbilical stump is suspended with forceps. An assistant can help hold up the stump above the abdomen using the forceps. The umbilical stump itself and 3 to 4 cm of surrounding abdominal skin are washed carefully with an antiseptic solution as discussed in section III.B. Following this, the abdomen is draped with sterile towels.

   e. Umbilical (twill) tape is then placed as a simple tie around the skin at the base of the cord. Care must be taken to loosen the tie after the procedure. The tape is used to gently constrict the cord to prevent bleeding. The cord stump is then cut cleanly horizontally with a scalpel to a length of 1.0 to 1.5 cm to reveal a cross-section of the umbilical vessels.

   f. The cord is stabilized with a forceps or hemostat, and the arteries are identified.

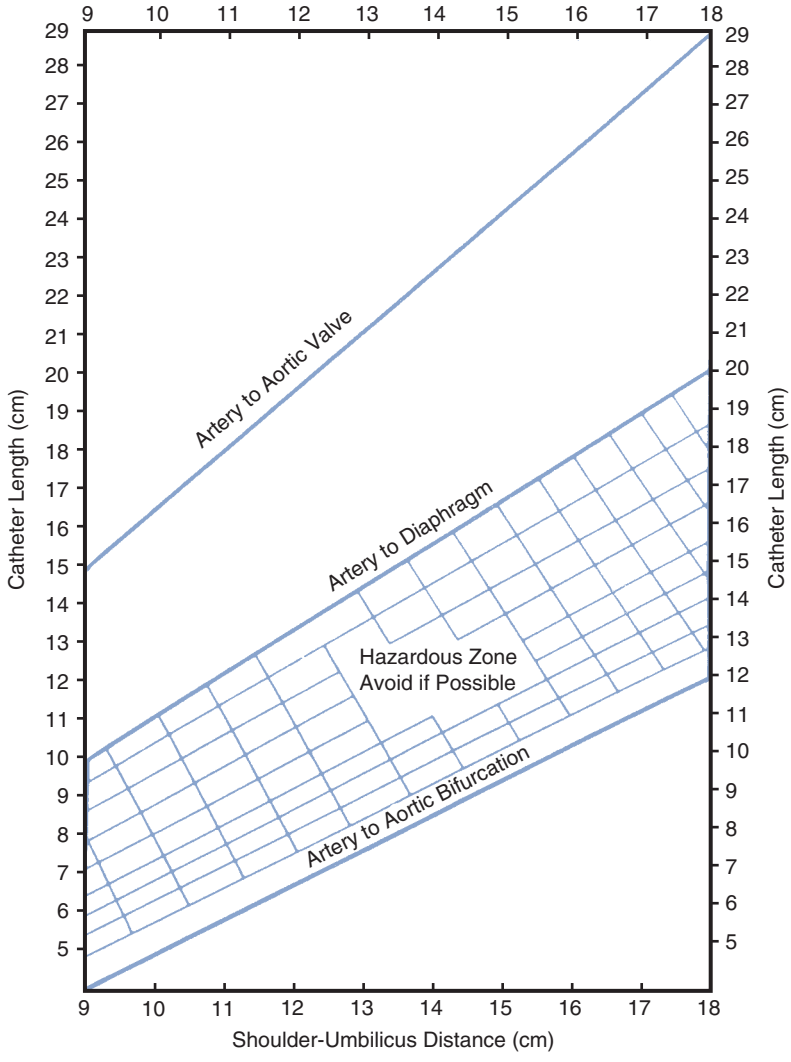

Figure 69.4. Distance from shoulder to umbilicus measured from above the lateral end of the clavicle to the umbilicus, as compared with the length of umbilical artery catheter needed to reach the designated level. (Modified from Dunn PM. Localization of the umbilical catheter by postmortem measurement. *Arch Dis Child* 1969;41[215]:69. Copyright © 1966 with permission from BMJ Publishing Group Ltd.)

g. One of the tips of an open iris forceps is inserted into an arterial lumen and gently used to **dilate the vessel**, and then the closed tip is inserted into the lumen of an artery to a depth of 0.5 cm. Tension on the forceps tip is released, and the forceps is left in place to dilate the vessel for approximately 1 minute. This pause may be the most critical step for ensuring successful insertion of the catheter.

h. The forceps is withdrawn, and a sterile saline–filled 3.5 or 5 French single-lumen umbilical vessel catheter with an end hole is threaded into the artery (see earlier text for determination of catheter size). A slightly increased resistance will be felt as the catheter passes through the base of the cord (near the cord tie) and as it navigates the umbilical artery–femoral artery junction. The catheter should be inserted to predetermined depth (see IV.B.2.a). When the catheter is advanced to the appropriate distance, placement should be confirmed by easy return of blood and radiographic examination. The catheter should be secured in place with a suture using silk thread and a tape bridge or a silicon adhesive added for further stability.

3. Potential difficulties with placement of UAC:

a. False tracking may occur. If the first catheter has made a false track and is no longer in the lumen of the umbilical artery, leaving the original catheter in place and gently passing a second catheter alongside can sometimes allow for successful passage of the catheter inside the vessel lumen.

b. The catheter may pass into the lower aorta but then loop caudad into the contralateral iliac artery, loop within the aorta, or exit into a side artery. There may be difficulty advancing the catheter, and cyanosis or blanching of the leg or buttocks may occur. This happens more frequently when a small catheter (3.5 French) is placed in a large baby. Sometimes, using a larger, stiffer catheter (5 French) will allow the catheter to advance up the aorta. Alternatively, retracting the catheter into the umbilical artery, rotating it, and readvancing it may result in aortic placement. If this fails, the catheter should be removed, and placement is attempted through the other umbilical artery. The catheter may also enter any of the vessels coming off the aorta. If the catheter cannot be advanced to the desired position, the tip should be pulled to a low position (L3–L4) or the catheter removed. A peripheral arterial line placement can be considered as an alternative.

4. UAC removal

a. The incidence of complications associated with umbilical artery catheterization appears to be directly related to the length of time the catheter is left in place. The need for the catheter should be reassessed daily, and the catheter should be removed as soon as possible. The UAC should be removed when any one of the following criteria is met:

- **i.** The infant improves such that continuous monitoring and frequent blood drawings are no longer necessary.
- **ii.** A maximum dwell time of 7 days is recommended by the Centers for Disease Control and Prevention (CDC) to reduce infectious and thrombotic complications.
- **iii.** Immediate removal if any complications occur

b. Method of catheter removal. The catheter is removed slowly over a period of 30 to 60 seconds allowing the umbilical artery to constrict at its proximal end while the catheter is still occluding the distal end. Removal can be extended even longer if concern for bleeding risk such as a coagulopathy. This usually prevents profuse bleeding. Old sutures should be removed. If bleeding should occur despite this method, pressure should be held by pinching the stump of the umbilical artery until the bleeding ceases taking care not to apply excessive direct abdominal pressure. This may take several minutes. In some cases, use of a topical hemostatic agent or blood clot–inducing material can be helpful for ongoing oozing.

5. **Complications associated with umbilical artery catheterization.** Significant morbidity can be associated with umbilical artery catheterization. These complications are mainly due to vascular accidents, including thromboembolic phenomena to the kidney, bowel, legs, or, rarely, the spinal cord. These may manifest as hematuria; hypertension; signs of necrotizing enterocolitis or bowel infarction; and cyanosis or blanching of the skin of the back, buttocks, or legs. Other potential complications include infection, disseminated intravascular coagulation, and vessel perforation. All these complications are indications for catheter removal. Close observation of the skin, monitoring of the urine for hematuria, measuring blood pressure, and following the platelet count may alert providers to complications.

   a. Blanching of a leg following catheter placement is the most common complication noted clinically. Although this often occurs transiently, it deserves careful attention. One technique that may reverse this finding is to warm the opposite leg. If the vasospasm resolves, the catheter may be left in place. If there is no improvement, the catheter should be removed.

   b. Thrombi. If clinical concern for vascular complications exists, Doppler ultrasonographic examination of the aorta and renal vessels should be obtained. If thrombi are observed, the clinical team should consider removal of the line versus consultation with interventional radiology or hematology about risks/benefits of the use of local anticoagulation therapy such as tissue plasminogen activator. For small thrombi or minor clinical symptoms such as hypertension, often medical treatment of hypertension (see Chapter 28) and following the thrombi by ultrasound examination until resolution is indicated. For significant vascular compromise in setting of significant thrombosis (such as loss of pulses and impairment of perfusion), anticoagulation with close monitoring of partial thromboplastin time (PTT) or unfractionated heparin levels and fibrinolytic agents (see Chapter 44) may be considered in consultation with hematology if not contraindicated (e.g., coagulopathy or intraventricular hemorrhage [IVH]). Surgical treatment of thrombosis is rare.

C. Umbilical vein catheterization (UVC) (see Figs. 69.3 and 69.5)

1. **Indications and contraindications.** **UVCs**, when passed through the ductus venous and near the right atrium, are used for monitoring of central venous pressure, infusion of vasopressors, and as the primary route of venous access for infusion of fluids. Low UVCs can be used for exchange transfusion or as emergency vascular access for infusion

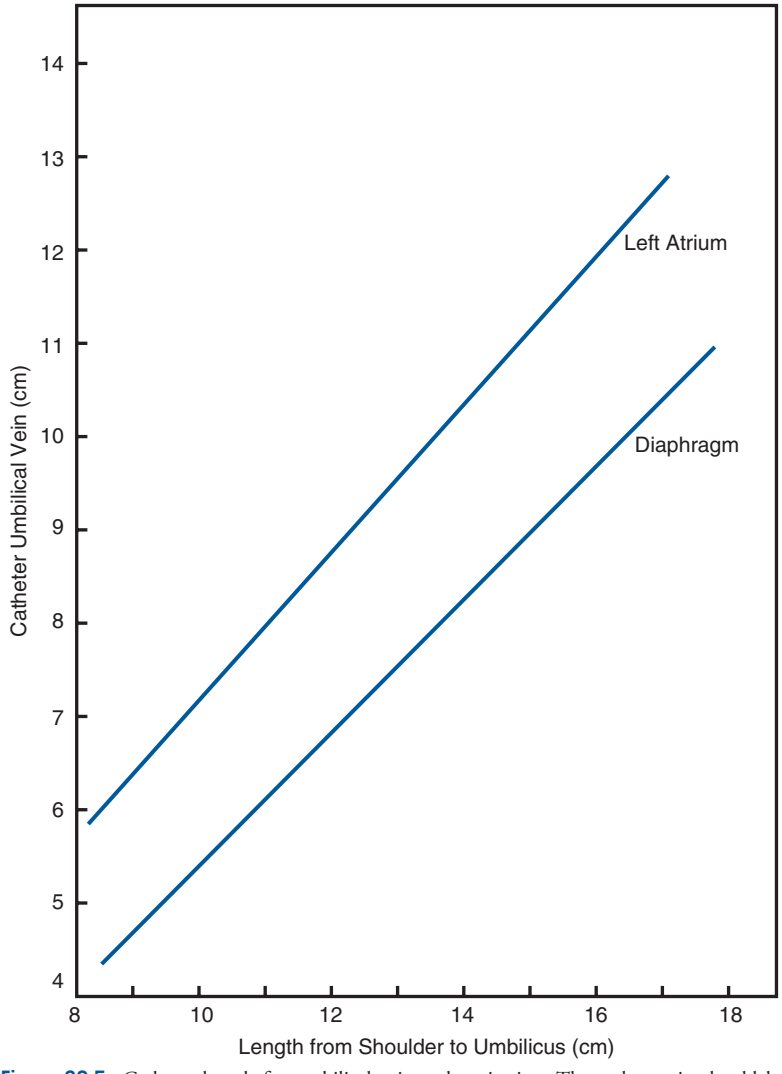

Figure 69.5. Catheter length for umbilical vein catheterization. The catheter tip should be placed between the diaphragm and the left atrium. (Modified from Dunn PM. Localization of the umbilical catheter by post-mortem measurements. *Arch Dis Child* 1966;41[215]:69. Copyright © 1966 with permission from BMJ Publishing Group Ltd.)

of fluid, blood, or medications until alternate access can be obtained. Contraindications include omphalitis, abdominal wall defects (e.g., omphalocele), and peritonitis.

2. **Technique**

a. Determine catheter size and length of insertion for umbilical artery catheterization (see Fig. 69.5). In babies <1.5 kg, usually a 3.5 French catheter is used, and in larger babies, a 5 French catheter is placed. Placement of a double- or triple-lumen catheter into the umbilical vein provides additional venous access for administration of incompatible solutions (e.g., those containing vasopressor agents, sodium bicarbonate, or calcium). The use of a multiple-lumen catheter significantly reduces the need for multiple peripheral IV catheters and skin punctures and is often preferred in very low birth weight infants. The disadvantage is that infusions must be maintained through lumens that are no longer needed, which can alter the ability to provide full nutritional support or appropriately adjust fluid therapy. Two methods are typically used for determining the length of placement: A depth of insertion of two-thirds of the distance from the shoulder to the umbilicus or use of the equation of UVC insertion length (cm) = [(birthweight (kg) × 3) + 9] / 2. Add the length of the umbilical stump to the calculated insertion length.

b. Catheter is prepared according to unit guidelines. Some providers attach T-connectors to each lumen and then flush the lumens with sterile heparinized saline solution through an attached syringe. Others attach a stopcock to the end of the catheter lumens, hubs onto each stopcock end, and then connect to a syringe to flush the catheter lumens. The catheter should never be left open to the atmosphere because negative intrathoracic pressure could cause an air embolism. In some cases, non-heparinized solutions may be used for flush, but continuous infusions are typically heparinized.

c. Sterile technique and preparation of the umbilicus and procedural field are performed (see earlier text).

d. The umbilical vein is identified and any visible clots are removed with forceps. The umbilical vein is gently dilated as with the umbilical artery in section IV.B.2.g.

e. The UVC is inserted while gentle traction is exerted on the cord. Once the catheter is in the vein, one should try to slide the catheter cephalad just under the skin, where the vein runs very superficially. If the catheter is being placed for emergency vascular access, it should be advanced only as far as is necessary to establish good blood flow (usually 2 to 4 cm plus the length of the umbilical stump). If the catheter is being used for continuous infusion or to monitor central venous pressure, it should be advanced through the ductus venosus into the inferior vena cava and its position verified by x-ray.

f. UVC should be secured in place with a suture using silk thread and a tape bridge or silicon adhesive added for further stability (see Chapter 65).

3. **Potential difficulties with placement of UVC.** If difficulty occurs during advancement of the catheter through the ductus venosus, one troubleshooting technique is to pull the catheter back to about 4 cm and then advance the catheter while rotating it in a clockwise direction.

A second method is to place a second catheter side by side next to the malpositioned catheter. The malpositioned catheter may functionally "block" the aberrant path allowing the second catheter to pass through the ductus venous and into the IVC. If that occurs, the original malplaced catheter should be carefully removed once the second catheter is placed in the proper position. A third option that has been successful with or without the use of ultrasound is to use external manipulation of the liver by gently pressing on the right upper quadrant of the abdomen in an effort to align the catheter with the ductus venosus and allow for passage of the catheter into the IVC.

4. **Considerations.** **Only isotonic solutions should be infused** until the position of the catheter is verified by x-ray studies. If the catheter tip is in the inferior vena cava, hypertonic solutions may be infused.
5. **Catheter removal.** **Ideally, catheters should be removed by 7 days and no later than 10 days of age if necessary.** In the circumstance where a baby needs a few days of access to reach sufficient enteral nutrition, to avoid placement of a second central line, a peripheral IV should be considered. If this is not possible or feasible, the UVC could be kept up to 14 days. After 14 days, the increased risk of infections or other complications is excessive. In very low birth weight infants, often peripherally placed central venous catheters are inserted after the first week of life and UVCs are removed.
6. **Complications.** Catheter malposition and extravasation can occur and cause serious complications such as cardiac tamponade if occurring in pericardial space or liver damage and ascites if in the abdomen. To avoid these serious complications, immediate cessation of fluid administration and removal of UVC is indicated if malposition occurs. If concerned about a pericardial effusion, the provider can attempt to withdraw fluid prior to removal of the catheter. Other complications include thrombosis and infection.
7. **Emergency UVC placement** may be required in situations such as a newborn undergoing cardiopulmonary resuscitation. The key steps are (i) use an umbilical tie (tape) to prevent hemorrhage, (ii) flush the catheter prior to placement to prevent air embolus, (iii) pay attention to safety of those in the immediate area with scalpel use when cutting the cord, (iv) use appropriate PPE for the providers at the beside, and (v) if possible, quickly clean the cord with an agent such as povidone-iodine, although typically without waiting for a full application and dry time. Some practitioners will give antibiotics after an emergency UVC is placed. The line should be removed as soon as possible if it was inserted in a nonsterile fashion and replaced sterilely with alternative venous access.

D. Peripheral artery catheterization

1. **Indications and contraindications.** Placement of an indwelling peripheral artery catheter is a useful alternative to umbilical artery catheterization to monitor arterial blood gas levels and blood pressure. Peripheral artery catheters are indicated if umbilical arteries cannot be cannulated or arterial access is needed after UAC is removed, if preductal arterial sampling is needed, or if necessary to avoid any risk of

thrombosis of major vessels, a risk with umbilical vessel catheterization. Contraindications include inadequate circulation to the extremity or absent pulse, local skin infection, or uncorrected coagulopathy.

2. **Technique**

a. Determine catheter size and location for placement. In infants, a 22G or 24G IV cannula with a stylet and a T-connector should be flushed with heparinized saline solution. If a safety catheter is used that does not allow for attachment of a T-connector prior to the puncture, a flushed one should be readily available to attach to the cannula hub once in appropriate place. The radial, posterior tibial, and dorsalis pedis arteries are common sites for placement in infants.

b. It is recommended to assess adequacy of collateral circulation prior to cannulation of peripheral arteries.

c. The extremity should be positioned prior to procedure to optimize access to, and avoid occlusion of, the artery and to enable observation of distal extremity perfusion. For example, for radial arterial lines, the wrist should be gently extended, or for arteries in the foot, it should be slight dorsiflexed. Leave all fingertips or toes exposed to observe color changes.

d. The site is prepared with **antiseptic technique** and the site of maximum arterial pulsation is palpated. Transillumination or ultrasound can be used to identify vessel position. The catheter is inserted through the skin at an angle <30 degrees to horizontal and slowly advanced into the artery. When the artery is entered, as evidenced by blood return into the hub of the catheter, the stylet is removed, and the catheter is advanced in the artery. If there is no blood return, the needle may have punctured through the distal wall of the artery. The stylet can then be removed, and the catheter slowly pulled back until blood return occurs, and then the catheter can be advanced into the vessel.

e. Heparinized saline is infused through the catheter with a minimum infusion rate of 0.5 to 0.8 mL/hour and maximum of 1 to 2 mL/hour.

3. **Complications are rare and include arterial thrombosis and subsequent impaired tissue perfusion.** If there are signs of compromised perfusion at any time (distal extremity cool, pale, dusky, or mottled), the catheter should be removed immediately. When the catheter is removed, pressure should be applied at the site to ensure hemostasis. Other complications could include aneurysm of punctured artery, hematoma, bleeding, infection, damage to peripheral nerves, infection, or air embolus.

E. Percutaneous central venous catheterization

1. **Indications and contraindications.** Central venous catheters are used for long-term access for prolonged parenteral nutrition, antibiotics, or sedation; for pressor administration; or occasionally to monitor central venous pressure. There are no absolute contraindications to placement, but severe coagulopathy should be corrected.

2. **Technique**

a. The central venous catheter is inserted into a **peripheral vein and advanced into the central circulation**. A specialized team of nurses, neonatal nurse practitioners, and/or physicians who are responsible for

placing these lines improves rates of successful line placement and adherence to infection control measures.

b. Catheter selection depends on the size of the infant and vessel; typically, a 1.1, 1.9, or 2.7 French silicone or double-lumen polyurethane catheter is used.

c. Measure distance for catheter insertion by using a nonsterile tape measure. For superior vena cava tip placement, measure from the insertion site along the track of the vein to the head of the clavicle on the right side. Then, measure down from the head of the right clavicle to the third intercostal space just to the right of the sternum. For inferior vena cava tip placement, measure along the path of the vein to the level of the xiphoid process.

d. Careful attention to **aseptic technique** is required. The operator should be assisted by another caregiver who can obtain additional equipment as needed, ensure integrity of the sterile field, and monitor the progress of the procedure using a specific step-by-step checklist. The infant is placed supine. An appropriate vein of entry is selected. This may be a basilic, greater saphenous, or, more rarely, axillary or femoral vein. The cephalic vein should be avoided because central placement is more difficult. Ultrasound guidance can be used to identify vessel and/or for placement of catheter. Excess catheter length can be trimmed to the measured insertion length with no more than 1 to 2 cm excess prior to placement to avoid excess external portion of catheter. The manufacturer recommendations for trimming should be followed, and the total final length of the catheter should be documented in the procedure note. The entry site is prepared with an antiseptic solution such as chlorhexidine (for infants with mature skin) or alcohol, and the introducer needle is inserted into the vein until blood flows freely. The silicone catheter is inserted through the needle with forceps and is slowly advanced the predetermined distance for central venous positioning. The introducer needle is removed, any extra catheter length is coiled on the skin near the insertion site, and the site is covered with silicon adhesive. The catheter tip is positioned at the junction of the vena cava and right atrium, as confirmed by radiography. Especially with the smaller gauge catheters, visualization is best accomplished by an oblique radiograph to separate the catheter position from that of the cardiothymic silhouette. It is important to note the arm position of the infant at time of radiograph as changes in arm position can cause a shift in tip position. Injection of a small amount of isotonic contrast material can aid in visualization.

e. Surgical techniques including vessel cutdown can be used if unable to cannulate vessel with peripheral attempts.

3. **Complications** are rare and include hemorrhage during insertion, infection, and thrombosis of the catheter. Some babies will develop a thrombophlebitis, usually within 24 hours of catheter placement. If the tip of the catheter is in the right atrium, a rare but potentially lethal complication is pericardial tamponade. Early diagnosis and treatment by pericardiocentesis are critical. Care must be taken when flushing or infusing to minimize the pressure on the catheter, which could cause catheter rupture. By using a larger syringe (10 mL), infusion pressure is reduced over that obtained with a smaller (3 mL) syringe.

F. Intraosseous (IO) needle placement

1. **Indications and contraindications.** An IO needle/line should be placed in emergent situations where vascular access is needed and unable to be obtained by other means. Contraindications include local site infections, bone deformities, or fractures.
2. **Technique**
   a. Identify the site for insertion and prepare site with aseptic technique. Potential locations include proximal tibia (anteromedial surface 1 to 2 cm below tibial tuberosity) or the distal tibia (proximal to the medial malleolus).
   b. Place IO needle through use of battery-operated driver or manually. With both methods, the needle is inserted at a 90-degree angle to the bone. If placing manually, use downward pressure and a twisting motion. In both methods, the needle is advanced only until a sudden loss of resistance is noted as the needle passes through the cortex of the bone. Do not advance further to avoid needle going through the distal side of the bone. The stylet is then removed, and the position is checked by aspiration of blood and marrow contents or by ability to flush readily without evidence of extravasation.
   c. The needle is then flushed slowly with saline solution and can be used for emergency medication or fluid administration.
3. **Potential complications** include extravasation of fluid into skin, periosteal or muscle compartment, infection, bone fracture, or microemboli.

V. BLADDER CATHETERIZATION

A. Indications and contraindications. Obtaining urine specimens for culture and for relief of urinary retention. Coagulopathy and therapeutic anticoagulation are relative contraindications (especially in the patient on extracorporeal membrane oxygenation [ECMO]). In these situations, if the benefits are thought to outweigh the risk, then catheterization by an experienced provider such as a urologist should be considered. In addition, if there are any visible anomalies or concerns for urethral anomalies, urology should be consulted, if possible, prior to attempted bladder catheterization.

B. Analgesic considerations. Oral sucrose can be given for pain relief during catheterization.

C. Technique

1. Specific catheters have been designed for bladder catheterization including those for straight catheterization (i.e., not intended as an indwelling catheter) and Foley catheters intended to be maintained in place. Water-soluble lubricant should be applied to the catheter to aid in advancement.
2. An antiseptic (povidone-iodine) should be used to cleanse the area. A sterile field should be established, and the provider should wear sterile gloves.
3. A second provider is frequently needed to help maintain visualization of the urethral meatus and help with maintenance of sterility, especially in female patients. In males, care must be taken to not retract the foreskin

excessively due to the risk of phimosis. The foreskin should only be retracted until the urethral meatus is visualized.

4. Once, the urethral meatus is identified, the catheter is gently advanced into the bladder until urine is obtained. Resistance to insertion should be minimal. If obstruction is sensed, it is usually best to abort the procedure and consult urology as indicated.

D. Complications. Trauma to the urethra or bladder, unsuccessful procedure, introduction of infectious agents, and subsequent urinary tract infection

VI. LUMBAR PUNCTURE

A. Indications and contraindications. Spinal fluid is most frequently obtained in neonates to evaluate for meningitis. Other indications include metabolic studies or for the temporizing relief of posthemorrhagic hydrocephalus in preterm patients (although more frequently, specifically designed ventricular reservoirs are placed for this). Contraindications include coagulopathy, severe thrombocytopenia, and therapeutic anticoagulation as well as any anatomic concerns such as myelomeningocele or tethered cord. In addition, although rare in the neonate, if there are any concerns for a condition that could increase the risk of herniation, a lumbar puncture should be avoided and neurosurgical consultation obtained.

B. Analgesic considerations. Various regimens of analgesics have been studied for use during lumbar puncture. The options include oral sucrose, topical lidocaine, intradermal lidocaine, as well as IV agents. The choice of agent will depend on the clinical status of the patient as well as the urgency of the procedure. For example, for an intubated patient, use of an IV opiate may be the most effective. For a nonintubated patient, where there is adequate time to achieve effectiveness, topical lidocaine with oral sucrose would be appropriate.

C. Technique

1. The infant should be placed in the lateral decubitus or sitting position with legs straightened. The assistant should hold the infant firmly at the shoulders and buttocks so that the lower part of the spine is curved. Neck flexion should be avoided so as not to compromise the airway.
2. A sterile field is prepared and draped with towels, and the skin of the back cleansed with antiseptic solution, usually povidone-iodine. Chlorhexidine should not be used on the skin prior to a lumbar puncture because it is specifically not intended to be introduced into the central nervous system.
3. A 22G to 24G spinal needle with a stylet should be used. Avoid the use of a nonstylet needle, such as a 25G butterfly needle because this may introduce skin tissue into the subarachnoid space.
4. The needle is inserted in the midline into the space between the fourth and fifth lumbar spinous processes and angled slightly superior to follow the intervertebral space. The needle is advanced gradually in the direction of the umbilicus, and the stylet is withdrawn frequently to detect the presence of spinal fluid. In infants, the insertion distance is only a few millimeters. Usually a slight "pop" is felt as the needle enters the subarachnoid space.

5. The cerebrospinal fluid **(CSF)** is collected into three or four tubes, each with a volume of 0.5 to 1 mL.
6. The needle is withdrawn and an occlusive dressing placed over the site.

D. Complications. CSF leak, infection, uninterpretable results due to a bloody specimen.

E. Examination of the spinal fluid. CSF should be inspected immediately for turbidity and color. In many newborns, normal CSF may be mildly xanthochromic, but it should always be clear. Below is a general guide as to what studies to obtain from the sequential tubes:

1. **Tube 1.** Cell count and differential
2. **Tube 2.** Glucose and protein
3. **Tube 3.** Culture and sensitivity studies
4. **Tube 4.** Repeat cell count if the fluid is bloody. The fluid can be sent for other tests (such as polymerase chain reaction amplification for herpes simplex virus, metabolic studies, etc.).

   If there is limited fluid obtained and the patient has not been pretreated with antibiotics, then the studies sent should be prioritized by the most important studies for that patient (i.e., viral studies, cell count in the case of pretreatment, or culture if not pretreated). If more fluid is able to be obtained, sending the cultures studies from the later tubes is preferred to minimize the risk of blood contamination that could lead to a false positive.

VII. INTUBATION

A. Endotracheal intubation

1. **Indications and contraindications.** Endotracheal intubation is indicated for neonates with respiratory failure when noninvasive support has failed, for neonatal resuscitation when bag mask ventilation is unsuccessful, as indicated based on a congenital anomaly such as congenital diaphragmatic hernia, as well as for elective surgical procedures. The only contraindication is patients with advanced directive that stipulates no intubation. Relative contraindications are circumstances in which the procedure may be difficult such as airway anomalies, in which case consideration should be given to alternatives such as noninvasive approaches to ventilation.
2. **Analgesic considerations.** Endotracheal intubation is a painful and stressful procedure. In addition, premedication, specifically including a muscle relaxant has been shown to improve intubation success. In the circumstance of a nonemergent intubation, premedication should be provided. Ideally, the exact regimen is standardized at the unit or institutional level. Components of regimens generally include a vagolytic, analgesic, anxiolytic, and/or muscle relaxant unless the patient's condition is a contraindication to any of these medications (see Chapter 70).
3. **Technique**

   a. Choice of tube size and length. The correct tube size (see Chapter 4) and insertion depth can be estimated using various methods. For oral ETTs, the most common estimation of insertion depth is weight in kilogram + 6 cm.

Other methods include gestational age based or use of the nasotragal length + 1 cm. It is most important to remember that all of these methods are estimates, and insertion depth must be confirmed by physical examination and radiograph if the tube is to remain in place.

b. Choice of laryngoscopy equipment and size. In general, Miller blades size 00, 0, or 1 are used based on the patient size. Increasingly, video laryngoscopes are being used for intubation of neonates. These devices offer the possibility of concurrent observation of tube placement by other observers, and easier, more reliable tube insertion. Among the available devices, each has its particular characteristics in terms of size or design.

c. Route. Contradictory data exist over whether oral or nasal endotracheal intubation is preferrable. Oral ETTs can cause a palatal groove, and nasal ETTs can cause asymmetry of the nares and nasal erosion. In most circumstances, local practice and provider experience should guide this selection.

d. The patient should be ventilated using bag and mask to ensure that the patient has normal oxygen saturations (appropriate for gestational age) before laryngoscopy if possible.

e. Throughout the intubation procedure, **observation of the patient and monitoring of the heart rate are mandatory**. Pulse oximetry should also be used when available. Electronic monitoring with an audible pulse rate enables the team to be aware of the heart rate throughout the procedure. If bradycardia is observed, especially if accompanied by hypoxia, the procedure should be stopped and the baby ventilated with bag and mask.

f. The baby's neck should be slightly extended (the "sniffing" position) with the baby's body aligned straight. The operator should stand looking down the midline of the body.

g. The **laryngoscope** should be held in the operator's left hand and the mouth opened with the right hand. The laryngoscope blade is then gently advanced into the oropharynx on the right side of the mouth over the tongue, sweeping it out of the way. The blade tip should be advanced into the vallecula and the handle of the laryngoscope raised to an angle of approximately 60 degrees relative to the bed. The blade should then be lifted while maintaining the same angle, with care being taken not to rock the laryngoscope blade. Visualization of the vocal cords may be improved by providing cricoid pressure, pushing down slightly on the larynx with the fourth or fifth finger of the left hand (or having an assistant do it) to displace the trachea posteriorly. The anatomic structures of the larynx and pharynx have different appearances. The esophagus is a horizontal posterior muscular slit. The glottis, in contrast, consists of an anterior triangular opening formed by the vocal cords meeting anteriorly at the apex. This orifice lies directly beneath the epiglottis, which is lifted away by gentle upward traction with the laryngoscope (Fig. 69.6).

h. The **ETT** is held with the right hand and inserted between the vocal cords to the appropriate estimated depth and ETT marking. During nasotracheal intubation, the tube can be guided by small Magill-type forceps or by moving the baby's head slightly.

i. The **ETT position** is checked by auscultation of the chest to ensure equal aeration of bilateral lungs and observation of chest movement with

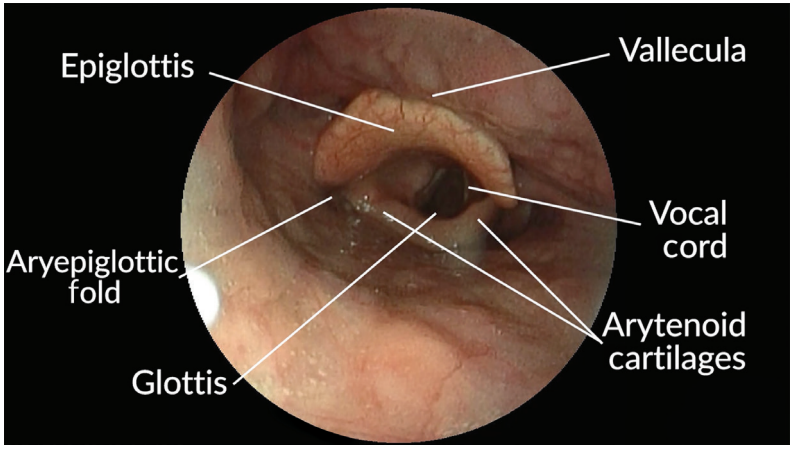

Figure 69.6. Anatomic landmarks of the neonatal airway. (Image attributed to Med Chaos, CC BY-SA 3.0, via Wikimedia Commons; Creative Commons Attribution-ShareAlike 3.0 Unported license. https://creativecommons.org/licenses/by-sa/3.0/.)

positive-pressure inflation. Mist will usually be observed in the ETT if it is correctly placed in the trachea. Either qualitative (colorimetric) or quantitative (end-tidal) carbon dioxide (CO_2) devices are recommended to confirm the intratracheal position of the tube. Once correct position is ascertained, the tube should be held against lips/nose or the palate until it can be taped securely in place; the position of the tube should be confirmed by radiograph as soon as possible.

4. **Complications.** The complications associated with endotracheal intubation include mainstem intubation, bradycardia, cardiac arrest, esophageal intubation, and oropharyngeal/glottic/tracheal trauma.

B. Supraglottic/laryngeal mask devices

1. **Indications and contraindications.** Placement of supraglottic devices are indicated when either bag mask ventilation or intubation is unsuccessful or when there are no providers trained in neonatal intubation. There are no true contraindications for placement of a laryngeal mask. Limitations include the use in patients with airway anomalies at or below the level of the vocal cords such as subglottic stenosis due to the positioning of the mask of the device above these structures as well as the possibility for inability to transmit adequate pressures to the trachea if high pressures are needed for resuscitation. In addition, the ability to place the supraglottic device may be limited in patients with restricted mouth opening or small size of the oral cavity such as in extremely low birth weight patients.
2. **Analgesic considerations.** In general, the placement of a supraglottic device is not painful. It can, however, induce a vagally mediated bradycardia; thus, a vagolytic agent such as atropine may be considered prior to placement, if time allows.

3. **Technique**

   a. A size 1 laryngeal mask is appropriate for most neonates and recommended for infants weighing 1.5 to 5 kg. There are very few reports of successful laryngeal mask use in patients <1.5 kg. Note that the dimensions and shape of the device are dependent on the manufacturer. It is useful to use water-soluble lubricant on the side of the device that will be advanced against the palatal ridge (the posterior surface). The integrity of the cuff, if present, should be checked by adding air into the cuff and then deflated prior to placement.

   b. Similar monitoring should be used as for endotracheal intubation.

   c. To place the laryngeal mask, the mouth should be opened with either hand. Frequently, it is also useful to secure the tongue with the thumb of the hand not being used to advance the device. The device is then advanced along the hard palate and into the hypopharynx until resistance is felt. If the device has a cuff, it should then be inflated until a gentle rise is noted. Breath sounds with positive pressure ventilation and/or CO_2 detection by qualitative or quantitative devices are indications the device is situated properly. The laryngeal mask can then be taped to secure it in place if it is needed for continued respiratory support.

4. **Complications.** Beyond vagal mediated bradycardia and inability to obtain adequate positioning, very few complications are reported with placement of a laryngeal mask.

VIII. THORACENTESIS AND CHEST TUBE PLACEMENT (see Chapter 38)

IX. ABDOMINAL PARACENTESIS FOR REMOVAL OF ASCITIC FLUID

A. Indications and contraindications. Therapeutic indications include respiratory distress resulting from abdominal distension (e.g., infants with hydrops or urinary ascites) for which removal of ascites will reduce thoracoabdominal competition. In addition, interference with urine production or lower extremity perfusion resulting from abdominal compartment syndrome may be improved by paracentesis. Diagnostic indications include the evaluation of suspected peritonitis, chylous ascites, or to differentiate urinary ascites from other processes. There are no absolute contraindications in setting of emergent indication. Some relative contraindications include large abdominal wall defects, massive hepatosplenomegaly, or uncorrected coagulopathy.

B. Technique

1. An 18G or 22G IV catheter is attached to a three-way stopcock and a 10- to 50-mL syringe. In some cases, a safety catheter is used and this is attached to a T-connector and three-way stopcock and syringes to pull off fluid.
2. The lower abdomen is prepared with antiseptic solution, and sterile drapes are placed. If the bladder is distended, it is drained with manual pressure or a urinary catheter.
3. A local anesthetic such as 1% lidocaine (Xylocaine) is infiltrated into the subcutaneous tissues when possible.

4. A syringe is attached to the catheter and then inserted just lateral to the rectus sheath (about 1.5 cm lateral to the midline) about one-third of the distance between the umbilicus and the symphysis pubis. A midline entry is also acceptable.
5. As the catheter is inserted through the abdominal wall, the syringe is aspirated. The catheter is advanced approximately 1 cm until the resistance of passing through the abdominal wall diminishes or fluid is obtained. Five to 10 mL of fluid is removed for diagnostic paracentesis, whereas 10 to 20 mL/kg should be removed for therapeutic effect.
6. The catheter is removed and the site bandaged. Ultrasound guidance can be useful, especially in situations when the volume of intraperitoneal fluid is minimal and may be difficult to locate, or an abdominal viscus could accidentally be punctured during the procedure.

C. Potential complications

1. Cardiovascular effects, including tachycardia, hypotension, and decreased cardiac output, may result from rapid redistribution of intravascular fluid to the peritoneal space following removal of large amounts of ascites.
2. Bladder or intestinal aspiration occurs more frequently in the presence of a dilated bladder or bowel. These puncture sites usually heal spontaneously and without significant clinical findings.

X. PERICARDIOCENTESIS

A. Indications and contraindications. If a pericardial effusion is suspected based on physical examination (muffled heart sounds, sinus tachycardia, narrow pulse pressure, and signs of diminished cardiac output), chest radiograph (cardiomegaly [not always present]), evidence of cardiac failure, or in situations of pulseless electrical activity with no other explanation, emergency drainage may be necessary. Sudden cardiorespiratory decompensation when a central line is in place, especially if the tip is in or near the right atrium, should prompt serious consideration of pericardial effusion with tamponade physiology. In most cases, even significant effusions produce little or no symptoms or signs. Diagnosis may be suspected based on physical exam, vital sign, and radiographic findings and should be confirmed by ultrasonographic examination before drainage is attempted if time permits. There are no absolute contraindications to the procedure, but an uncorrected coagulopathy is a relative contraindication.

B. Technique

1. The patient should be prepared and the area cleaned with antiseptic solution according to standard sterile technique. This should include the subxiphoid area extending up over the left anterior chest.
2. If time permits, the procedure should be performed with ultrasonographic guidance; however, this potentially lifesaving intervention often cannot be delayed.
3. Drainage is typically performed using a 22G or 24G IV catheter. The needle is inserted, just below the xiphoid process and just to the

left of midline (to avoid puncturing the right atrium), and angled at 30 to 45 degrees toward the left shoulder. The needle is advanced forward until the pericardial sac is entered while monitoring for arrhythmias that can signal needle advancement into the myocardium. Once fluid or air is obtained, the catheter is slightly advanced, the introducer needle is removed, and a 10-mL syringe and three-way stopcock is attached. Fluid or air is then aspirated via the catheter. Once no further fluid or air can be aspirated, the three-way stopcock is turned off to the catheter and the catheter is removed. The entry site is covered with occlusive gauge and transparent dressing. An alternative method is to use a 20G or 23G needle (e.g., a butterfly needle) with a 10-mL syringe and three-way stopcock attached for the procedure.

C. Potential complications. Cardiac puncture, pneumopericardium, pneumothorax, or transient dysrhythmias may occur. Ultrasonographic guidance may lower the risk of these complications.

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70 Preventing and Treating Pain and Stress Among Infants in the Newborn Intensive Care Unit

Carol Turnage Spruill and Michelle A. LaBrecque

KEY POINTS

- Pain and the effects of analgesia can be assessed using validated instruments.
- Lack of physical and behavioral responses to a painful condition or stimulus does not indicate an absence of pain.
- Pain treatment is selected based on the type, location, intensity, and duration of the pain stimulus.
- Pain exposure is decreased by minimizing the frequency and length of painful procedures.
- Preemptive analgesia is provided for postoperative pain management and for anticipated painful procedures.
- Nonpharmacologic interventions are used alone or as an adjunct to pharmacologic therapy.
- Monitoring for adverse effects of opioids and benzodiazepines such as respiratory depression and hypotension are an essential part of safe pain control.

I. BACKGROUND. Recognition that both premature and full-term infants experience pain has led to increasing appreciation of the prevalent problem of undertreatment of stress and pain of hospitalized infants. Both humanitarian considerations and scientific principles favor improved management strategies to prevent pain and stress whenever possible and, when discomfort is unavoidable, to provide prompt and appropriate treatment. Optimal pain management should be individualized and requires an understanding of developmental analgesic pharmacology, neonatal physiology, pain assessment, and techniques for providing pain relief.

A. Fetal and neonatal physiologic responses to pain. There is considerable maturation of peripheral, spinal, and supraspinal neurologic pathways necessary for nociception by late in the second trimester. By 20 weeks'

gestation, cutaneous sensory nerve terminals are present in all body areas and a full complement of cortical neurons is present within the central nervous system. Research using near-infrared spectroscopy (NIRS) shows a specific pattern of activation of the somatosensory cortex in preterm infants after noxious stimulation suggesting that painful stimuli reach the cerebral cortex. Peripheral sensory fibers have larger, more overlapping receptive fields and inhibitory cortical descending pathways such as the dorsolateral funiculus that modulate pain postnatally, suggesting that neonates and young infants have hyperresponsiveness to pain.

Infants exhibit predictable pain response patterns with respect to stress hormone levels, changes in heart rate, blood pressure, and oxygen saturation. Although the fetus is capable of mounting a stress response beginning at approximately 23 weeks' gestation, physiologic parameters are nonspecific and are not necessarily reliable indicators of pain, particularly among critically ill neonates who may be hemodynamically unstable, septic, or mechanically ventilated. As a result, pain assessment tools in infants are composite scales that typically combine physiologic parameters with observed distress behaviors. Behavioral and physiologic responses are less reliable among infants exposed to chronic or persistent noxious stimuli.

B. Medical and developmental outcomes

1. **Neonatal medical and surgical outcomes.** Neonatal responses to pain may worsen compromised physiologic states such as hypoxia, hypercarbia, acidosis, hyperglycemia, respiratory dyssynchrony, and pneumothorax. Changes in intrathoracic pressure due to diaphragmatic splinting and vagal responses produced in response to pain following invasive procedures precipitate hypoxemic events and alterations in oxygen delivery and cerebral blood flow. Early studies of surgical responses showed a more stable intraoperative course and improved postoperative recovery among infants who received perioperative analgesia and anesthesia.
2. **Neurodevelopmental outcomes.** There is evidence that infants have the ability to form implicit memory of pain and that there are negative behavioral consequences of untreated pain. Behavioral and neurologic studies suggest that preterm infants who experience numerous painful procedures and noxious stimuli are less responsive to painful stimuli at 18 months' corrected age. Neonatal males who were circumcised with little or no analgesia showed significantly increased pain responses when immunized at 2, 4, and 6 months of age compared to infant males who were not circumcised or who received adequate analgesia. Evidence suggests that neonatal pain and stress influence neurodevelopment and affect later perceptions of painful stimuli and behavioral responses and that prevention and control of pain are likely to benefit infants. Newborns undergoing cardiac surgery for patent ductus arteriosus (PDA) ligation who receive less opioid analgesia experienced a significantly greater stress response and more postoperative morbidities compared to infants receiving adequate opioid analgesia.

There are few large randomized clinical trials of pain management in neonates. One such trial (NEOPAIN trial) evaluated preemptive analgesia with morphine infusion up to 14 days among ventilated preterm infants and showed no difference overall in the primary composite outcome (i.e., neonatal death, severe intraventricular hemorrhage [IVH], or periventricular leukomalacia) between placebo and preemptive morphine-treated groups. Concerns were raised, however, when post hoc analyses revealed an increased risk of severe IVH among morphine infusion–treated infants in the subgroup born at 27 to 29 weeks of gestation. Subsequent analyses suggested the adverse outcomes were limited to infants who were hypotensive before morphine therapy was initiated. These data indicate that treatment with prophylactic morphine infusion should be limited to infants who are normotensive. There is limited data on the long-term consequences of opioid analgesia in infants, and preliminary studies show mixed results. The potential risk associated with morphine use as indicated in the NEOPAIN trial must be weighed against the known risk of untreated pain in the neonatal population, including increased sensitivity to subsequent painful stimuli and potential negative effects in neurodevelopment. Animal research suggests morphine may be either neuroprotective or neurotoxic depending on the presence or absence of pain, but how that translates to newborns is unknown. Further research is needed to identify safe and effective options for pain management in term and preterm infants.

II. RECOMMENDATIONS ON PREVENTION AND MANAGEMENT OF PROCEDURAL PAIN IN THE NEONATE FROM THE COMMITTEE ON FETUS AND NEWBORN AND SECTION ON ANESTHESIOLOGY AND PAIN MEDICINE OF THE AMERICAN ACADEMY OF PEDIATRICS (AAP).

Each institution should have written guidelines, based on existing and emerging evidence, for a stepwise pain prevention and treatment plan, which includes minimizing the frequency and duration of invasive procedures, routine assessment of pain, use of both pharmacologic and nonpharmacologic therapies for the prevention of pain associated with routine minor procedures, and effective medications to minimize pain associated with surgery and other major procedures. Validated neonatal pain assessment tools should be consistently used before, during, and after painful procedures to monitor the effectiveness of pain relief interventions. Nonpharmacologic strategies, such as facilitated tucking, Skin-to-skin (STS), nonnutritive sucking, provision of breastfeeding or providing expressed human milk, or sensorial stimulation (SS), have been shown to be useful in decreasing pain scores during short-term mild to moderately painful procedures and should be consistently used. Oral sucrose and/or glucose solutions can be effective in neonates undergoing mild to moderately painful procedures, either alone or in combination with other pain relief strategies.

Health care professionals who care for neonates must weigh potential and actual benefits and burdens when using pharmacologic treatment methods based on available evidence. Some medications can potentiate the respiratory

depression and hypotension that can occur with opioids and infants receiving them should be carefully monitored. Caution should be exercised when considering newer medications for which data in neonates are sparse or nonexistent. Neonatal health care providers should receive continuing education regarding the recognition, assessment, and management of pain in neonates, including new evidence as it becomes available. To address the gaps in knowledge, more research should be conducted on pain assessment tools and pharmacologic and nonpharmacologic strategies to prevent or ameliorate pain. Studies on pharmacokinetics and pharmacodynamics of newer medications are needed to prevent therapeutic misadventures in the most vulnerable patients in pediatric practice. With adequate training, family members can play a critical and rewarding role in the prevention, assessment, and treatment of pain.

III. EVALUATING NEONATAL PAIN AND STRESS.

A number of validated and reliable scales of pain assessment are available. Behavioral indicators (e.g., facial expression, crying, and body/extremity movement) as well as physiologic indicators (e.g., tachycardia or bradycardia, hypertension, tachypnea or apnea, oxygen desaturation, palmar sweating, vagal signs) are useful in assessing an infant's level of discomfort. Biochemical markers for pain and stress such as plasma cortisol or catecholamine levels are not typically used in the clinical setting but may be useful for research.

Physiologic responses to painful stimuli include release of circulating catecholamines with rise in heart rate, blood pressure, and intracranial pressure. Because the stress response of the immature fetus or preterm infant is less robust than that of the more mature infant or child, gestational age, and postmenstrual age (PMA) must be considered when evaluating the pain response. Among preterm infants experiencing pain, a change in vital signs associated with the stress response (e.g., tachycardia, hypertension) and agitation are not consistently displayed. Even among infants with an intact response to pain, a painful stimulus that persists for hours or days exhausts sympathetic nervous system output and obscures the clinician's ability to objectively assess the infant's level of discomfort.

Changes in vital signs are not specific to pain and may be unreliable when used alone to identify pain. Changes in facial activity and heart rate are the most sensitive measures of pain observed in term and preterm infants. By 25 to 26 weeks, the facial expression that conveys pain is the same as that for children/adults. Before that, various facial components of a grimace may be observed separately, such as eye squeeze. The Premature Infant Pain Profile (PIPP) scores the facial components separately to capture the premature infant who may be limited in the ability to produce and sustain a full grimace.

A. Assessment of pain and stress in the newborn

1. Newborns should be assessed for pain routinely (at least every 4 to 6 hours and before and after invasive procedures) by caregivers who are trained to assess pain using multidimensional tools. The pain scales used should help guide caregivers to provide effective pain relief. Because small variations in scoring points can result in under- or overtreatment, the proficiency of individual caregivers using the chosen pain scale should be reassessed periodically to maintain reliability.

2. Selecting the most appropriate tool for evaluating neonatal pain is essential to effective management. Physicians, nurses, and parents express different perceptions of pain cues when presented with the same infant pain responses. A caregiver's bias can influence both judgment and action when evaluating and treating pain. A pain scoring tool with appropriate age range, acceptable psychometric properties, clinical utility, and feasibility may reduce bias. Many tools exist, and a few of the more common ones are shown in Table 70.1.
3. Documentation of pain is critical. In general, pain scores that are documented along with vital signs can be monitored most easily for trends and subtle patterns so that unrelieved pain or opioid tolerance can be identified early.
4. Because no pain tool is completely accurate in identifying all types of pain in every infant, other patient data must be included in the assessment of pain. Pain that is persistent or prolonged, associated with end-of-life care, or influenced by medications cannot be reliably measured using current pain instruments.

B. Critically ill infants. Pain responses are influenced by the PMA and behavioral state of an infant. Most pain scales that have been tested use acute pain for the stimulus (heel stick), and very few tools that measure prolonged or chronic pain have been adequately tested. Critically ill infants may not be able to exhibit indicators of pain due to their illness acuity. Few scales include parameters of nonresponse to pain that may be present when an infant is severely ill or extremely premature. A lack of response does not mean an infant is not in pain. The caregiver must base treatment decisions on other data such as type of disease, health status, pain risk factors, maturity, invasive measures (i.e., chest tubes), medications that blunt response, and scheduled painful procedures. Existing pain instruments do not account for the extremely premature infant whose immature physiologic and behavioral responses are challenging to interpret. Infants with neurologic impairment can mount a similar pain response to healthy term infants, although the intensity of that response may be diminished. The pain response can be increased in individual infants based on prior pain history and handling before a painful event.

C. Chronic or prolonged pain. Physiologic and behavioral indicators can be markedly different when pain is prolonged. Infants may become passive with few or no body movements, little or no facial expression, diminished heart rate and respiratory variation, and consequently, lower oxygen consumption. Caregivers may erroneously interpret these findings to indicate that these infants are not feeling pain due to their lack of physiologic or behavioral responses. Quality and duration of sleep, feeding, quality of interactions, and consolability combined with risk factors for pain may be more indicative of persistent pain. A promising tool for assessment of prolonged pain in preterm infants is the EDIN (Échelle de la Douleur Inconfort Noveau-Né [Neonatal Pain and Discomfort Scale]), although psychometric evaluation is incomplete. There is evidence that repetitive and/or prolonged exposure to pain may increase the pain response (hyperalgesia) to future painful stimulation and may even result in pain sensation from nonpainful stimuli (allodynia).

Table 70.1. Summary of Neonatal Pain Assessment Tools With Psychometric Testing

Pain Assessment Tool (Frequency of Use in Studies)	Validated ages	Physiologic and Behavioral Indicators	Validity and Reliability Data	Type of Pain Procedural Prolonged Surgical	Adjusts for Prematurity	Scale Metric
PIPP, PIPP-R (154) (Premature Infant Pain Profile) (Premature Infant Pain Profile—Revised)	28–48 weeks 26–37 weeks	GA Behavioral state Max heart rate, oxygen saturation Alertness, brow bulge, eye squeeze, nasolabial furrow	Construct Content Face IR: 0.94–0.98 IC: 0.71	Procedural	Yes	Preterm: 0–21 Term: 0–18
CRIES (7) (Cries, Requires Oxygen, Increased Vital Signs, Expression, Sleeplessness)	32–56 weeks	Blood pressure, heart rate, oxygen saturation Cry, expression, sleeplessness	Face Content Discriminate IR: >0.72	Postoperative	No	0–10
NIPS (84) (Neonatal Infant Pain Scale)	26–47 weeks	Breathing pattern Facial expression, cry, arms, legs, alertness	Face Construct IC: 0.87–0.95 IR: 0.92–0.97	Procedural	No	0–7
NFCS (33) (Neonatal Facial Coding System)	25 weeks to term	Brow bulge, eye squeeze, nasolabial furrow, open lips, stretch mouth (vertical and horizontal), lip purse, taut tongue, chin quiver	—	Procedural Prolonged Surgical (ventilated)	No	0–10

(continued)

Table 70.1. Summary of Neonatal Pain Assessment Tools With Psychometric Testing *(Continued)*

Pain Assessment Tool (Frequency of Use in Studies)	Validated ages	Physiologic and Behavioral Indicators	Validity and Reliability Data	Type of Pain Procedural Prolonged Surgical	Adjusts for Prematurity	Scale Metric
N-PASS (10) (Neonatal Pain, Agitation, and Sedation Scale)	23–42 weeks 0–100 days	Heart rate, respiratory rate, blood pressure, oxygen saturation Crying/irritability, behavioral state, facial expression, extremities/tone	Construct IR: 0.86–0.93 IC: 0.84–0.89	Procedural Prolonged (ventilation) Sedation	Yes	Pain: 0–10 Sedation: 10–0
EDIN (6) (Échelle de la Douleur Inconfort Noveau-Né [Neonatal Pain and Discomfort Scale])	25–36 weeks	Facial activity, body movements, quality of sleep, quality of contact with nurses, consolability	Construct: $P = .0009$ IR: 0.59–0.74 IC: 0.86–0.94	Prolonged	No	0–15
BPSN (16) (Bernese Pain Scale for Neonates)	27–41 weeks	Respiratory pattern, heart rate, oxygen saturation Alertness, duration of cry, time to calm, skin color, brow bulge with eye squeeze, posture	Construct: $P < .001$ IR: 0.86–0.97	Procedural	No	0–27

GA, gestational age; IR, inter-rater reliability; IC, internal consistency.

Source: Adapted from Walden M, Spruill CT. Pain in the newborn and infant. In: Kenner C, Altimier L, Boykova M, eds. *Comprehensive Neonatal Nursing Care*. 6th ed. New York, NY: Springer; 2019:539–555.

IV. MANAGEMENT: PAIN PREVENTION AND TREATMENT. Attention to the intensity of diagnostic, therapeutic, or surgical procedures commonly performed in the neonatal intensive care unit (NICU) is fundamental to the development of strategies appropriate for mild, moderate, or severe pain levels. This should include consideration of the history, clinical status, and PMA of the patient. Choice of pain management option depends on the invasive procedure being performed (Table 70.2).

Caregivers often underuse nonpharmacologic measures for pain relief. When used appropriately, these approaches to pain relief have been shown to be effective, either use on their own or as an adjunct to pharmacologic treatment of pain. Parental involvement to provide facilitated tucking, STS, nonnutritive sucking, and breastfeeding during and after painful procedures should be used whenever possible to reduce stress and pain.

A. Environmental modification. Painful or stressful procedures should be reviewed daily in order to eliminate any that are redundant or unwarranted (e.g., blood sampling). Combining painful procedures with nonurgent, routine care or prior handling may intensify the pain experience.

1. **Light** should be shielded from an infant's eyes especially when procedural lights are used or the infant is positioned where light is directed toward the face.
2. **Sound** often occurs at levels and frequencies that disturb rest and sleep in neonatal patients. Efforts are made to minimize sound levels to promote a restful environment in the unit and around the bedside.
3. **Positioning** infants comfortably is a skill all caregivers should acquire regardless of discipline. It is even more important when risk factors for pain are present. The use of supportive positioning aids may be needed to assist positions of comfort and enhance the effects of other forms of pain management.
4. **Facilitated tucking** or "hand swaddling" consists of placing a hand on a baby's head or back and feet keeping extremities flexed and contained close to the trunk where an infant is not restricted but can push against the gentle containment, moving as needed. This technique has been successful in relieving the pain of endotracheal suctioning and heel stick.

B. STS holding or kangaroo care refers to placing an infant on a parent's chest inside the clothes, clad only in a diaper and hat usually with a warm blanket laid over the infant. Enzymes and hormones that are released during STS chemically elevate the pain threshold resulting in better tolerance of painful procedures and a decreased crying response. For both STS and facilitated tucking, the analgesic effect remains only for as long as an infant is held.

Multisensory stimulation, massage, and music therapy may assist with pain management. These interventions need much more investigation to understand how they work and how they compare to other options in terms of both efficacy and safety.

C. Taste-mediated analgesia is frequently combined with environmental modifications, hand containment, facilitated tucking, or STS holding, and

Table 70.2. Summary of Procedures and Recommendations for Pain Relief

Skin-Breaking Procedures*,†	Proposed Interventions	Comments
Heel stick	Use nonpharmacologic measures + mechanical lance, squeezing the heel is the most painful phase	Venipuncture is more efficient, less painful; local anesthetics, acetaminophen, heel warming do not reduce heel stick pain
Venipuncture	Nonpharmacologic measures, use topical local anesthetics	Requires less time & less resampling than heel stick
Arterial puncture	Nonpharmacologic measures, use topical and subcutaneous local anesthetics	More painful than venipuncture
IV cannulation	Nonpharmacologic measures, use topical local anesthetics	—
Central line placement	Nonpharmacologic measures, use topical local anesthetics, consider low-dose opioids or deep sedation based on clinical factors	Some centers prefer using general anesthesia
Finger stick	Nonpharmacologic measures and use mechanical device	Venipuncture is more efficient, less painful; local anesthetics, acetaminophen, or warming may not reduce finger stick pain
Subcutaneous injection	Avoid if possible, use nonpharmacologic measures and topical local anesthetics if procedure cannot be avoided	—
Intramuscular injection	Avoid if possible, use nonpharmacologic measures and topical local anesthetics if procedure cannot be avoided	—
Lumbar puncture	Nonpharmacologic measures and topical local anesthetic, lidocaine infiltration, careful positioning	Use IV analgesia/sedation, if patients are intubated and ventilated

(continued)

Table 70.2: ***(Continued)***

Skin-Breaking Procedures*,†	Proposed Interventions	Comments
Peripheral arterial line	Nonpharmacologic measures and topical local anesthetic, lidocaine infiltration, consider IV opioids	—
Circumcision	Nonpharmacologic measures and topical local anesthetic, lidocaine infiltration, IV/PO acetaminophen before and after procedure	Lidocaine infiltration for distal, ring, or dorsal penile nerve blocks (DPNB); liposomal lidocaine is more effective than DPNB
Suprapubic bladder aspiration	Nonpharmacologic measures and topical local anesthetic, lidocaine infiltration, consider IV fentanyl (0.5–1.0 mcg/kg)	—
Arterial or venous cutdown	Nonpharmacologic measures and topical local anesthetic, lidocaine infiltration, IV fentanyl (1–2 mcg/kg), consider deep sedation	Most arterial or venous cutdowns can be avoided, consider referral to interventional radiology
Peripherally inserted central catheter (PICC)	Nonpharmacologic measures and topical local anesthetic, lidocaine infiltration, consider IV fentanyl (1 mcg/kg) or IV ketamine (1 mg/kg)	Some centers prefer using deep sedation or general anesthesia
ECMO Cannulation	Propofol 2–4 mg/kg, ketamine 1–2 mg/kg, fentanyl 1–3 mcg/kg, muscle relaxant as needed	—
Tracheal intubation (e.g., for mechanical ventilation)	Give fentanyl (1 mcg/kg) or morphine (10–30 mcg/kg), with midazolam (50–100 mcg/kg), ketamine (1 mg/kg) use muscle relaxant only if experienced clinician, consider atropine	Superiority of one drug regimen over another has not been investigated
Gastric tube insertion	Nonpharmacologic measures, consider local anesthetic gel	Perform rapidly, use lubricant, avoid injury
Chest physiotherapy	Gentle positioning, fentanyl (1 mcg/kg) if a chest tube is present	Avoid areas of injured or inflamed skin, areas with indwelling drains or catheters

(continued)

Table 70.2. Summary of Procedures and Recommendations for Pain Relief *(Continued)*

Skin-Breaking Procedures*,†	Proposed Interventions	Comments
Removal of IV catheter	Solvent swab, nonpharmacologic measures	—
Wound treatment	Nonpharmacologic measures, use topical local anesthetics, consider low-dose opioids, or deep sedation based on extent of injury	See also "Dressing change"
Umbilical catheterization	Nonpharmacologic measures, IV acetaminophen (10 mg/kg), avoid sutures to the skin	Cord tissue is not innervated, but avoid injury to skin
Bladder compression	Consider nonpharmacologic measures or IV acetaminophen (10 mg/kg) if severe or prolonged	—
Tracheal extubation	Use solvent swab for tape, consider nonpharmacologic measures	—
Dressing change	Nonpharmacologic measures and topical local anesthetic, consider deep sedation if extensive	—

*Nonpharmacologic measures include pacifier, oral sucrose, swaddling, skin-to-skin contact with mother.

†The frequency of procedures can be reduced without sacrificing the quality of neonatal intensive care.

Source: Reprinted from Hall RW, Anand KJS. Pain management in newborns. *Clin Perinatol* 2014;41(4):895–924. Copyright © 2014 Elsevier. With permission.

nonnutritive sucking. For repetitive painful procedures, taste-mediated analgesia is more effective than environmental modification alone.

1. **Sweet-tasting analgesia (STA)** (sucrose or glucose) given orally 2 minutes before and again just prior to a painful procedure decreases the pain response in infants up to 12 months of age (Fig. 70.1).
   a. For procedures that last longer than 5 minutes, repeated dosing should be considered.
   b. Optimal dosing of STA has not been established. Long-term outcomes from repeated dosing of STA in early infancy and in preterm infants are not known. A Cochrane Review recently presented concerns regarding repeated sucrose dosing or use in extremely premature or critically ill neonates due to limited data on long-term outcomes.
   c. STA must be given on the tongue where taste buds for sweet taste are concentrated. It is not effective if given by nasogastric tube.

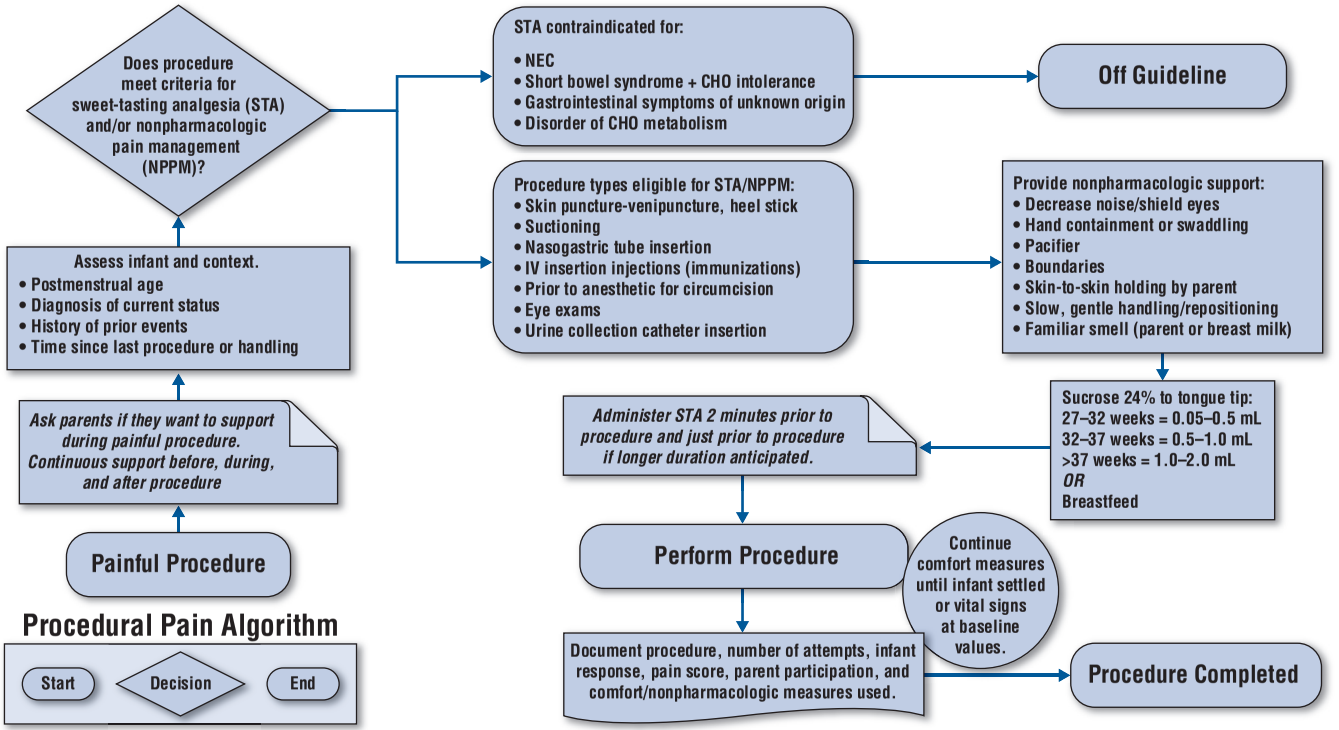

Figure 70.1. Procedural pain algorithm for minor procedures. NEC, necrotizing enterocolitis; CHO, carbohydrates.

d. It is even more effective when combined with other nonpharmacologic strategies such as nonnutritive sucking (e.g., gloved finger or pacifier).

2. **Breastfeeding** is an effective pain intervention strategy decreasing both crying time and pain reaction. This may be due to the sweetness of breast milk or the combined effects of STS holding, smell, touch, containment, and general sensory ambiance.
   a. An additional advantage of this approach is that mothers have an active role in alleviating their infants' pain.
   b. Breast milk alone as an analgesic is inconclusive with some reports concluding that it may be as effective as sucrose but others that it is only as effective as water for pain management.
3. **Nonnutritive sucking** is more effective when used in conjunction with glucose or sucrose administration. As long as the infant is sucking, the analgesic properties are maintained.

V. PHARMACOLOGIC TREATMENT OF PROCEDURE-RELATED PAIN

A. Topical anesthetics

1. Topical anesthetics may provide a minor reduction of procedural pain in neonates but, if used, should be done in combination with other pain-relieving measures.
2. EMLA (lidocaine-prilocaine), a common topical agent, has shown minimal to no benefit when compared to other pain relieving measures such as breastfeeding or STA for venipuncture and heel-stick blood draws.
3. Topical agents should be used with caution and repeated doses should be limited because they can be toxic when used over large areas of the skin in substantial amounts. EMLA is contraindicated in infants <1 year of age who concurrently take methemoglobin-inducing agents (i.e., sulfas, acetaminophen, phenobarbital).
4. New topical anesthetics (e.g., 4% tetracaine and 4% liposomal lidocaine) are faster acting but not as effective as EMLA.

B. Analgesia for invasive procedures

1. General principles

a. Pain prevention versus treatment: Opioid analgesia given on a scheduled basis as a preventative measure results in a lower total dose and improved pain control compared with "as needed" dosing.
b. Prematurity: Pain should be assumed and treatment initiated in the immature, acutely ill infant who may be incapable of mounting a stress response to signal discomfort. The inability of the infant to mount an appropriate response is especially relevant when the infant is extremely immature or the painful stimulus is severe and/or prolonged.
c. The AAP does not recommend routine opioid administration during mechanical ventilation of preterm infants.
d. Opioids and sedatives (e.g., benzodiazepines) are often used in treating critically ill newborns undergoing invasive or very painful diagnostic or therapeutic procedures.

e. Alleviating pain is the most important goal. Therefore, treatment with analgesics is recommended over sedation without analgesia.

f. The most commonly used opioids are morphine and fentanyl; however, others are used including sufentanil, tramadol, and short-acting opioids such as alfentanil and remifentanil.

g. For most invasive procedures, pharmacologic **premedication** is recommended. Except in instances of emergency intubation when it may not be feasible, newborns should be premedicated for invasive procedures. Examples of procedures for which premedication is indicated include elective intubation, chest tube insertion or removal, peripheral arterial catheter placement, laser surgery, and circumcision.

2. Intubation (see Intubation Sedation Guidelines in Appendix B)

a. The AAP recommends medication with fentanyl 1 to 3 μg/kg. Fentanyl must be infused slowly (no faster than 1 μg/kg/minute) to avoid the complication of chest wall rigidity. As an alternative to fentanyl, remifentanil has been recommended for use over morphine when a short-acting opioid is desired. Intranasal fentanyl may be an alternative if timely intravenous (IV) access cannot be obtained.

b. Among infants >35 weeks' PMA, midazolam 0.1 mg/kg may be used in addition to opioid analgesia to lessen agitation and potential movement-related trauma. As with fentanyl, intranasal midazolam 0.2 mg/kg may be an alternative in patients with no IV access. We recommend administration with an intranasal mucosal atomization device for optimal delivery.

c. The addition of a short-acting muscle relaxant given after analgesia administration may decrease the procedure duration and number of attempts needed, thereby decreasing the potential for severe oxygen desaturation. Before adding a short-acting muscle relaxant (rocuronium, succinylcholine) for intubation, airway control, and the ability to perform effective bag-and-mask ventilation must be assured. Rocuronium-induced blockade may be reversed by sugammadex if indicated.

3. During mechanical ventilation

a. The AAP guideline on pain management does not recommend routine continuous opioid infusions for mechanically ventilated newborns because of concern about short-term adverse effects and lack of data on long-term outcomes.

b. If analgesia is needed, medication with fentanyl 0.5 to 2 μg/kg or morphine 0.02 to 0.1 mg/kg can be given as a continuous infusion or intermittently every 4 hours.

4. Circumcision

a. Pretreatment includes both oral (24%) sucrose analgesia and acetaminophen 15 mg/kg and, for the procedure, dorsal penile block or ring block with a maximum 0.5% lidocaine dose of 0.5 mL/kg.

b. Developmental positioning of the upper extremities using a blanket and restraining only the lower limbs may decrease the stress of medical immobilization.

c. Following the procedure, an infant may benefit from acetaminophen dosed as appropriate for PMA for 24 hours.

5. **Chest drains**
   a. **Analgesia for chest-drain insertion comprises all of the following:**
      i. General nonpharmacologic measures
      ii. Systemic analgesia with a rapidly acting opiate such as fentanyl
      iii. Slow infiltration of the skin site with a local anesthetic such as buffered lidocaine before incision unless there is life-threatening instability
   b. **Indwelling chest drains**
      i. Discomfort from indwelling chest drains varies. Pain management with general nonpharmacologic measures, acetaminophen, and opioids is individualized based on infant's pain assessment.
   c. **Analgesia for chest drain removal comprises the following:**
      i. General nonpharmacologic measures (especially positioning/swaddling)
      ii. Short-acting, rapid-onset systemic analgesia
6. **Ophthalmology procedures**
   a. Data show anesthetic drops, sucrose, and containment reduce the pain response to eye exams (e.g., for retinopathy of prematurity).
   b. Intranasal fentanyl significantly reduced the pain of retinal exams in a double-blind, randomized control trial (RCT) of preterm neonates between 30 and 34 weeks' PMA without increasing the incidence of respiratory depression. More research with large RCTs are required to substantiate that intranasal fentanyl is safe and efficacious for acute procedural pain in neonates.
   c. There are no data on the effects of bright lighting following dilatation for eye exams. A thoughtful approach to minimize discomfort after an exam may be to decrease lighting or shield the infant's eyes from light for 4 to 6 hours.
   d. Retinal surgery should be considered major surgery, and effective opiate-based pain relief should be provided.

C. Postoperative analgesia. Tissue injury, which occurs during all forms of surgery, elicits profound physiologic responses. The more marked these responses, the greater the morbidities. Thus, minimizing the endocrine and metabolic responses to surgery by decreasing pain has been shown to significantly improve outcomes after neonatal surgery. Anticipation and planning for pain management is essential to the success of any pain management program. It should be tailored to each individual patient taking into account PMA, acuity, comorbidities, type of procedure or surgery, and respiratory support along with standard handoff communication to reduce variation in pain management.

1. Health care facilities providing surgery for neonates should establish a protocol for pain management with input from anesthesia, surgery, neonatology, nursing, and pharmacy. Sufficient anesthesia and analgesia is provided to prevent perioperative pain and stress responses and adequately control postoperative pain.
2. Improving pain management and outcomes in the neonate requires a team approach and a coordinated multidimensional strategy of pain reduction. A postoperative pain algorithm guides practice and provides

a standard of care for most infants during the postoperative period (Fig. 70.2). Factors considered in developing a postoperative pain management plan include the following:

a. History of pain and opioid/sedative use

b. Severity of procedure (invasiveness, anesthesia time, and amount of tissue manipulation)

c. Airway management postoperatively (expected extended intubation, short-term intubation, or not intubated)

d. Desired level of sedation postoperatively

3. The goal of postoperative pain management is preventive analgesia rather than trying to "catch up" after pain has begun. Central sensitization is induced by noxious inputs, and the administration of analgesic drugs immediately postoperatively (prior to "awakening" from general anesthesia) may prevent the spinal and supraspinal hyperexcitability caused by acute pain, resulting in decreased analgesic use.
4. Opioids are the basis for postoperative analgesia after moderate/major surgery in the absence of regional anesthesia. During the immediate postoperative period, opioids are most effective when scheduled at regular intervals or provided as a continuous drip; data is limited about which offers more benefit. As needed (PRN) dosing can lead to a delay in treatment, a missed dose, or fluctuating drug levels that do not provide consistently adequate pain relief. Morphine and fentanyl provide a similar degree of analgesia. Morphine has greater sedative effect, less risk of chest wall rigidity, and produces less tolerance yet carries a greater risk of hypotension. Fentanyl has faster onset; shorter duration of action; and has less effect on gastrointestinal (GI) motility, hemodynamics, and urinary retention.
5. Elimination of opioids may be influenced by enterohepatic recirculation and elevated plasma concentrations; therefore, side effects should be monitored for several hours after opioids are discontinued.
6. Acetaminophen is often used as an adjunct to regional anesthetics and opioids for postoperative pain management. Acetaminophen has been shown to provide effective analgesia as an adjunct to regional anesthesia or opioid therapy and decrease cumulative opioid exposure in postoperative neonates. Acetaminophen can be administered immediately after surgery as an adjunct when indicated. Acetaminophen is not recommended if PMA $<$28 weeks due to inadequate pharmacokinetic data for appropriate dosage calculation. Acetaminophen should be used with caution in patients with hepatic impairment; lower doses or an alternative therapy may be indicated. Rectal administration route is avoided in patients following anorectal procedures; alternatively, the enteral route may be used if adequate GI motility. IV acetaminophen is used when both rectal and enteral routes are not optimal. The administration of acetaminophen for procedural pain management has not been established as effective.
7. Postoperative analgesia is used for as long as pain assessment scales and clinical judgment indicate that it is required. The dose and/or

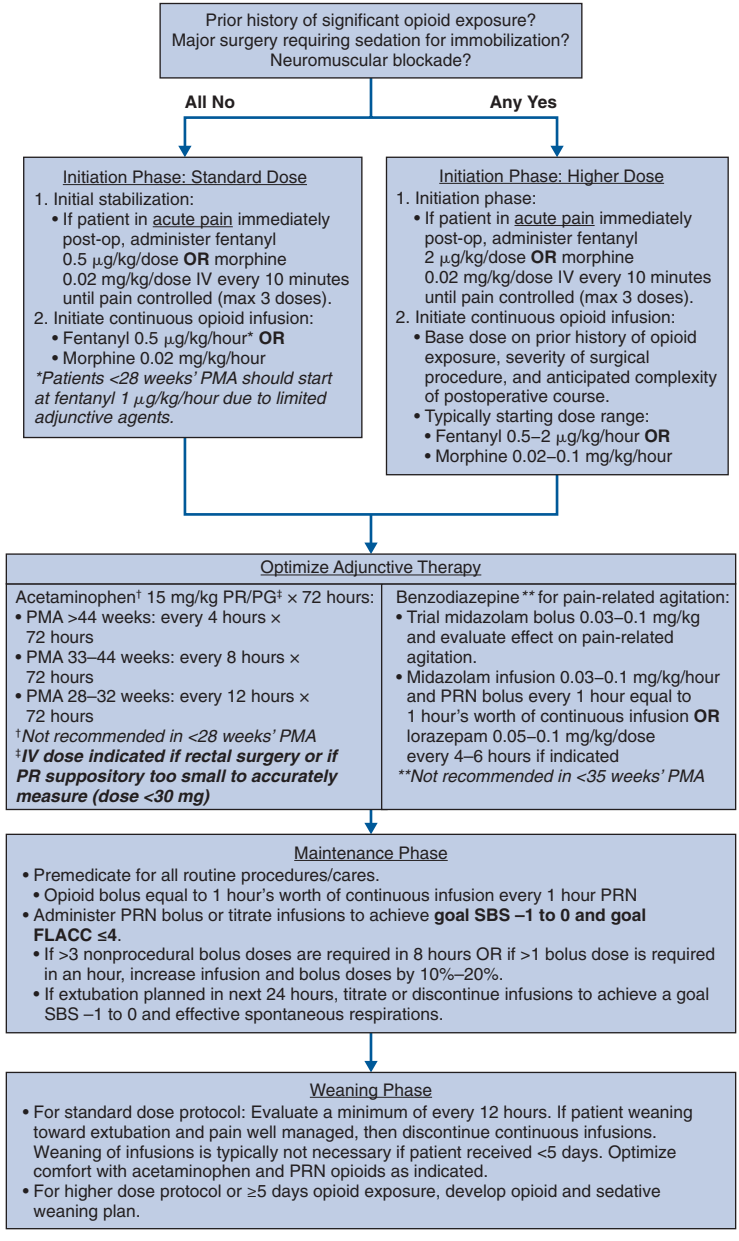

Figure 70.2. Postoperative pain management algorithm for moderate/major surgery. post-op, postoperation; PMA, postmenstrual age; PR, per rectum; PG, per gastric; PRN, as needed; SBS, State Behavioral Scale; FLACC, faces, legs, activity, cry, consolability scale.

interval may be weaned when appropriate to maintain adequate pain control.

8. Nonpharmacologic methods of pain management should be optimized in addition to minimizing noxious stimuli. Use of distraction techniques and other nonpharmacologic measures helps to decrease anxiety.

D. Naloxone for reversal of opioid side effects. Naloxone (Narcan) is used to treat the side effects of excessive opioid, most commonly respiratory depression. In an infant receiving opioid analgesia, carefully dosed naloxone can be used to reverse the adverse effects without exacerbating pain. If the infant's clinical status permits, one approach is to titrate administration of naloxone, giving it in increments of 0.05 mg/kg until the side effects are reversed. Of note, to reverse the adverse effect of chest wall and laryngeal rigidity, airway management equipment and a neuromuscular blocker agent must be immediately available in case severe hypoxemia and the inability to ventilate; naloxone will not immediately reverse these life-threatening effects.

E. Opioid tolerance. Prolonged opioid administration may lead to tolerance manifested as recurrence of pain behaviors, disruption of sleep, decreased interaction, or potentially a high-pitched cry or tremors during handling. In this case, increase the dose, typically in increments of 10% to 20%, to relieve symptoms.

F. Benzodiazepines are often given in conjunction with pain medication for intubated neonates postoperatively or for medical conditions in which sedation is required, such as pulmonary hypertension or to safely maintain a critical airway.

1. Sedatives (i.e., benzodiazepines) do not provide analgesia but may be given to manage agitation related to other factors such as mechanical ventilation.
2. Sedatives postoperatively can be administered in combination with analgesia to reduce opioid requirements and associated adverse effects.
3. Sedatives and opioids with sedative properties (fentanyl, morphine) may cause respiratory depression, and their use should be restricted to settings where respiratory depression can be promptly recognized and treated by clinicians experienced in airway management.
4. Caution should be used in administering benzodiazepines in patients $<$35 weeks' PMA due to the potential for neurotoxicity including the induction of myoclonic jerking movements.
5. Benzodiazepine exposure in rodent models extends cortical apoptosis, alters developing γ-aminobutyric acid (GABA) receptors, and results in long-term behavioral and cognitive impairment. Thus, cautious use of sedatives during early brain development is recommended. Additional studies on the use of midazolam infusions in preterm neonates have shown conflicting results on neurologic outcomes.

G. Dexmedetomidine, a highly selective centrally acting α2-adrenergic agonist which has been shown to provide adequate sedation with minimal respiratory depressant effects compared to other sedating agents.

1. The activation of α2-adrenergic receptors in the medullary vasomotor center leads to reduction in norepinephrine turnover and sympathetic

nervous system signaling from the locus coeruleus, leading to increased endogenous GABAergic activity, which causes sedation. Separate release of substance P from the dorsal horn of the spinal cord leads to analgesia and can potentiate the effect of opioids.

2. Several reports have described the successful use of dexmedetomidine in neonates postcardiac surgery, preterm neonates, and infants with hypoxic ischemic encephalopathy, without significant complication. In particular, dexmedetomidine has promise as a neuroprotective sedative agent which prevents neuronal apoptosis, in contrast with the potential negative effects of benzodiazepines on neuronal migration. Previous studies have demonstrated the ability of dexmedetomidine to reduce postoperative patient exposure to sedative agents such as midazolam and morphine among patients with congenital heart disease.
3. With the goal of reducing benzodiazepine exposure among infants requiring sedation, dexmedetomidine has been successfully added to sedation guidelines as an alternative to benzodiazepines. These guidelines have achieved adequate sedation goals with no clinically significant adverse effects including on rates of unplanned extubations. They have succeeded in reducing benzodiazepine exposures and have had no effect on opioid exposure.
4. Continuous cardiopulmonary monitoring and pulse oximetry are used while infusing dexmedetomidine. More frequent blood pressures are assessed with titrations as hypotension, hypertension, and bradycardia are known adverse effects.
5. Typical initial dose of dexmedetomidine is 0.2 to 0.5 μg/kg/hour, increasing to achieve goal sedation in increments of 0.2 μg/kg/hour up to a max dose of 2 μg/kg/hour.
6. Abrupt discontinuation of dexmedetomidine may lead to withdrawal as evidenced by hypertension, tachycardia, agitation, and jitteriness. A recommended weaning schedule is 0.2 to 0.3 μg/kg/hour every 12 hours as tolerated for patients on dexmedetomidine >5 days or on dosages >1 μg/kg/hour.

H. Opioid and sedative weaning. Prolonged use of opioids and sedatives can result in iatrogenic physical dependence. Opioids and sedatives are weaned with a goal to avoid both excess exposure to these medications and unsafe symptoms of withdrawal. Long-term effects of exposure to these agents on neonatal neurodevelopment are not fully understood (see Chapter 12 for neonatal abstinence syndrome due to intrauterine exposure).

1. Neonates exposed to continuous or higher doses of opioids for >5 days are at increased risk for opioid withdrawal; therefore, weaning rather than abrupt discontinuation is recommended. Opioid withdrawal is more prevalent and may occur earlier in infants receiving fentanyl compared to morphine.
2. An overall opioid and sedative weaning plan should be developed and individualized prior to implementation. Factors considered in developing an opioid and sedative weaning plan include the following:
   a. Length of opioid and sedative exposure
   b. History of previous opioid and sedative exposure and weans

c. Patient stability and ability to tolerate symptoms of withdrawal
d. Enteral feeds
e. IV access

3. Opioids and sedatives are weaned by a percentage of the original dose the patient is receiving when weaning begins, typically in 10% increments. For example, a patient receiving morphine 0.2 mg/kg/hour would wean by 10% or 0.02 mg/kg at each wean.
   a. The weaning frequency is tailored to the individual patient; every 8 to 12 hours for moderate lengths of exposure and every 24 to 48 hours for longer lengths of exposure. This strategy continues throughout weaning unless symptoms of withdrawal or a change in condition occur.
   b. Weaning is further individualized by using a withdrawal assessment tool such as the Modified Finnegan Neonatal Abstinence Scoring (NAS) system or Withdrawal Assessment Tool-1 (WAT-1) to monitor symptoms and guide the frequency of weaning and potential need for rescue doses.
4. Nonpharmacologic comfort methods are essential in addition to minimizing noxious stimuli. Removing noxious environmental stressors, protecting sleep, swaddling, and rocking have been used to support infants undergoing withdrawal.
5. In general, feeding should be encouraged, and continuous feedings may be considered if bolus feeds are not tolerated.
6. Withdrawal assessment is continued until opioids and/or sedatives have been discontinued for a minimum of 72 hours and there is no evidence of withdrawal symptoms.
7. Clonidine, an α2-adrenergic agonist, may be used during opioid weaning for relief of withdrawal symptoms. Clonidine should be considered in the weaning plan for infants with prolonged exposure (e.g., >20 days) to opioids and sedatives. Clonidine is administered as a subdermal patch or by the enteral route with a typical starting dose of 5 μg/kg/day. Dose may be titrated up in increments of 2.5 μg/kg/day if withdrawal assessment scores are greater than goal score. Clonidine may be weaned last, typically decreased by 20% per day until off. Blood pressure is monitored while weaning clonidine.

I. **Epidural analgesia** is the administration of analgesics and local anesthetic agents into the epidural space as a single or intermittent bolus or continuous infusion.

1. Advantages of epidural anesthesia and postoperative analgesia in preterm and term neonates are effective analgesia at lower doses of systemic opioids and earlier extubation. This may be a better option than general anesthesia for former preterm infants with chronic lung disease because it decreases the need for intubation during surgical procedures such as hernia repair or ileostomy takedown/repair.
2. In some institutions, a pain service manages patients with epidural analgesia and is responsible for the continuous infusion and any bolus requirements until the epidural is discontinued.

3. Postoperative complications include accidental injection of local anesthetic agents into the intravascular system, venous air embolism, local or systemic infection, and meningitis.
4. Cardiorespiratory monitoring and assessment of the infant's respiratory status, sensory responses, pain behaviors, integrity of dressing, urine output, and any changes in pump settings or additional bolus requirements are essential.

VI. CONCLUSION. Research on the safety and efficacy of current and new medications is ongoing in the search for better pain management with less potential for undesirable effects. Teamwork with anticipatory planning before painful, invasive procedures optimizes timely, effective pain management (Tables 70.3 and 70.4).

Table 70.3. Opioids

Drug	Advantages	Disadvantages
Morphine	Potent pain relief Better ventilator synchrony Sedation Hypnosis Muscle relaxation Inexpensive	Respiratory depression Arterial hypotension Constipation, nausea Urinary retention Central nervous system depression Tolerance, dependence Long-term outcomes not studied Prolonged ventilator use
Fentanyl	Fast acting Less hypotension	Respiratory depression Short half-life Quick tolerance and dependence Chest wall rigidity Inadequately studied
Remifentanil	Fast acting Degraded in the plasma Unaffected by liver metabolism	—

Source: Reprinted from Hall RW, Anand KJS. Pain management in newborns. *Clin Perinatol* 2014;41(4):895–924. Copyright © 2014 Elsevier. With permission.

Table 70.4. Benzodiazepines

Drug	Advantages	Disadvantages
Benzodiazepines	Better ventilator synchrony Antianxiety Sedation Hypnosis Muscle relaxation Amnesia Anticonvulsant	No pain relief Arterial hypotension Respiratory depression Constipation, nausea Urinary retention Myoclonus Seizures Central nervous system depression Tolerance, dependence Alters bilirubin metabolism Propylene glycol and benzyl alcohol exposure
Midazolam	Most studied benzodiazepine Quickly metabolized	Short acting Benzyl alcohol exposure
Lorazepam	Longer acting Better anticonvulsant	More myoclonus reported Propylene glycol exposure
Diazepam	—	Not recommended in the neonate

Source: Reprinted from Hall RW, Anand KJS. Pain management in newborns. *Clin Perinatol* 2014;41(4):895–924. Copyright © 2014 Elsevier. With permission.

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71 Racial Disparities in the Neonatal Intensive Care Unit

Heather H. Burris

KEY POINTS

- Non-Hispanic Black infants in the United States are disproportionately born preterm, low birth weight, and are more than twice as likely to die in the first year of life compared to White infants.
- Long-standing racism has caused residential, educational, and workplace segregation that leads to different social and physical environmental exposures by race.
- Excess exposure to both social stressors (racism, discrimination, violence) and physical stressors (air and water pollution) leads to multiple complex disorders such as cardiovascular disease, cancer, and, relevant to neonatologists, preterm birth.
- In the neonatal intensive care unit (NICU), there is some evidence of differential quality of care by race/ethnicity, often as measured by provision of maternal milk.

I. BACKGROUND. Non-Hispanic Black infants die in the United States at more than twice the rate of White infants (11.4 vs. 5.0 per 1,000 live births, respectively). Most of the disparity in death is due to differences in preterm birth and specifically extremely preterm birth; Black women are 3 times more likely to deliver before 28 weeks of gestation. As such, neonatal intensive care units (NICUs) are disproportionately populated by Black infants and their families. Although the resolution of disparities in preterm birth will require a movement to address racism, neonatal providers can work toward rectifying the consequences of racism in their units by diversifying their workforce, while partnering with and empowering, families of color, and disadvantaged families to optimize outcomes for their infants.

II. DISPARITIES IN CAUSES OF INFANT MORTALITY. In the United States, there are racial disparities for each of the five leading causes of infant mortality (Fig. 71.1). Black infants account for 15% of all births but 29% of all infant deaths. Although birth defects are the leading cause of death overall, **preterm birth** is the leading cause of death among Black infants. This is because 14% of Black infants are born preterm compared to just 9% of White infants.

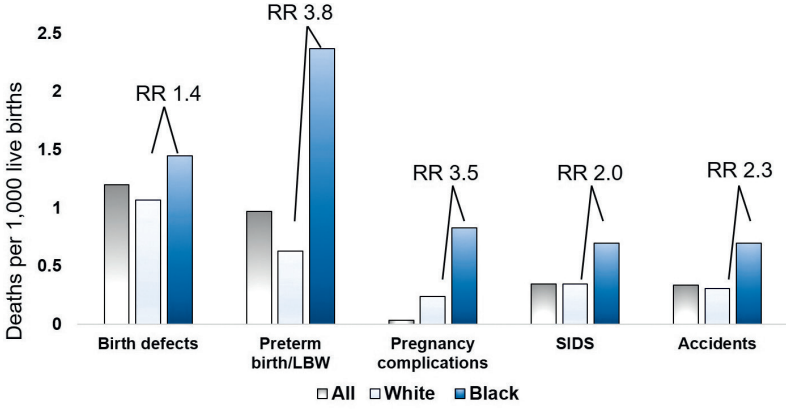

Figure 71.1. Black–White disparities in the five leading causes of infant mortality in the United States. RR, relative risk; LBW, low birth weight; SIDS, sudden infant death syndrome.

The racial disparity is even more pronounced at the lowest gestational ages with the highest mortality risk. Black infants (1.5%) are >3 times more likely than White infants (0.4%) to be born <28 weeks of gestation. Although data are limited data on racial disparities in other countries, data from the United Kingdom also demonstrate higher rates of preterm birth among Black women compared to White women. Notably, rates of preterm birth in the United Kingdom are lower for Black and White women than they are in the United States, pointing to possible environmental factors as drivers of differences in preterm birth rates across populations.

III. CAUSES OF RACIAL DISPARITIES IN PRETERM BIRTH

A. The pathophysiology of preterm birth is incompletely understood. Preterm birth arises from a heterogeneous set of conditions that range from infections such as chorioamnionitis that can lead to spontaneous preterm labor and birth to preeclampsia which can lead to a medically indicated preterm birth via induction or cesarean delivery. As with other phenotypically heterogeneous, multifactorial conditions such as cardiovascular disease, asthma, and cancer, the genetic contributions to preterm birth are small. Environmental factors both at the individual and population level are the largest risk factors of preterm birth. Fundamentally, the root cause of differences in preterm birth by race in the United States is racism. Due to generations of formal and informal segregation as well as ongoing discrimination, Black families are disproportionately exposed to many adverse environmental factors that lead to unequal chances of a healthy term birth.

B. Racial disparities in preterm birth are not due to racial genetic differences. Race is a **social construct** in the United States. The biologic effects of race are primarily due to differences in lived experiences. This can be a difficult concept for physicians who learned about disease such as sickle cell disease

(SCD) and cystic fibrosis (CF) which are due to single gene mutations and largely track with race or ancestry. All of human health conditions exist on a continuum from entirely genetic (such as SCD and CF) to entirely environmental such as death from car accidents or gun violence. Simply because a condition tracks with race does not mean that the disorder is due to genetics. Along the continuum of genetic to environment, preterm birth is much closer to the environmental end of the spectrum due to its complex, heterogeneous phenotype. Although small genetic contributions to preterm birth have been identified in homogeneous populations, the differences between racial groups cannot be attributed to genetics. This is due to several factors: (i) There is more variation in genetics across the genome within racial groups than between groups. Ancestral markers, which track (although incompletely) with race, have not been identified as pathogenic sequences for preterm birth. (ii) Among Black women, preterm birth risk is not uniform across socioeconomic strata. Restricted to singleton, nonsmoking Black women, in 2016 to 2018 in the United States, Black women with less than a high school education had a 12.6% preterm birth risk. Black women with a high school diploma or some college education had an 11.8% risk, and women who graduated college had a 9.6% risk. Although these rates are higher than among White women, the gradient demonstrates that this is not genetic in origin but due to exposures and lived-experiences. (iii) The most compelling data to support that racial disparities in preterm birth are largely environmental come from data comparing immigrant Black women to U.S.-born Black women. Black immigrants to the United States have similar birth outcomes to White Americans. It is only with subsequent generations that Black infants are more likely to be born preterm. Genetic sequence does not change that quickly. Although some have argued that it is a gene-environment interaction among Black women in the United States, the fact that Black women in Canada have better birth outcomes than in the United States argues against that hypothesis. There is something about being Black in the United States for at least a generation that leads to a higher rate of preterm birth. Structural racism in the United States affects life in countless ways, leading to differential exposures that confer risk to Black women and protection for White women.

IV. RACIAL DISPARITIES IN THE NICU

A. In addition to disproportionately populating NICUs due to higher rates of preterm birth, there is evidence of racial disparity in care of infants in the NICU. Specifically hospitals that serve high proportions of Black infants are more likely to have less favorable nursing staffing and higher risk-adjusted infant mortality rates.

B. There is also evidence of differences in care of patients within NICUs by race. One of the quality metrics that differs the most by race/ethnicity is the provision of maternal milk in the NICU. Although societal factors affect breastfeeding/breast milk provision, there is much work to do within NICUs to achieve equity in this important quality metric.

C. For care after discharge, there is evidence of lower rates of referral to high-risk infant follow-up clinics and early intervention programs among Black patients.

V. RECOMMENDATIONS

A. Structural racism and implicit biases are present in all aspects of life in the United States, and perinatal medicine is no exception.

B. Recommendations to address these structural and culture factors include the following:

1. Diversify the workforce (faculty, nursing, allied health, trainees, support staff).
2. Prioritize equity.
   - **a.** Measure and report quality metrics by race/ethnicity.
   - **b.** Develop equity-focused quality improvement projects.

C. Partner with families and communities.

1. Ask questions about experiences of racism and discrimination in the NICU.
2. Pay families for their time to consult on improvements in NICU (do not solely rely on parent volunteers who often are White and privileged).
3. Overcome barriers to participating in care in NICU.
   - **a.** Transportation
   - **b.** Childcare
   - **c.** Food vouchers

D. Recognize that the same environments that led to increased risk of preterm birth also will confer risks after discharge and as such ***empower*** families for improved postdischarge outcomes.

1. Arm families with achievable tasks to optimize outcomes, e.g., follow-up visits, wrap-around services with minimal administrative barriers such as WIC (Special Supplemental Nutrition Program for Women, Infants, and Children) offices colocated with pediatric offices, and complex scheduling assistance.
2. Ensure basic human needs are met for families during the hospitalization and after discharge by linking with community resources to address food and energy insecurity as well as safety in the home.

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72 Patient Safety and Quality Improvement

Munish Gupta and Michael Posencheg

KEY POINTS

- Health care organizations seek to help patients and families achieve the best possible health care outcomes. Historically, improving outcomes was driven by research efforts to expand understanding of disease or develop new therapies. It is now recognized that patient outcomes are also driven by systems of care. Insuring that our systems deliver optimal care reliably and consistently is the domain of patient safety and quality improvement (QI).
- Health care quality was originally centered on patient safety, with a focus on the contribution of individual actions and behaviors to error and harm. Attention has shifted, however, from encouraging individual responsibility to developing reliable processes and systems of care.
- Patient safety and QI are closely intertwined. Although safety traditionally focuses on single events and avoiding errors, whereas quality focuses on outcomes for populations of patients, both strive to improve outcomes by using organized efforts to examine care systems and processes.
- Numerous tools and frameworks can help organizations and neonatal intensive care units (NICUs) develop a robust infrastructure for quality and safety.

I. PATIENT SAFETY

A. Introduction and definitions

1. In 1999, the Institute of Medicine (IOM) report *To Err Is Human: Building a Safer Health System* helped create the field of patient safety that we understand today. In this report, the committee estimated that between 44,000 and 98,000 Americans died each year from a medical error.
2. **An error is defined as a failure of a planned action to be completed as intended or the use of a wrong plan to achieve an aim.** Many errors do not lead to injury or impact on patients. Two types of errors have been described: active errors, which result from acts committed by people, and latent errors or conditions, which are weakness in systems and structures that predispose to errors and mistakes. Systems in health care have many layers, and each layer has many inherent defenses designed

to avoid errors. However, each layer has weaknesses that can manifest as active errors or latent conditions. A commonly used framework considers these layers to be like slices of Swiss cheese, with weaknesses being holes in each slice; on occasion, the holes in multiple layers will line up and an error can reach the patient and cause an adverse event.

3. **An adverse event is defined as injury that results from a medical intervention not due to the underlying condition of the patient.** Some adverse events are known complications of providing medical care, whereas others are due to error and deemed to be preventable. The relationship between medical errors, adverse events, and preventable adverse events is shown in Figure 72.1.
4. **An active error** is when a person makes a mistake, like ordering the wrong medication or the incorrect dose. Active errors are easier to detect but may be more challenging to prevent. **A latent error** is also referred to as an unsafe condition. An example may be an electronic medical record (EMR) that does not dose-check medications with guard rails, ensuring a dose of medication is within a range appropriate for a patient. These errors are harder to detect but are arguably more important to address.
5. To address latent errors and prevent them from reaching the patient, it is important to understand that outcomes (as well as adverse events) are produced by systems. A system is defined as the combination of people,

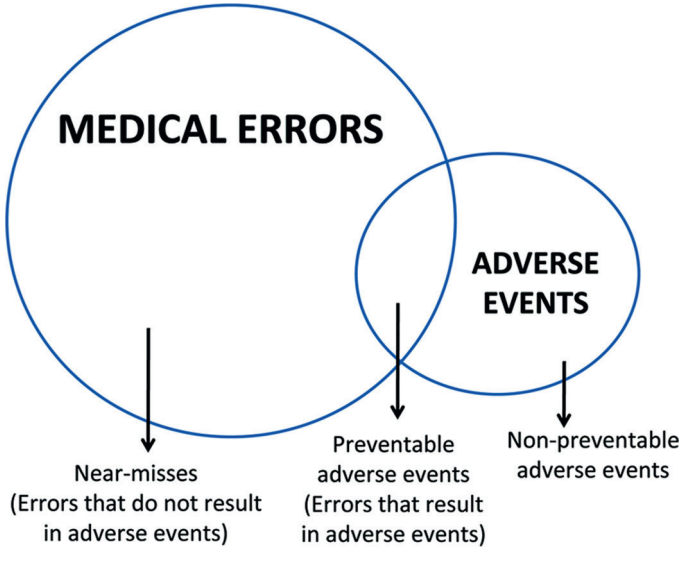

Figure 72.1. Medical errors, adverse events, and preventable adverse events. (Reprinted by permission from Nature: Raju TN, Suresh G, Higgins RD. Patient safety in the context of neonatal intensive care: research and educational opportunities. *Pediatr Res* 2011;70[1]:109–115.)

processes, and tools that come together to produce an outcome. To change an outcome (or prevent an adverse event), you have to change the system that produces it.

6. Although it is important to recognize the importance of redesigning systems to prevent errors and not blame individuals, there are certain agreed upon standards of practice that individuals should and must be accountable for. When investigating medical errors, it is important to differentiate whether an individual knowingly deviated from an acceptable standard or made an honest mistake. Punitive response to all errors will interfere with a health care safety culture that allows individuals to openly report errors when they occur.

B. High reliability organizations (HROs)

1. The airline and nuclear power industries are exemplars of an open and healthy error reporting system. They realize that to continue to identify opportunities for improvement, they must be aware when precursor events occur.
2. An HRO is one that is in continual pursuit of defect-free operation, or in the setting of health care, zero harm to our patients. In health care, we have two different but closely related constructs that help us define what it means to be an HRO. Regardless of the construct used, these five key behaviors or principles are important to drive to zero harm:
   a. Preoccupation with failure: Investigate events, especially precursor events before they reach the patient.
   b. Sensitivity to operations: Pay attention to activity on the front lines to see how humans interact with the system.
   c. Reluctance to simplify: Don't take the first and often easiest answer to solve a problem because issues are normally more complex and nuanced.
   d. Commitment to resilience: Detect, contain, and bounce back from errors.
   e. Deference to expertise: Ask and give decision-making authority to those with the most experience in a given area, regardless of rank.
3. The first construct of HRO in health care is from the Joint Commission Center for Transforming Healthcare. This model incorporates the triad of leadership's commitment and participation, the principles and practice of a safety culture, and adoption and deployment of process improvement tools to drive organizations to be highly reliable toward achieving zero harm for patients.
4. The second construct comes from the Institute for Healthcare Improvement in partnership with Safe and Reliable Healthcare and is entitled *A Framework for Safe, Reliable, and Effective Care*. There are nine key elements in this framework that map to two broad categories: a Learning System and Culture. These nine elements include Psychological Safety, Accountability, Teamwork and Communication, Negotiation, Continuous Learning, Improvement and Measurement, Reliability, Transparency, and Leadership. The Leadership element maps to both categories. Engagement of the patient and family is in the center of this framework.

C. Patient safety tools

1. **Morbidity and mortality conferences** are commonly used by clinical departments to review errors and adverse events. These conferences should use patient safety tools to investigate events resulting in morbidity or mortality, with the goal of identifying contributing causes and system-based issues that can be addressed to minimize future risk and improve care.
2. **Root cause analysis** is an exercise designed to investigate a serious error after it has occurred. As part of this exercise, tools such as a fishbone diagram and 5 whys are often used individually or in concert as part of the investigation of key causes of the error. Another tool, the Failure Mode and Effects Analysis (FMEA), is used proactively to think about errors that could occur in a particular high-risk set of processes.
   a. **Cause-and-effect diagram**
      i. The cause-and-effect diagram, also known as a fishbone diagram or the Ishikawa diagram, is a tool used to describe the many causes or factors that could have resulted in the problem or "effect" being investigated. The design of the diagram resembles a fish with the problem or effect being placed at the "head" of the fish, usually on the right, and causes or factors being placed along the "bones" of the fish. The main "bones" of the fish represent categories of factors contributing to the problem being solved. Traditionally, these categories include (i) people, (ii) environment, (iii) materials, (iv) methods, and (v) equipment. However, it is more important that the names of the categories help the team group their factors in a framework that is understandable to them; the category names can be altered as needed.
      ii. Once categories are determined, the team should start to identify specific causes in each category and place them on the diagram on "branch bones." Subcauses can also be identified and represented along additional branching "bones." It is important to identify subcauses as often the original factors identified may not lead to identification of the true "root cause" of the problem. An example of a fishbone diagram addressing an infection control issue in a neonatal intensive care unit (NICU) is given in Figure 72.2.
   b. **5 whys**
      i. When teams start to investigate causes to a problem, they often quickly come to solutions that may represent just another symptom of the problem and not the true root cause. A tool to help assist teams get to the root cause and create an appropriate countermeasure is 5 whys. The theory behind 5 whys is that the first factor thought of during error investigation often does not identify the primary reason that the error occurred. By asking "why" repeatedly, the team will have a better chance of identifying the primary cause of failure.
      ii. An example of using 5 whys to address a breast milk error is given in Table 72.1. If investigation had stopped at the first or second questions identifying staff errors in bringing the wrong breast milk to the bedside, interventions may have focused on staff education or staff policies. By continuing with the additional

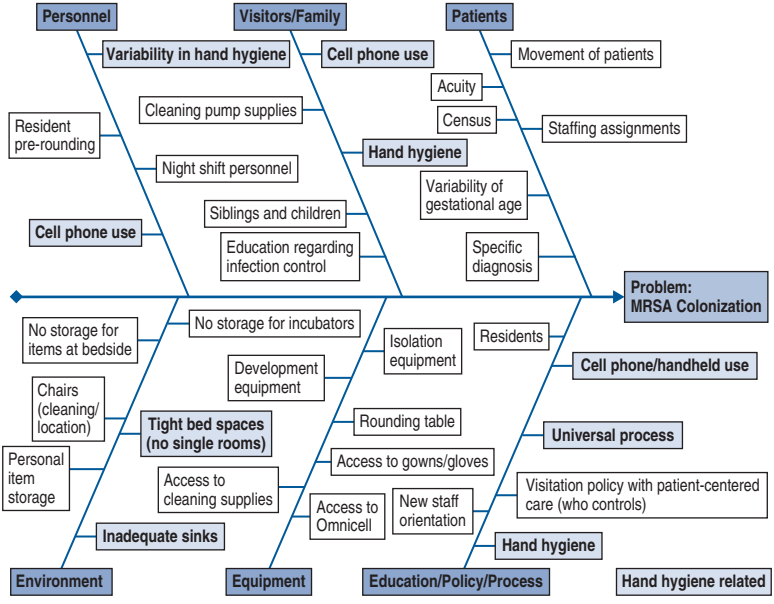

Figure 72.2. Example of cause-and-effect diagram used to identify factors potentially contributing to increasing methicillin-resistant *Staphylococcus aureus* (MRSA) colonization in the neonatal intensive care unit. The team highlighted those factors related to hand hygiene, their first target area.

Table 72.1. Example of Using 5 Whys

Problem: An infant received breast milk that was expressed by a different mother.	
1. Why was the wrong breast milk given to the infant?	The wrong breast milk was brought to the bedside.
2. Why was the wrong breast milk brought to the bedside?	The breast milk was taken from a different infant's bin.
3. Why was breast milk taken from a different infant's bin?	The bin was right next to another infant's bin, and all the bins look alike other than infant label.
4. Why were different bins right next to each other?	Many bins are in the breast milk refrigerator, with one bin for each infant.
5. Why are many bins in the breast milk refrigerator?	There is only one breast milk refrigerator for that section of the NICU.
Potential solutions: Improve storage system to reduce risk of accidental removal of breast milk from a different bin; can consider different color bins, larger labels, barriers between bins, and individual infant refrigerators.	

levels of questions, structural issues around breast milk storage were identified; interventions addressing these structural issues will likely be more impactful in mitigating future risk.

c. FMEA

i. An FMEA is another powerful tool for error investigation. It can be applied to any process in health care where an error and adverse event can potentially occur. As opposed to many tools in patient safety that evaluate the causes of an error after it has occurred (like a fishbone diagram and 5 whys), this tool is used proactively to evaluate each step of a process and anticipate the errors that may occur in the process as it exists currently. An FMEA is best performed with a multidisciplinary team representing all who have a role in the process of care being evaluated. Because the focus is prevention, the process addressed is often deemed either high risk for failure or one where failure would be cause substantial harm. Once all steps are discussed and potential errors are identified, the errors are further evaluated to prioritize how they should be addressed. The goal is that error-prone areas are identified and eliminated before significant adverse events ever occur. This tool is at the cornerstone of HROs due to its proactive nature and mitigation of precursor events.

ii. The steps to performing an FMEA are listed and described in Table 72.2. The Institute for Healthcare Improvement provides an interactive tool for performing an FMEA on their website (http://app.ihi.org/workspace/tools/fmea/).

D. Patient safety in neonatology

1. Unfortunately, neonatal patients are not immune to medical errors or the subsequent adverse events. In fact, neonates may be at particularly high risk for errors and adverse events. A 2010 workshop organized by the National Institute of Child Health and Human Development (NICHD) examined patient safety specifically in the context of neonatal intensive care and identified numerous concerns specific to neonatal patients. The size and fragility of infants in the NICU leads to small margins of safety; errors or complications will be more likely to lead to injury and harm.
2. Definitive data on the frequency of errors and injury in neonatal care is not available, although all NICUs can likely confirm adverse events are not infrequent.

II. QUALITY IMPROVEMENT

A. Definitions and frameworks

1. There is not one universally accepted definition of health care quality. Many current definitions are based on the IOM report from 2001 defining six domains of quality: safe, effective, patient-centered, timely, efficient, and equitable. These are described in Table 72.3.
2. There is not one universally accepted definition of quality improvement (QI). A commonly cited definition provided by Batalden and Davidoff in 2007 describes QI as "the combined and unceasing efforts

Table 72.2. Steps to Perform a Failure Modes Effect Analysis
1. Identify the process that requires investigation.
2. Convene a multidisciplinary team representative of the disciplines involved in the process.
3. List each step in the process in as much detail as you can.
4. Evaluate the errors or failures that can happen in each step using the following construct:
a. Failure modes (What could go wrong?)
b. Failure causes (Why would the failure happen?)
c. Failure effects (What would be the consequence of each failure?)
5. Rate each failure mode using the following criteria and scale:
a. Likelihood of occurrence (1–10)—10 is most likely to occur.
b. Likelihood of detection (1–10)—10 is most likely NOT to be detected.
c. Severity (1–10)—10 is most severe harm to the patient.
6. Calculate the risk profile number (RPN) for each failure mode by multiplying the likelihood of occurrence × likelihood of detection × severity to get a score between 1 and 1,000.
7. Develop action items to address the highest prioritized failure modes as identified by the RPN.

of everyone – healthcare professionals, patients and their families, researchers, payers, planners, and educators – to make the changes that will lead to better patient outcomes (health), better system performance (care), and better professional development (learning)."

3. Several key elements of this definition include (i) QI is continuous; (ii) QI seeks measurable improvement; and (iii) QI is the responsibility of everyone in health care.
4. Numerous frameworks offer structured approaches and tools for improvement. Although the frameworks differ on specific elements, they share foundations of continuous improvement, measurement, and learning through small tests of change. Common frameworks include the Model for Improvement, Lean, and Six Sigma.
   a. **The Model for Improvement** is based on the work of W. Edwards Deming and is anchored on continuous learning through small tests of change. It was formalized by the Associates in Process Improvement and the Institute for Healthcare Improvement and first shared in the 1996 textbook *The Improvement Guide*. It is likely the most common approach used in health care.

Table 72.3. Dimensions of Health Care Quality from Institute of Medicine

Dimension	Definition
Safe	Avoiding injuries to patients from the care that is intended to help them
Effective	Providing services based on scientific knowledge to all who could benefit and refraining from providing services to those not likely to benefit
Patient-centered	Providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions
Timely	Reducing waits and sometimes harmful delays for both those who receive and those who give care
Efficient	Avoiding waste, including waste of equipment, supplies, ideas, and energy
Equitable	Providing care that does not vary in quality because of personal characteristics such as gender, ethnicity, geographic location, and socioeconomic status

Source: Republished with permission of National Academy Press, from Institute of Medicine Committee on Quality of Health Care in America. *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington, DC: National Academies Press; 2001:5–6; permission conveyed through Copyright Clearance Center, Inc.

b. Six Sigma focuses on improving a process through reducing unwanted variability. The term refers to six standard deviations from the mean, with a goal of achieving <3.4 defects among 1 million events. The most common Six Sigma approach to improvement is often referred to as DMAIC: define, measure, analyze, improve, and control.

c. Lean anchors improvement through focusing on the value of the patient, elimination of waste, and respect for people. Core tools of Lean improvement include direct observation of current work processes and using the expertise of frontline staff.

B. The Model for Improvement

1. The Model for Improvement asks teams to begin improvement efforts by asking and answering three questions.

a. Aim: The first question is "What are we trying to accomplish?" This question asks teams to determine the aims and goals of the QI effort.

i. QI projects should target quality and safety concerns considered high priority for a given unit or hospital. Numerous systems and approaches can help identify potential targets for improvement, including the following:

a) Local review of adverse events and unanticipated outcomes, often identified through patient safety tools described earlier

b) Evaluation of quality of care delivered using the IOM domains of quality
c) Monitoring of quality metrics, including metrics reported externally to regulatory groups and metrics tracked internally
d) Performance benchmarking of local performance using data from external networks such as Vermont Oxford Network, the Children's Hospitals Neonatal Consortium, Pediatrix, and the National Healthcare Safety Network
e) Specific areas identified as opportunities for improvement by families or staff

ii. Often, initial improvement targets will be fairly general and will need to be narrowed in focus and scope. The narrowed focus can then be further refined into a specific aim statement, which should clearly and explicitly state the goals of the improvement effort including measures of success and time frame for achievement. A commonly used framework is to develop "SMART" aims: specific, measurable, achievable, relevant, and time-bound.

iii. An example of developing a general improvement goal and a specific aim statement around a family engagement project is provided in Figure 72.3.

b. Measures: The second question is "How will we know that a change is an improvement?" This question asks teams to identify measures that can be used to guide and evaluate improvement efforts.

i. Measurement is critical to improvement.

ii. Several types of measures can be useful in QI.

a) **Structural measures** describe the health care setting and the environment. They are not typically patient-specific but rather describe the general resources of the health care system.
b) **Process measures** examine performance of the health care system and activities of health care providers. Process measures

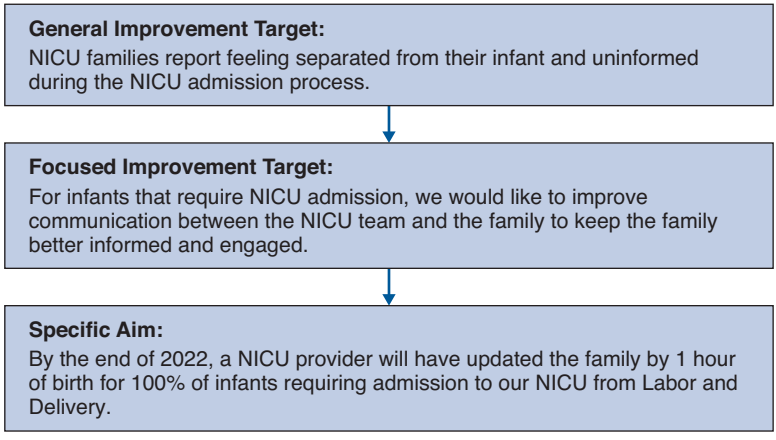

Figure 72.3. Example of moving from general improvement target to specific aim. NICU, neonatal intensive care unit.

can be closely linked to care processes and are commonly used for testing and implementing changes and interventions.

c) **Outcome measures** assess the impact of care on patients or populations. These are typically the measures that matter most to patients and families but are often complex with multiple drivers and thus may be slow to show improvement related to practice changes.

d) **Balancing measures** monitor for negative impacts of improvement efforts or alternative explanations for improvement in outcome measures. Although QI should not generally be implementing changes with unknown benefits, the complexity of health care systems warrants consideration of unintended consequences of process changes.

e) Although outcome measures intuitively represent the most important goals of health care in general as well as QI, structure and process measures can be more effective for guiding and evaluating improvement efforts. This requires, however, that structure and process measures are robustly linked to outcomes.

f) Examples of these types of measures for a hypothetical respiratory care project are provided in Table 72.4.

iii. Measurement for improvement differs from measurement for research. For QI, data collection should focus on what is needed to guide improvement, with the goal being usefulness of data rather than perfection. Data collection is ideally incorporated into the daily workflow rather than requiring dedicated resources. Sampling can be a useful strategy to limit data collection burden.

iv. Analysis of data is also different for QI than research. Whereas research often uses statistical tests of significance to compare two populations at a given point, QI uses techniques that examine dynamic changes in performance over time. Time-series data analysis can be one of the most powerful tools available to QI teams for understanding system performance. Statistical process control (SPC) is a commonly used approach for time-series data analysis for QI and incorporates several statistical tools including run charts and control charts.

c. **Changes**: The third question is "What change can we make that will result in improvement?" This question asks teams to consider and identify potential changes or interventions that can lead to their improvement goal.

i. Changes in practice are necessary to improve. On the other hand, not all changes will lead to improvement. Thoughtful selection of potential change ideas will increase likelihood of changes leading to improvement.

ii. The best change ideas typically are generated by examining and understanding local processes and contexts. Numerous tools can aid teams in analyzing current processes; three such tools are brainstorming, cause-and-effect diagrams, and process maps. Driver diagrams which link change ideas to project aims can also be used to support process analysis.

Table 72.4. Measure Types in Quality Improvement

Type	Description	Examples in Improvement Project Targeting Neonatal Respiratory Care
Structure	Measures of the health care setting and environment	■ Participation of respiratory therapist on rounds ■ Availability of bubble CPAP in the delivery room
Process	Measures of delivery of care and activities of the health care system	■ Percentage of very low birth weight infants requiring positive pressure respiratory support whose first mode of support was CPAP ■ Average time to surfactant administration after intubation among very low birth weight infants receiving surfactant
Outcome	Measures of the impact of care on patients or populations	■ Percentage of very low birth weight infants with bronchopulmonary dysplasia, defined as need for oxygen or positive pressure respiratory support at 36 weeks' postmenstrual age
Balancing	Measures of potential negative or unintended consequences of improvement efforts in other outcomes or other parts of the system	■ Percentage of very low birth weight infants with pneumothorax

CPAP, continuous positive airway pressure.

Source: Reprinted by permission from Nature: Gupta M, Kaplan HC. Measurement for quality improvement: using data to drive change. *J Perinatol* 2020;40(6):962–971.

iii. Beyond understanding local processes, experiences of other institutions can be valuable sources of change ideas. In addition to learning from informal discussions with colleagues from other institutions, a rapidly growing literature of QI publications can provide detailed descriptions of other improvement efforts.

iv. Change concepts are general approaches to change that can also help teams develop specific change ideas for their particular improvement efforts. Change concepts that have been found useful in health care include simplifying a process, improving work flow, making processes easier to follow, identifying and reducing variation, and changing the work environment. An example of

using a change concept in a specific QI effort could be to address variation in an improvement project targeting family communication after NICU admission by observing admissions to identify current variation and then testing a checklist with the goal of standardizing practice.

2. After these three questions are asked and answered, the Model for Improvement asks teams to make changes to practice through rapid-cycle testing.
   - **a.** Testing changes before implementing is a critical foundation of QI.
   - **b. The Plan-Do-Study-Act (PDSA) cycle** offers a structured approach to testing and learning. It is based on the scientific method of generating and then testing a hypothesis.
     - **i.** Plan: Define the goals of the test and the questions the cycle is going to address, predict outcomes and learnings, clarify how the test will be conducted, and identify data that will be collected to evaluate the test.
     - **ii.** Do: Conduct the test and collect relevant data, including observations from staff involved regarding successes or challenges.
     - **iii.** Study: Analyze data and staff observations to evaluate the test and compare outcomes to original predictions, including unexpected findings.
     - **iv.** Act: Based on analysis of data and learnings from the test, determine next steps for change tested, including plans for next test.
   - **c.** A commonly used approach for acting on a PDSA cycle is to decide whether the change should be adapted (if test suggested that modifications to the change are needed), adopted (if the test was successful and next step would be test on a larger scale or implement), or abandoned (if test was unsuccessful and a new change idea is needed).
   - **d.** Initial tests of changes are often most useful when performed on the smallest scale possible. Often, the best initial tests are performed on a scale of one, such as a test on one patient, one provider, or one day. The size of the initial test can be based on degree belief in the change idea, cost of failure, and resistance to change; changes with high degree of belief, low cost of failure, and low resistance to change may be able to start with larger tests.
   - **e.** After the initial test, larger scale tests using the PDSA model can follow, where the change is tested with more patients and more providers and under more conditions; this is commonly referred to as a PDSA ramp. As confidence grows that the change leads to improvement, the change can be implemented as part of the standard workflow.

C. Driver diagram

1. A driver diagram can be a powerful tool to support improvement efforts. It can help a team develop and summarize its theory of knowledge of how changes in process can lead to the desired improvement goal. It links the aims of the improvement work to current structures and processes to potential changes. A driver diagram can incorporate some or all elements of the Model for Improvement into one document that can become a shared mental model for the improvement team and broader unit staff.

2. Driver diagrams often share a common structure, although this structure can be adapted to meet the needs of different improvement projects. The specific aim or outcome of the improvement project is linked to drivers, which are elements of the current system thought to impact the outcome of interest. These drivers are then linked to change concepts or change ideas. Measures can be associated with the aim and selected drivers and changes; often, an outcome measure will be associated with the aim, whereas process and structure measures will be associated with drivers and changes.
3. Driver diagrams should be dynamic and revised as the theory of knowledge is updated over the course of an improvement project.
4. An example of a key driver diagram for a bronchopulmonary dysplasia improvement effort is given in Figure 72.4.

III. QUALITY DASHBOARDS

A. Quality dashboards are visual display tools that summarize performance on a selected set of measures. They are meant to present leaders and clinical providers with data in an understandable, concise, relevant, and timely format. They are used at all levels of health care, from national or regional systems to large health care organizations to individual clinical units. For NICUs, they can be an important element of unit infrastructure to support patient safety, quality assurance, and QI efforts.

B. An extensive literature describes dashboard use in business and in health care. There does not appear to be one best or preferred dashboard format. Some general principles for dashboard design and use include the following:

1. The total number of measures included should be limited.
2. Measures chosen for a quality dashboard are typically static, meaning the measures are not changed often. The measures included should reflect areas of safety and quality that are considered ongoing priorities for the unit.
3. Measures on a dashboard can be organized into categories to facilitate understanding and interpretation. These categories ideally align with the strategic goals or core values of the unit or organization. A common approach is to organize measures using the IOM domains of quality (safe, effective, patient-centered, timely, efficient, and equitable).
4. Data should be displayed graphically over time.
5. Dashboards should be updated and reviewed frequently, with the most recent data possible. Many health care dashboards are updated and reviewed monthly. In NICUs, some outcome measures for smaller populations (such as very low birth weight [VLBW] infants) may be better updated quarterly or even yearly, but even small NICUs will likely have some structural or process measures that should be reviewed monthly.
6. Goals can be helpful, although overreliance on predetermined thresholds should be limited. Many dashboards use colors to indicate levels of performance, such as red, yellow, or green; although this allows for a visually powerful method of quickly identifying areas needing attention, this may mask important trends in data that reveal more than whether or not current performance is at a certain level.

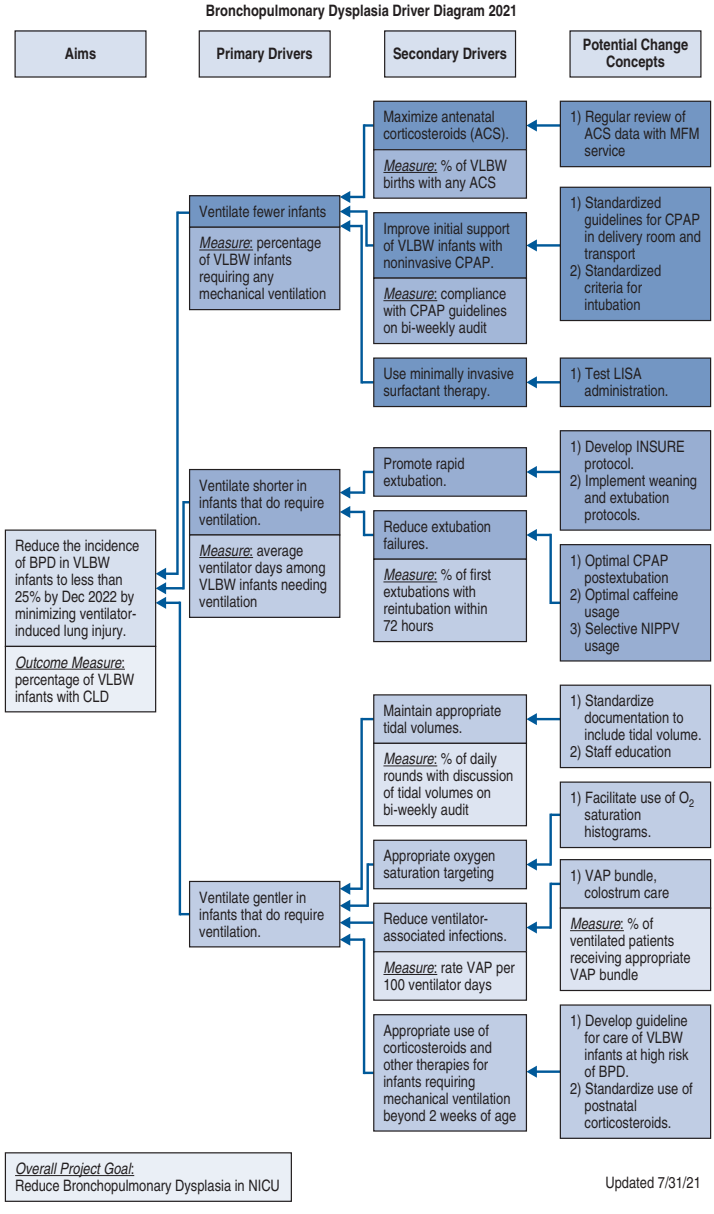

Figure 72.4. Example of driver diagram for bronchopulmonary dysplasia improvement project. Example of driver diagram developed by improvement team seeking to reduce incidence of bronchopulmonary dysplasia in their neonatal intensive care unit (NICU) through a focus on ventilator-induced lung injury. MFM, maternal–fetal medicine; VLBW, very low birth weight; CPAP, continuous positive airway pressure; LISA, less invasive surfactant administration; INSURE, intubate, surfactant, extubate; BPD, bronchopulmonary dysplasia; NIPPV, nasal intermittent positive pressure ventilation; CLD, chronic lung disease; VAP, ventilator-assisted pneumonia.

C. Most measures used for quality assurance or quality dashboard will be selected locally, meaning those measures reflect priority areas for that particular unit or hospitals. Some measures are reported externally and monitored by public health agencies, payors, and quality organizations.

1. Organizations that monitor and report perinatal and neonatal measures include The Joint Commission, the Leapfrog Group, and Centers for Medicare & Medicaid Services, in addition to many state public health agencies and payors.
2. Perinatal measures that have been reported externally include antenatal corticosteroid use, cesarean section delivery, early-term elective delivery, episiotomy rate, exclusive breast milk feeding, neonatal mortality, nosocomial infection, central line–associated bloodstream infection, newborn bilirubin screening, and unexpected neonatal complications.

IV. DEVELOPING A QUALITY AND SAFETY INFRASTRUCTURE

A. The earlier sections highlight core principles for patient safety and QI. These represent a small subset of the available knowledge and tools, and there are many books and articles describing organizational journeys toward robust quality and safety systems.

B. Although it is not possible to develop a comprehensive list of quality and safety activities for a NICU, listed in the following are selected activities that are high yield and relatively achievable.

1. Use a robust incident reporting system to allow staff (and families) to freely share safety and quality concerns, with capacity for evaluation and response from medical and nursing leaders.
2. Share deidentified patient safety stories in meetings and other forms of communications.
3. Foster a just culture where errors are viewed as an opportunity to learn without fear of unwarranted blame.
4. Have daily multidisciplinary unit-based huddles to raise awareness and capture information about patient safety events.
5. Partner with obstetrical colleagues on a shift-by-shift basis to foster communication about upcoming deliveries for continual readiness.
6. Debrief significant delivery room resuscitation events and in-unit code events for the purposes of learning and improving future performance.
7. Review significant mortality and morbidity cases in a peer-protected, multidisciplinary forum for the purposes of learning from events and creating action items for modifiable processes of care. Root cause analysis tools should be used. A safety statement at the beginning of the conference to create a safe space for discussion is important.
8. Use a standard framework for shift-to-shift handoff like SBAR, ISBARQ, or I-PASS to allow for clear and bidirectional communication.
9. Hold regular patient safety walk-rounds by unit leadership to interact with frontline providers, demonstrating leadership commitment to patient safety as well as learning from those who have the most experience at the bedside.

10. Benchmark performance data with networks like Vermont Oxford Network, Pediatrix, and the Children's Hospitals Neonatal Consortium.
11. Use a quality dashboard to track and display quality and safety metrics and make this dashboard available to frontline staff.
12. Develop a standardized framework for QI efforts and educate staff broadly on this framework.
13. Target one to two QI initiatives per year. Ongoing improvement will contribute to unit culture; however, too many simultaneous initiatives will be difficult to manage and can limit staff buy-in and engagement.
14. Enable and empower frontline staff members to participate and lead QI initiatives.
15. Involve parents in all levels of safety and quality, with a patient and family council or similar. Support for family time and engagement should be provided.

Suggested Readings

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Appendix A

Neonatal Emergency Drug Dosing Guide

Name: _____ Weight: _____ kg

Completed by: _____ Date: _____

Medication	Dose	Patient-Specific Dose	Indication	Comments
Epinephrine IV: 0.1 mg/mL ETT: 1 mg/mL	0.01–0.03 mg/kg IV push 0.05–0.1 mg/kg via ETT		Asystole or severe bradycardia (HR <60 beats/minute)	Repeat PRN every 3–5 minutes. Do not give in artery. Do not mix with sodium bicarbonate ($NaHCO_3$).
Volume expanders ■ **Normal saline** ■ **Whole blood** ■ **PRBC**	10–20 mL/kg IV over 5–10 minutes		PRBC: known or suspected blood loss and HR not responsive to other resuscitative measures	
Glucose **$D_{10}W$**	2 mL/kg IV push		Hypoglycemia	Give more slowly if nonemergent.
Naloxone (Narcan) 0.4 mg/mL (see Chapter 67)	0.1 mg/kg for acute opioid exposure IV push, via ETT (If ETT, give 0.2 mg/kg), IM, SQ		Narcotic depression	Repeat PRN every 2–3 minutes. May need repeat dose every 20–60 minutes IM/SQ absorption delayed especially if poor perfusion
$NaHCO_3$ 0.5 mEq/mL	1–2 mEq/kg IV (**not via ETT**) over 2 minutes		Metabolic acidosis in setting of adequate ventilation	Give more slowly if nonemergent or preterm infant.
Calcium gluconate 10% 100 mg/mL	100 mg/kg IV over 10 minutes		Symptomatic hypocalcemia or hyperkalemia	Stop infusion if HR <100 beats/minute.

IV Route is always preferred.

If in delivery room, use Neonatal Resuscitation Program (NRP) dosing.

ETT, endotracheal tube; HR, heart rate; PRN, as needed; PRBC, packed red blood cell; $D_{10}W$, dextrose 10% in water.

Appendix B

Intubation Sedation Guidelines (see Chapter 70)

Name: _____ Weight: _____ kg

Completed by: _____ Date: _____

Medication	Dose	Patient-Specific Dose	Duration of Effect	Comments
Analgesic medications				
Fentanyl	IV: 0.5–3 µg/kg/dose		30–60 minutes	Infuse over 1–3 minutes. May cause chest wall rigidity with rapid infusion Neuromuscular blocking agent if suspect chest wall rigidity Antidote: naloxone
Morphine	IV: 0.05–0.1 mg/kg/dose		2–4 hours	Infuse over 5 minutes. Use with caution in patients with hypotension. Antidote: naloxone
Sedative medications				
Midazolam (Versed)	IV: 0.05–0.1 mg/kg May be given IM: 0.1 mg/kg Intranasal (5 mg/mL conc.): 0.2–0.3 mg/kg		1–4 hours	Infuse over 2–5 minutes. Do not use if <35 weeks' post-menstrual age. Antidote: flumazenil

(continued)

Medication	Dose	Patient-Specific Dose	Duration of Effect	Comments
Short-acting neuromuscular blocking agents—only use if able to provide adequate facial/mask PPV				
Rocuronium	IV: 0.6–1.2 mg/kg/dose		20–40 minutes (peak effect 30–60 seconds)	Rapid IV push Antidote: sugammadex or neostigmine
Succinylcholine	IV: 2 mg/kg/dose May be given IM		4–6 minutes (peak effect 30–60 seconds)	Always administer atropine first (see dose in the following text). Rapid IV push Do not repeat dose. Do not use in patients with history of musculoskeletal disease, hyperkalemia, renal dysfunction, or trauma.
Anticholinergic medication				
Atropine	IV: 0.02 mg/kg/dose		4–6 hours	Infuse over 1 minute. No further minimum weight or dose

ETT size: _____ Distance from tip of tube to ☐ nares ☐ lip _____.

PPV, positive pressure ventilation; ETT, endotracheal tube.

Index

Note: Page numbers followed by an "*f*" denote figures; those followed by a "*t*" denote tables.

B

C

D

E

F

G

H

I

J

K

L

M

O

Q

R

S

T

U

V

W

X

Z